Evidence-Based Procedural Dermatology

Murad Alam
Editor

Second Edition

Springer

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To my parents, Rahat and Rehana Alam,
my sister, Nigar Alam, my nephew Ali,
and my (favorite) niece, Noor.

To my mentors, Ken Arndt, Jeff Dover, David Bickers,
Leonard Goldberg, Randy Roenigk, Ron Moy,
June Robinson, Hal Brody, Scott Dinehart,
Desiree Ratner, Bill Coleman, Tri Nguyen,
Elizabeth McBurney, Amy Paller, Dirk Elston,
Alex Miller, and George Hruza.

Preface to the Second Edition

Since the first edition of this text, much has changed. The methodologic quality of the literature in dermatologic surgery has continued to improve [1, 2]. Journals are encouraging, and authors are accepting, the importance of well-designed studies that are also written up in accordance with appropriate reporting guidelines, like those maintained by Equator [3].

For therapeutic and interventional studies, the importance of carefully selected outcome measures is increasingly apparent. As the Cochrane Collaboration and others have found, research waste can result when the results of small studies cannot be pooled because the outcome measures used are too disparate to reconcile [4, 5]. This problem may ultimately be rectified by the development of core outcome sets, or minimum groups of agreed-upon outcomes that would be employed by all investigators studying a particular disease or condition. In dermatologic surgery, the IMPROVED group is a US-based collaboration working on relevant core outcome sets for the treatment of skin cancers and cosmetic conditions.

High-quality patient-level data may also soon be forthcoming from the many qualified clinical data registries being created by professional specialty societies in the United States. While the presumptive primary incentive for such registries is to facilitate practitioners' ability to report required quality metrics to the federal government, the data collected will also be a fruitful resource for a range of clinical questions. Registries in dermatology, such as DataDerm at the American Academy of Dermatology, are currently "maturing" but within 5 years may be being mined by interested researchers. In dermatologic surgery, the American College of Mohs Surgery has initiated the MohsAIQ Registry, and the American Society for Dermatologic Surgery (ASDS) has planned a registry to track adverse events specifically.

Funds for clinical and comparative effectiveness research in dermatologic surgery are still sparse. A notable bright spot is the ASDS' new Brandt grant program, which specifically supports multicenter clinical research in dermatologic surgery. Investigators are learning to work across centers in ways that are cost- and time-efficient.

The first edition of *Evidence-Based Procedural Dermatology* was named after the ACGME-approved advanced fellowship in dermatologic surgery started in 2003. More recently, this fellowship has been modified to exclude most cosmetic procedures and has been renamed Micrographic Surgery and Cutaneous Oncology (MSDO). A new fellowship program, Cosmetic Dermatologic Surgery, has arisen under the auspices of ASDS to fill the

training gap in advanced cosmetic and laser procedures. Collectively, there are now about 100 fellowship positions in dermatologic surgery each year, with approximately 1 in 4 US dermatology residents choosing to obtain advanced dermatologic surgery training. Perhaps even more importantly, dermatologic surgery is permeating residency training in dermatology, with young dermatologists better trained in the surgical management of relevant conditions. The techniques pioneered by dermatologic surgeons have also entered other specialties, including plastic surgery, head and neck surgery, ophthalmology, vascular surgery, medical and surgical oncology, and many others. As a consequence, this text is more relevant than ever. The growing cadre of specialists in dermatologic surgery need current, authoritative, and comprehensive information that weighs the benefits and limitations of various treatment approaches for conditions of concern.

We have opted to stay with the moniker "Procedural Dermatology," which concisely conveys the breadth of our charge. But the second edition is much expanded from the first. More topics are addressed, and more outstanding chapter authors are included. I am deeply grateful to the many gifted, busy, and generous dermatologic surgeons who have written this book.

Chicago, IL, USA Murad Alam, MD, MSCI, MBA

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Designing Randomized Clinical Trials in Dermatologic Surgery

1

Murad Alam

Abstract

There are many ways to better understand how to diagnose and treat our patients. An unusually powerful tool is the randomized controlled trial (RCT). The first well-reported RCT assessed utility of streptomycin for the treatment of tuberculosis in 1948 (Williams, How to critically appraise a randomized controlled trial. In: Williams H, Bigby M, Herxheimer A, Naldi L, Rzany B, Dellavale R, Ran Y, Furue E (eds) Evidence-based dermatology, 3rd edn. Wiley, New York, pp 39–45, 2014). Although a relatively newcomer to the scientific toolbox, the blinded RCT is now widely acknowledged as the key building block that underpins high-level medical evidence.

Keywords

Outcome · Patient · RCT · Surgery · Trial · Intervention · Core

There are many ways to better understand how to diagnose and treat our patients. An unusually powerful tool is the randomized controlled trial (RCT). The first well-reported RCT assessed utility of streptomycin for the treatment of tuberculosis in 1948 [1]. Although a relatively newcomer to the scientific toolbox, the blinded RCT is now widely acknowledged as the key building block that underpins high-level medical evidence.

Potential Benefits of a Blinded RCT [1]

Since performing a blinded RCT is time-consuming and costly, it is helpful to consider why undertaking this burden may be worth the trouble. The specific benefits include reduction of bias and elimination of unknown confounders. Since patients in such a trial are randomly assigned in a concealed manner to two or more groups, patients' characteristics are likely to be similar across groups. Selection bias is therefore avoided. Since outcome assessment is also blinded, we would also expect the absence of detection bias, meaning the outcome of interest is not likely to be observed and measured differently across groups.

The avoidance of unknown confounders is inherent to the randomization process and difficult to achieve in any other experimental design [2]. As an example, let us say we know patients of different ages and genders have different inherent susceptibilities to postoperative dehiscence, and we want to compare two different methods for prevention. We may choose to perform a prospec-

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tive cohort study, with two groups matched for age and gender. But what if dehiscence rates are also directly correlated with BMI, which we have not considered or matched for? Now, if one preventive technique turns out to be superior, this may be due not to the intrinsic superiority of that technique but to the greater abundance of obese patients in the group receiving the other technique. When we randomize, we need not identify every potential confounder, which is generally impossible. Instead, the process of randomization helps ensure that the prevalence of every confounder is more or less equal in each group.

Elements of a Well-Designed RCT

Power, Sample Size, and Procedure Specification [3, 4]

Before beginning a study, it is crucial to consider, and then to write out in extreme detail, exactly what will be done, step by step. Recruitment, blinding and randomization, interventions, follow-ups, outcomes, and statistical analyses must all be prespecified. It may be helpful to consult with other content experts, as well as epidemiologists and experts in trial design. Study design errors are rectifiable at this stage, but less so later. Failure to prespecify and double-check study design elements before initiating the study may lead to inconsistent or changing study procedures, which impairs the quality of your data.

Also necessary at this time is a statistical analysis. Given the comparison you are trying to make, the primary outcome measure you are planning on using, and the expected difference across groups on this measure, a biostatistician will be able to tell you how many patients you will need to enroll. Depending on the power, or ability to detect a difference, you preselect for your study (typically 0.8 or 0.9 for dermatologic surgery studies), the statistician will be able to tell you the sample size that will likely be sufficient to detect a difference of a particular magnitude, if in fact such a difference exists. Simple power studies can be performed without a statistician's assistance; however, if in doubt as to the accuracy of your calculation, it is preferable to hire a professional who can detect mistakes earlier, thereby saving time and money later. It is possible that the sample size for certain studies may be prohibitive and impractical, and so you may choose not to conduct the study. Conversely, fewer patients than expected may be required, and this may free you and your staff to work on other projects.

Randomization and Blinding

These elements are well described elsewhere, and so we will review them briefly. First, the allocation to groups should be truly random. Alternating enrollment between group 1 and 2 is not random but in fact quite determined. A random number generator or table should be used, as just writing down numbers, say 1 s and 2 s, as they come to you has also been shown to be not random. Finally, the random allocation must be concealed from the investigator assigning patients to groups. Concealment may entail opaque envelopes (although these can sometimes be tampered with or backlit) with randomization information inside that you tear open right when you need to assign [1]. Or you may call another investigator at a different site who may tell you which group is next by clicking on a database link. The specific method should be thought out in advance, with different investigators instructed regarding their roles, so that errors and confusion about the steps required do not inadvertently lead to unblinding. Blinding is important because even a well-meaning unblinded investigator may preferentially assign sicker or needier patients to the intervention believed to be more effective or safer. Alternatively, an investigator with a stake in seeing the success of a particular treatment may allocate to that arm patients who are more likely to respond. Either of these cases would, of course, introduce selection bias. Even when blinding is maintained, by chance alone, randomization can be unsuccessful in creating two or more similar groupings. This is more common with smaller sample sizes, just as it is not uncommon to flip a fair coin and get three heads in a

row, but it is much less likely to have this happen consecutively 300 times. It is customary to include a table showing the salient demographic and other characteristics of the several groups to reassure the reader that randomization was successful.

Importantly, blinding remains important throughout the study, through to the point when results are being analyzed. For many dermatologic surgery studies, especially those assessing skin scar evolution or cosmetic interventions, the primary outcome measure may be visual assessment of outcomes. While live, in-room assessors may capture more information than those who perform delayed assessments based on standardized photographs, photographic assessments are easier to blind. Also, with photographic assessments, it is feasible to compare before and after outcomes, since pictures exist of both. Live assessments are not only notoriously difficult to blind; they are further impractical in that the same observer may not be available to observe each patient at every assessment visit. If there are two blinded rater assessments for each observation, the practical obstacles only grow in magnitude.

Similarity of Interventions and Sham Arms

For intervention trials, which are common in dermatologic surgery, what happens to patients in the two or more groups after assignment should be kept as similar as possible. Patients should be treated identically, except for the intervention(s) being compared across groups. As a counterexample, if those receiving surgery A are receiving care in an air-conditioned, sterile operating room at a flagship hospital and those receiving surgery B are treated in a hot, stuffy procedure room under clean rather than sterile conditions, the perceived better outcomes of surgery A may be attributable to the environment and not the procedure. Another benefit to maintaining similarity across groups is that this may allow the patient to remain blinded as to treatment allocation. This can be particularly helpful in avoiding bias if patient-reported outcomes are among the primary study outcomes. Sometimes, it will be impossible to keep the patient blinded. For instance, if one arm is a laser treatment and one is a cutting surgery, the patient will hear different sounds, feel different types of anesthesia, and ultimately see different types of scars or sequelae at the treatment sites. When possible, sham treatments may be of utility in preserving blinding. For example, if the study is comparing the use or avoidance of cautery during Mohs repairs, those not assigned to the cautery intervention may be kept blinded if the investigator cauterizes pigs' foot tissue at the appointed time, thus creating the sound and smell of cautery, while pressing down on the patient's surgery site. The illusion may be better maintained if all patients in the study have their eyes covered during the procedure. Note that sham treatment arms may not always be ethical, especially if they create substantial additional risk for patients not receiving a particular treatment. Institutional review boards should be asked to carefully vet any proposed sham procedures.

Dropouts and Intention-to-Treat

Studies involving human subjects will commonly have dropouts. After being consented, some patients may fail to come for their initial visit, others may not complete all their interventions, and yet others may miss follow-up visits. To avoid attrition bias, these dropouts should be noted and they should be included in the statistical analysis of the primary outcomes. This is so because while it is possible that dropouts are due to factors unrelated to the study, such as job relocation or unrelated illness, dropouts may also indicate study-related issues, such as adverse events, intraoperative pain, or delayed healing. Intention-to-treat (ITT) analyses take into account everyone who was initially randomized, regardless of whether they completed the study. So-called per protocol analyses just analyze those who completed all of the study procedures. Whenever possible, ITT analyses should be reported in addition to per protocol analyses. Reports of RCTs should also include a flow chart

that graphically illustrates the movement of patients through the study, including dropouts, which are specified by number, reason for exit, and time point of exit.

Appropriate Outcome Measurement

Most RCTs will have primary and secondary outcome measures. Outcome measures should be (1) relevant for the purpose of the study, (2) sufficient but not excessive in number, (3) adequate to capture the patient experience, and (4) inclusive of relevant core outcome measures for the disease or condition studied.

A relevant outcome measure is one that is able to answer the question raised by the RCT. For instance, if a study is comparing infection risk associated with surgery on the ear versus surgery on the lip, a bacterial culture may be a relevant outcome measure. Purulent drainage may also be a relevant feature but overall skin-related quality of life or precise assessment of the resulting scar using a validated scar scale would not be. A fine, well-developed outcome measure can still be entirely inappropriate for a particular study.

While there is a natural tendency to include as many outcome measures as are relevant and feasible, this is not a good practice. At the 5% significance level, there is small risk that a single outcome measure will show a difference across groups by chance alone. However, if five, or a dozen, or more outcomes are evaluated, the chance that at least one will be a false positive is quite substantial. In general, it is best to select a small group of highly relevant outcome measures.

In recent years, there has been increasing interest in understanding the patient experience during medical procedures. We have moved away from a paternalistic model, in which the physician decided what outcomes were most important, to one that asks patients what they prefer and how satisfied they are. It is highly advisable that RCTs now include at least one "patient-reported outcome." Validated scales are available, for instance, FACE-Q for skin cancer [5].

Another concern currently receiving attention is that results of RCTs on similar topics are often difficult to pool due to differences in the outcomes studied [6]. "Core outcome sets" (COS) are minimum groups' outcomes that based on expert and patient consensus should be used in all studies of particular conditions or diseases. Core outcome measures, or specific measures recommended for assessing each of the outcomes in a COS, are also available in some cases. Notably, a core outcome set is a minimum list of outcomes, and it is entirely proper and even expected that individual investigators will choose to assess additional outcomes.

The COMET group [7] maintains a database of currently available core outcome sets, as well as sets in development. The CSG-COUSIN group [8], affiliated with the Cochrane Collaboration, is specifically focused on skin-related COS. The IMPROVED group [9–12], based in the USA, is taking the international lead in developing COS for dermatologic surgery. Investigators in dermatologic surgery planning an RCT should consider consulting these research groups prior to finalizing their outcome measures.

Primacy of Preplanned Analyses

When an RCT is complete, the results are analyzed. As stated before, an ITT analysis should be provided when feasible, even if a per protocol analysis is also performed and reported. It is important that all analyses prespecified in the methods section be executed as planned. Omitting some analyses or changing the way in which others are done is strongly discouraged, as it can be perceived as evidence of cherry-picking or only showing the analyses that prove your point. On the other hand, doing additional analyses after you have completed preplanned analyses *is* allowed. If you choose to perform additional analyses, these should be labeled as ad hoc or unplanned analyses to avoid confusing the reader. Similarly, after you review your planned analyses, you may perceive an unexpected subgroup difference that you then choose to test statistically. Again, you should note that this was an unplanned subgroup analysis. Consider limiting the number of subgroup anal-

yses to those that are most interesting or reasonable. Performing too many comparisons will inevitably increase the risk of false-positive findings.

Complete Reporting of Results

It is important to report all the variables that were planned to be collected and all the analyses planned to be performed. Data tables should be complete, showing everything found, not just the outcomes considered interesting or those that supported the experimental thesis. It is appropriate to focus on the most relevant findings in the discussion section, but the results section should neither be unencumbered by excess editorial commentary nor overly abbreviated or truncated. Complete and clear reporting of all outcomes reassures the reader that there is no selective reporting bias.

Sometimes studies will be negative. In dermatologic surgery, failure to detect a difference may frequently be attributable to a small sample size rather than true absence of difference. RCTs in the field typically enroll a few dozen patients, with this number perhaps sufficient to reveal large differences but not small differences. While negative results may be disheartening for the principal investigator, it is still important to publish or otherwise disseminate the findings. Otherwise, publication bias, or the selective reporting of more positive studies than negative studies, can create a falsely optimistic perception of the effectiveness of an intervention. By reporting small negative studies and employing core outcome sets, investigators can facilitate pooling of their results with other similar studies to provide a more complete picture.

For RCTs, most high-impact journals will require written reports to conform to the CONSORT guidelines [13, 14]. The CONSORT checklist is a brief expression of these rules. Following the checklist ensures that the recommended types of information are included in each of the major subsections of the paper. If the writer wants further instruction on adhering to these reporting rules, there is a long elaboration document that describes each checklist item in detail and offers examples and rationales.

Role of RCTs in Dermatologic Surgery

Dermatologic surgery is responsible for many of the RCTs in dermatology [15, 16]. Every 5 years during the past decade the number of RCTs reported in the journal *Dermatologic Surgery* has doubled. From 2005 to 2010, more than 130 such trials have been published. Also, over a similar period, the reporting of these RCTs improved consistently, with ever greater adherence to the CONSORT reporting criteria [15, 16].

Many of the RCTs in dermatologic surgery are comparative effectiveness studies of surgical and procedural treatments. This is to be expected, because dermatologic surgery is a field that emphasizes therapeutics. Trials have been performed on both surgical interventions to treat skin cancer and other lesions and cosmetic and laser interventions to improve appearance and the visible signs of aging. It is perhaps surprising that so many RCTS have been performed in a procedural field, as the procedural arena has generally been viewed as less hospitable for such investigations. Contributing factors may include the low risk associated with most dermatologic surgeries, as well as the abundance of alternative procedural interventions for many dermatologic indications.

Practical Considerations Regarding RCTs in Dermatologic Surgery

Steps in Study Design, Personnel Management, Subject Recruitment, and Data Collection and Analysis

Randomized control trials are resource intensive. Before embarking on one, it is useful to contemplate how all the necessary elements will be assembled. Once a preliminary clinical question has been suggested for exploration via an RCT, a complete literature search performed by a skilled investigator is typically needed. The output of

this search will more precisely delineate the practice or research gap, with this in turn helping to narrow or redirect the research question. A rough draft of a proposed study plan, including patient selection, methods, analyses, and expected results, is then prepared. Biostatistical consultation and advice from a methodologist or clinical trials design expert may be helpful at this point. Sample size can be assessed and methodological oversights can be corrected before proceeding. Post-intervention follow-ups should be sufficient in number to provide long-term outcomes data but not so many as to unnecessarily deplete clinical resources. Similarly, if a series of interventions are required, as is common in cosmetic studies, these should be sufficient to achieve a measurable result, but not so many that they are prohibitively expensive in terms of equipment, supplies, and staff time. If it is desirable and possible, a sham treatment arm should be considered. Sufficient research personnel should be dedicated to the study, and their roles should be specified: these may include two or more data collectors; at least one investigator responsible for delivering the intervention; several personnel responsible for the randomization sequence and allocation; a senior research associate or staffer to oversee data collection and compliance, possibly an IRB consultant; and one or more biostatisticians, in addition to the principal investigator. A finalized study protocol will then be used to construct an IRB protocol submission. Specialized staff, possibly borrowed from a research core or hired on an hourly or per task basis, may assist with the generation of the IRB protocol, as well as requested revisions. A recruitment plan may be included in the IRB, especially if external advertising and promotion is needed.

After IRB approval is obtained, and before patient enrollment can begin, randomization sequences are prepared and secured. All necessary personnel, including clinical staff, data collection staff, and other research assistants, are apprised of their roles. For complex studies, a detailed standard operating procedure can be developed to ensure that patients receive interventions systematically, with preservation of blinding. A few mock patients may also be enrolled and treated so that the process is well understood by the staff, with any minor discrepancies corrected at this point. If certain process details are uncertain as they were overlooked in the research and IRB protocols, relevant procedures can now be codified to fill these gaps. Before the first patient is enrolled, the study must also be posted on clinicaltrials.gov. For investigators working in research institutions, this may mean working through an intermediary at the institution.

Once data collection commences, at least two primary data collectors are needed to ensure that data loss does not occur due to absence or unavailability. In addition, the investigator(s) or other individual(s) delivering the intervention are usually different and also need to be present. Space and equipment may need to be reserved. Scheduling, even for a study with relatively few subjects, may be a formidable task, as several treatment and follow-up visits may be required for each, and patients may frequently no-show or request rescheduling.

When patients are enrolled, randomized, and treated, their data will need to be carefully recorded. A senior research staffer may routinely review the paperwork submitted by the primary data collectors to confirm data integrity and compliance with IRB reporting requirements. After the first several patients, the research team may reconvene to correct any process problems. Should serious obstacles arise, the study may need to be suspended, modified, and resubmitted to IRB for approval prior to resumption.

Particularly resource-intensive studies may have a preplanned interim analysis, with a stopping rule. Since dermatologic surgery studies are usually extremely safe, a data safety monitoring board is seldom required. Interim analyses may instead be useful for seeing if the expected results have been obtained, which may presage early termination of the study. During the process of the interim analysis, a biostatistician may need to be unblinded but the remaining members of the team should remain blinded, if possible.

Once the study is completed and data collection is over, data tables are prepared for review. If some of the data were on paper and not previously entered into a database, data entry into

appropriate software will precede preparation of data tables. Looking at the data carefully allows the principal investigator to ensure that the data is valid and without error. Planned analyses are then performed by the biostatistician. Based on the outcome of these, additional ad hoc or subgroup analyses may be added. The report of the RCT is then written. This will generally be reviewed by multiple investigators prior to submission for publication.

Resource Allocation and Costs

In summary, performing a high-quality RCT does require resources. Even a small trial requires a significant number of staff with diverse responsibilities, although not all of them need to devote more than a fraction of their time to the endeavor. If the intervention is partly standard of care, and being delivered in standard clinic space, additional clinical staff and space may not be required, but if not, then they may. IRB approval can slow down the process. Recruitment rate can also be a limiting factor. Even with rapid recruitment and an efficient IRB, such as a non-institutional one, the timeline from inception to writeup for a longitudinal RCT in which treatments are delivered and long-term outcomes assessed will seldom be less than 1 year and often closer to 2.

Direct costs of the RCT will include at the very least: IRB submission fees; payment, either hourly or per project, to the biostatistician and methodologist; and the salary fractions of research staff on the study. Equipment or supplies required may also need to be bought, or they may be donated. Another cost may be reduction in efficiency of the clinical enterprise when research procedures are interjected into standard clinic days.

That being said, many dermatologic surgeons have sufficient staff to easily perform RCTs. Post-residency fellows, whether assigned to micrographic surgery and dermatologic oncology or cosmetic dermatologic surgery, may benefit from the research experience and are required to complete at least one research project during their year-long tenure. Clinical nurses and mid-level providers may enjoy participating in research in addition to the regular clinical duties. In Mohs services, histotechs may have downtime at the end of the day when they may be able to help, and these staff are generally very precise and detail-oriented, and as such, possibly well-equipped to review study paperwork. IRB approval is often easy for those in private practice, with high-quality external IRBs requiring as little as a week to approve low-risk studies. Finally, if a biostatistician or methodologist is not available, the dermatologic surgeon may consider reaching out to a colleague more experienced in the conduct of clinical trials for advice or to review a research protocol.

Closing Thoughts

Many, if not most, important questions in the field of dermatologic surgery remain unanswered. Those questions that have been addressed usually have not been definitively settled and await more data and higher-quality investigations. At the other end of the spectrum, dermatologic surgeons work in resource-rich environments where they can easily perform modest-sized RCTs without much direct expense. Indeed, they are already doing so, in large numbers. Moreover, RCTs can productively engage clinical staff, and at least some may find such work interesting. RCTs are particularly exciting for the principal investigator, who in a relatively brief period can develop a question, test it, find an answer, and communicate this to the world. The answer may change practice or it may not. But it will clear up a small mystery, in at least a small way, and thereby be a voyage of discovery for those on board and a valuable addition to our collective scientific know-how.

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2 Outcomes Assessment in Dermatologic Surgery

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Abstract

Whether performing a randomized controlled trial, a cohort study, or a case-control study, it is essential to select the outcomes to be measured (Dupuy et al, Outcome measures. In: Williams H, Bigby M, Herxheimer A, Naldi L, Rzany B, Dellavale R, Ran Y, Furue E (eds) Evidence-based dermatology, 3rd edn. Wiley, New York, pp 71–74, 2014; Alam et al, Rationalizing outcome measures in dermatologic surgery. Curr Derm Rep 4(3):140–146. doi:10.1007/s13671-015-0106-5, 2015; Alam, Evidence based procedural dermatology. In: Maibach HI, Gorouhi F (eds) Evidence based dermatology, 2nd edn. PMPH-USA, Shelton, pp 539–545, 2012). Deciding on appropriate outcomes requires consideration of the purpose of the study, the types of outcomes available, the number of outcomes that may be appropriate, outcomes that are commonly measured, and outcomes that convey patients' perceptions. Closely related to the task of outcomes selection is choosing specific outcome measures to represent these outcomes. For example, if scar appearance is a selected outcome, a particular validated scar scale may be the corresponding outcome measure.

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Whether performing a randomized controlled trial, a cohort study, or a case-control study, it is essential to select the outcomes to be measured [1–3]. Deciding on appropriate outcomes requires consideration of the purpose of the study, the types of outcomes available, the number of outcomes that may be appropriate, outcomes that are commonly measured, and outcomes that convey patients' perceptions. Closely related to the task of outcomes selection is choosing specific outcome measures to represent these outcomes. For example, if scar appearance is a selected outcome, a particular validated scar scale may be the corresponding outcome measure.

Selecting Outcomes Appropriate for the Clinical Question

Outcomes and outcome measures should be selected so that the underlying clinical question posed by the study can be answered. A study to measure recurrence rates of skin cancer may reasonably use a live clinical assessment by an expert dermatologist or diagnosis based on skin biopsy, but a measure of skin elasticity or color may be less appropriate, even if these features are accurately and precisely assessed.

Types of Outcomes

As there are different types of outcomes, outcome selection requires not just selecting the best individual outcome(s) but also deciding the categories from which to select. Outcomes can be classified by degree of objectivity, from highly objective, like linear distance, to highly subjective, like global assessment of appearance. Intermediate between these may be normed, validated scales for measuring specific parameters, like color or scar. Another way entails dividing outcome measures based on the type of mechanism used to collect the relevant data. In this formulation, outcomes may be measured by devices or machines; text instruments, like normed or validated questionnaires; or unaided humans. Outcomes that are measured by people, like scales and blinded assessments, can be further subdivided into those that are reported by neutral or blinded raters, those by physicians or investigators, and those by patients or participants. Indeed, these outcomes can otherwise be identical, with their valence impacted by who is doing the measuring. Outcomes can also be rated on the degree to which they conform to underlying theories of pathophysiologic mechanism of action. As an example, if an electronic pulse is said to induce apoptosis in basal cell carcinomas, and this apoptosis is said to manifest as increase in skin erythema, then a precise measure of skin erythema may be said to be an appropriate measure of the rate of apoptosis as well as the effectiveness of the electronic pulse. The problem with relying on a story regarding a proposed mechanism of action is that the story, however convincing, may soon be shown to be wrong, or at least incomplete. Yet another classification scheme considers the extent to which an outcome is insensitive to factors other than those it is expected to measure. If the goal is to measure the degree of collagen remodeling induced by an ablative laser 2 months after treatment, a computed photographic measure of cheek volume may be a poor measure since it may be altered not only by collagen thickening but also by residual post-treatment edema, which may be marked even months after such a procedure. Microscopic evaluation of a tissue biopsy may be better for specifically gauging the degree of collagen growth.

Characteristics of a Robust Outcome Measure

Regardless of type, outcome measures should meet three criteria. They should be accurate, precise, and sensitive to change. Accuracy means that they should truthfully measure the underlying construct. So a temperature measuring device should display the actual temperature, as verified by a reference device measuring temperature. Precision refers to how finely the construct being measured can be distinguished. In the case of a temperature gauge, one that measures to within 0.01 ° is less precise than another which measures to within 0.001 °. Sensitivity to change means that the outcome measure should change in response to changes in the relevant stimulus. If the day becomes cooler, the mercury in the thermometer should fall. Measures that are more sensitive to change may be better able to reveal minor differences over the course of a study. If a hair removal laser removes 5% of total hair per unit surface area per procedure, this may be detectable by a 10-gradation hairometer that provides integral values from 0 (no hair) to 10 (maximum hair), but not by a 3-gradation hairometer (1 = no hair, 2 = some hair, and 3 = maximum hair).

Limitations of Objective and Precise Outcome Measures

The choice of outcome measure is not always obvious. While it may seem like an objective, machine-generated statistic that is highly precise and incredibly sensitive to change would be optimal in most cases, this is not always so. An objective measure need not be accurate and despite the sleek, brushed aluminum case in which it is housed may not reflect with fidelity the real underlying construct it purports to represent. To be convincing, any such measure must be validated against a gold standard. One real-life

example that was not thus validated was a device for measuring fine textural change of facial skin introduced a few years ago. With much fanfare, eager acolytes predicted that this would be the optimal way to quantify the minor but definite degree of skin smoothening induced by some topical cosmeceuticals. In fact, it was not clear what the pretty color pictures the device produced were measuring and if these computed images accurately showed smoothness. Furthermore, the high levels of precision and sensitivity to change were punitively extreme. Indeed, washing the face, sweating a little, or just running a hand over the cheek in a sigh would completely change the character of the output.

Instances When Subjective Outcomes Measures Are Preferred

Even when objective measures are not intrinsically flawed, they may not be the most appropriate outcomes to include. In some cases, subjective outcomes and measures may be said to be philosophically superior and better able to measure what is observed. The clearest case is when grading the aesthetic appearance of facial skin. Since patients receive treatment to reduce facial acne scars or diminish the visible signs of aging in order to look better to themselves, family, friends, and colleagues, the best way to measure the success of such procedures is through visual examination by a perceptive human observer. If the patient looks improved to several such observers, then this is sufficient. Even if a highly accurate and precise electron microscope could detect numerous residual flaws, this is not interesting to the patient, whose friends cannot resolve such tiny features.

The Utility of Complex Outcome Measures

Another consideration is the complexity associated with a particular outcome measure. Some validated scales are extremely complex, with many parts and subparts, and may also require time-consuming internal computations. Study participants and data collectors may become exhausted during the measurement process. Unless the quality of these outcome measures is far superior to that of simpler measures, the more complex measures may be more resource intensive than they are worth.

Core Outcome Sets: What They Are and Why They Are Important [4–10]

In recent years, it has become apparent that heterogeneity in outcomes and outcome measures for studies of the same disease or condition lead to research waste. Since the combined results of many similar studies, or meta-analyses, are believed to be more reliable than the results of any single study, it is unfortunate when such studies report different outcomes, and thereby preclude pooling of their data. The leadership of the Cochrane Collaboration has expressed concern that this problem undermines the usefulness of Cochrane systematic reviews, which may defer specific conclusions and instead plead "insufficient evidence." The solution appears to be development of so-called core outcome sets or minimal groups of outcomes that are intended for use in all studies pertaining to a particular disease or condition. Individual investigators can use more than the core set of outcomes, ideally adding the core set to whatever other outcomes they wish to consider.

Core Outcome Sets: How They Are Developed and by Whom

The development of core outcome sets is a laborious process based on literature review and stakeholder consensus. A long list of outcomes is first produced from a literature search and data extraction. Then this is subjected to refinement and lumping by a steering committee. Several rounds of Delphi process are then used to identify the most important outcomes and those with the greatest degree of consensus. Stakeholders involved in the process may include physicians,

other health-care workers, patients, caregivers, support group representatives, researchers, industry representatives, regulators, methodologists, and others. Since the goal is to produce a set of outcomes that are of universal utility, stakeholders are drawn from many countries and diverse environments. The output of the Delphi process is subject to further refinement and lumping. A face-to-face consensus meeting is then convened to approve a small group of outcomes for the core set. Subsequent similar processes, including Delphi consensus, may be used to identify the best outcome measure for each outcome in the core set. The lead international consortium championing core outcome sets and advancing research methodology for developing these is COMET (Core Outcome Measures in Effectiveness Trials), based in the UK and in existence since 2010 [11]. COMET hosts meetings and also maintains a database of core outcome sets in development. CSG-COUSIN [12], based in Germany, is the core outcome set initiative of the Cochrane Skin Group and focuses on outcome measures relevant to dermatology. The IMPROVED (Measurement of Priority Outcome Variables in Dermatologic Surgery) group [13], based in the USA, is taking the lead in development of core outcome sets relevant to dermatologic surgery [5–7].

Patient-Reported Outcomes

Another new trend in outcome selection is the frequent inclusion of at least one patient-reported outcome in clinical trials. Investigators, government regulators and scientists, and private payers have conceded the obsolescence of the paternalistic model in which only physicians decide what should be measured and what is important for patients. It has become clear that patients' estimation of procedure effectiveness, safety, comfort, downtime, cost, overall satisfaction, and other parameters may differ from that of physicians. As those experiencing treatments, patients are obviously uniquely qualified to assess their impact. In fact, sometimes, patients may notice procedure-related effects that physicians have not even thought to measure. Validated, well-designed patient-reported outcome measures now exist for skin cancer treatment as well as facial rejuvenation.

Selecting a Suite of Outcomes

As explained in the preceding paragraph, selection of appropriate outcomes for a clinical study is a complex process. However, selection of outcomes need not be an either/or process. Outcome selection can be inclusive, with several outcomes all measured in a single study. An investigator may start with a condition-specific core outcome set, which may include some objective measures, and perhaps also a validated independent rater questionnaire or photographic assessment, as well as a patient-reported outcome measure. To this, the investigator may add one or more other outcome measures that he or she deems inadequately covered by the core set and specifically relevant to the particular clinical trial at hand.

When to Measure Outcomes

Once outcomes are selected, it must be decided when to measure them. A clinical trial in dermatologic surgery may have several treatment visits followed by several follow-ups. Some outcomes, such as standardized photographs, may be obtained at every visit, and others, like patient-reported satisfaction, may only be elicited a few times, perhaps just at the last visit. Measuring outcomes more often can be helpful in providing a clearer understanding of the impact of an intervention, including the length of post-procedure recovery time, time to maximum benefit, and the duration of persistence of benefit. But many measurements can also fatigue patients and data collectors, resulting in more patient dropouts, excess resource utilization within the research team, and possibly less accurate data. For many aesthetic studies, the most convincing results are long-term outcomes, after edema and erythema have resolved. On the other hand, asking patients to come back more than 6–12 months after treatment is unlikely to be fruitful. Keep in mind that adding two more follow-up visits to a study involving 50

patients means at least another 100 h of data collection, and possibly much more, if patients cancel and need to be rescheduled. Data collection in clinical trials is also often not contiguous, as patients come when they can and when they wish to, so 100 h of data collection may in fact be spread over many weeks, with some wasted time between visits.

Preplanning Outcomes

Outcome selection should occur before enrollment in a clinical trial commences. The methods section of the study protocol and IRB protocol should detail the outcomes that have been chosen, and when they are to be measured, as well as how and by whom. While multiple outcomes and outcome measures might be included, the total number should be judicious. Assessing very many outcomes is not only resource intensive but also increases the risk that at least one of these outcomes shows a difference by chance alone. The 5% significance level is reasonably protective if only one or a few comparisons are performed, but if numerous outcomes are assessed, the likelihood of a false positive arises.

Reporting of Outcomes

The results section of the report of a clinical trial, cohort study, or other clinical studies should present all of the outcomes that were mentioned in the methods section. If these are too numerous or cumbersome to discuss in the text, they may be displayed in tables or figures. Although some outcomes may be relatively more interesting or supportive of the experimental hypothesis, selective results reporting must be avoided, as it can bias the results.

Closing Thoughts

Determining the appropriate outcomes and outcome measures for a study is of primary importance. Haphazard outcome selection can result in research waste, as the data may not be useful or interpretable. There are different types of outcome measures, and a suite of such, including patient-reported outcomes, may be used for a particular study. Inclusion of a core outcome set, if available, can help aggregate the results of a given study with those of other studies of the same disease, condition, or intervention. Outcomes should be measured as often as needed, but not so often as to unnecessarily deplete resources. Reporting of preplanned outcomes should be complete, so that readers can draw their own conclusions.

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Level of Evidence and Strength of Recommendation

3

Murad Alam

Abstract

The purpose of this book is to convey the evidence (Guyatt et al, JAMA 274(22): 1800–1804, 1995; Guyatt et al, JAMA 284(10): 1290–1296, 2000) in support of procedural dermatology therapies for specific indications. After sifting the data, chapter authors provide their assessment in words and numerical ratings. Specifically, findings based on evidence are accompanied by the level of this evidence in parentheses immediately following. At the conclusion of each chapter, a table is provided that lists findings and recommendations, with numbers to represent the associated levels of evidence and strengths of recommendation.

Keywords

Evidence · Strength · Users · Medicine · Level Dermatology

The purpose of this book is to convey the evidence [1, 2] in support of procedural dermatology therapies for specific indications. After sifting the data, chapter authors provide their assessment in words and numerical ratings. Specifically, findings based on evidence are accompanied by the level of this evidence in parentheses immediately following. At the conclusion of each chapter, a table is provided that lists findings and recommendations, with numbers to represent the associated levels of evidence and strengths of recommendation.

Level of Evidence

Level of evidence is a hierarchical measure. At the top are meta-analyses of randomized control trials (RCTs) and individual RCTs, and expert opinion is far lower in the order. The hierarchy is not intended to denigrate the importance of findings supported by lower levels of evidence. Instead, the purpose of the hierarchy is to show the limits of the data. In some situations, RCTs may be impractical and lower levels of evidence may be all that is achievable or at least sufficient to justify therapeutic decisions.

Since the popularization of measures of level of evidence, many specific formulations have emerged [1–3]. Largely similar, these differ mostly in detail and nuance. We have chosen to use the 2009 Oxford scheme [4], shown below. We feel this is intuitive and easy to use, while also being sufficiently granular in its discriminations (Table 3.1).

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Table 3.1 Evaluating level of evidence for individual studies: Oxford Centre for evidence-based medicine 2009 levels of evidence

Level	Therapy/ prevention, etiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1 economic studies
1b	Individual RCT (with narrow confidence Interval)	Individual inception cohort study with >80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards or CDR tested within one clinical center	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none	All or none case series	Absolute SpPins and SnNouts	All or none case series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of Level > 2 economic studies
2b	Individual cohort study (including low-quality RCT, e.g., < 80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split sample or databases	Retrospective cohort study or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" research, ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual case-control study		Non-consecutive study or without consistently applied reference standards	Non-consecutive cohort study or very limited population	Analysis based on limited alternatives or costs and poor-quality estimates of data but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor-quality cohort and case-control studies)	Case series (and poor-quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis

Table 3.1 (continued)

Level	Therapy/ prevention, etiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, and Martin Dawes since November 1998. Updated by Jeremy Howick in March 2009
SR systematic review, *RCT* randomized clinical trial, *CDR* clinical decision rule, i.e. an algorithm or scoring system that leads to a prognostic estimation or a diagnostic category, *SpPin* a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis, *SnNout* a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis

Strength of Recommendation

Level of evidence attaches to any specific finding, which may or may not be prescriptive. Some findings, however, are not merely observations and may naturally lead to clinical recommendations. For such findings, it is helpful to assess how strongly the evidence supports the recommendation. Strength of recommendation is thus a way to practically interpret clinically relevant findings. We have selected the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme [5], below, for rating the strength of each recommendation proposed by our authors. We feel this system aligns well with our level of evidence ratings, is simple, and also takes into account the expected value of future research (Table 3.2).

Table 3.2 Assigning quality of evidence for each recommendation: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect Several high-quality studies with consistent results In special cases: one large, high-quality multi-center trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate One high-quality study Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain Expert opinion No direct research evidence One or more studies with very severe limitations

Source: GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team). Reprinted with permission from Essential Evidence Plus

Patient-Specific Factors and Clinical Decision-Making

Level of evidence and strength of recommendation are not the only factors that determine whether or not a therapy is appropriate for a patient. If there is high-level evidence that a treatment works, we still need to understand how much benefit can be expected [1]. In some cases, the degree of benefit may be very small and the associated costs may be

large, and so the treatment may fail to be widely adopted. The circumstances of the clinical problem, and the particular patient, may further impact whether the treatment is appropriate. The complexity of individual treatment decisions is beyond the scope of a rating scheme.

Additional Readings

There are many excellent sources on the methodology of evidence-based medicine. The journal *JAMA*, under the guidance of Guyatt and colleagues, has published a series of articles to educate the reader. Many of these have been compiled into a single-volume user's guide [6]. Dermatologists will also benefit from Hywel Williams' Evidence-Based Dermatology, now in its third edition [7]. This includes a part entitled "The Critical Appraisal Toolbox," edited by Michael Bigby, which is readable, succinct, and authoritative.

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Mohs Surgery

4

Arif Aslam and Sumaira Z. Aasi

Abstract

In the early 1940s, Dr. Frederic Mohs first published a technique for the removal of skin cancers utilizing in vivo tissue fixation by the application of a zinc chloride paste directly to the skin, followed by excision and specimen mounting for histologic evaluation the next day. The procedure was based on the principles that cutaneous malignancies grow in a contiguous manner from a central origin and complete removal is necessary and sufficient for local tumor control. Since that time, the practice of Mohs micrographic surgery (MMS) has evolved into the fresh tissue technique with frozen sections. This procedure omits fixation of the tissue in situ prior to excision and rapidly processes the tissue after excision using an embedding medium and a cryostat to freeze and section the specimen prior to histologic staining. MMS is divided into two phases: surgery and pathology.

Keywords

Basal cell carcinoma · Squamous cell carcinoma · Mohs micrographic surgery · Frozen sections · Frederic E Mohs · Orientation · Mapping

Introduction

In the early 1940s, Dr. Frederic Mohs first published a technique for the removal of skin cancers utilizing in vivo tissue fixation by the application of a zinc chloride paste directly to the skin, followed by excision and specimen mounting for histologic evaluation the next day. The procedure was based on the principles that cutaneous malignancies grow in a contiguous manner from a central origin and complete removal is necessary and sufficient for local tumor control. Since that time, the practice of Mohs micrographic surgery (MMS) has evolved into the fresh tissue technique with frozen sections. This procedure omits fixation of the tissue in situ prior to excision and rapidly processes the tissue after excision using an embedding medium and a cryostat to freeze and section the specimen prior to histologic staining. MMS is divided into two phases: surgery and pathology.

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Indications for Mohs Surgery

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN), a global alliance of cancer specialists, maintains that the goal of primary treatment of skin cancer is cure along with maximal maintenance of function and cosmetic outcome. MMS is indicated for low-risk basal cell carcinoma (BCC) after positive margins are found on excision with postoperative margin assessment and for all high-risk BCCs in those suitable for surgery. Similarly, for low-risk squamous cell carcinoma (SCC), MMS is indicated if margins are positive after excision, but another option is excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with permanent or frozen sections (2b) [1, 2].

High-risk cutaneous SCCs are those tumors which exhibit clinical or histological features that have been associated with increased risk for aggressive tumor behavior. However, there is no consensus on which features define high-risk cutaneous SCC. The following risk factors which may be the most significant drivers of poor outcomes in SCC include clinical tumor diameter 2 cm or greater, depth of invasion >6 mm or beyond the subcutaneous fat, poor differentiation, perineural invasion, location on the ear, and immunosuppression (2a) [3–5].

AAD/ACMS/ASDSA/ASMS 2012 Appropriate Use Criteria for Mohs Micrographic Surgery: A Report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery

Historically, determining which skin cancers are appropriate for MMS has been challenging, given the lack of consensus on the treatment guidelines for the use of MMS. However, this need was addressed in September 2012, when appropriate use criteria (AUC) for MMS were released by a collaboration of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Mohs Surgery, and American Society for Dermatologic Surgery. It evaluated 270 scenarios for which MMS is frequently considered and specified criteria for appropriate use based on available published data, clinical practice experience, and expert judgment (5) [6, 7]. The criteria incorporate a number of factors including location (high-, medium-, or low-risk sites), cancer subtype, size, recurrence, and immunocompromised status (Fig. 4.1).

Effectiveness of Mohs Surgery

Basal Cell Carcinoma and Squamous Cell Carcinoma

A randomized controlled trial of 612 facial BCCs treated with either MMS or standard excision (SE) was the first of its kind to demonstrate the advantage of MMS surgery in avoiding large defects and obtaining better cosmetic outcomes for primary aggressive and all recurrent facial BCCs (1b) [8]. The same group reported their 5-year follow-up data to show that MMS is preferred over surgical excision for the treatment of facial recurrent BCC, on the basis of significantly fewer recurrences after MMS than after surgical excision. However, they concluded that because there was no significant difference in recurrence of primary BCC between treatment groups, treatment with surgical excision is probably sufficient in most cases of primary BCC [9]. Their 10-year data showed fewer recurrences occurred after treatment of high-risk facial BCC with MMS compared to treatment with SE. The proportion of recurrences occurring more than 5 years post-treatment was especially high for primary BCCs, stressing the need for long-term follow-up in patients with high-risk facial primary BCC [10].

A randomized comparison of MMS and standard excision for small nodular BCCs was the first trial demonstrating MMS as a tissue-sparing

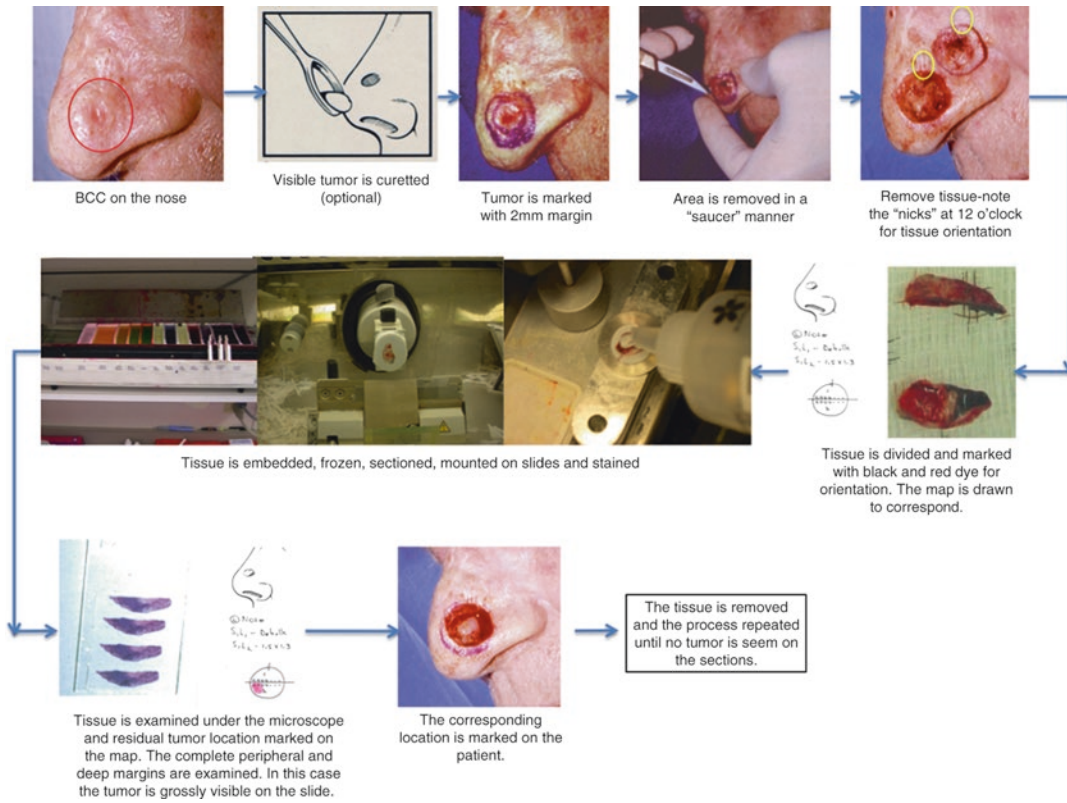

Fig. 4.1 Schematic of Mohs micrographic surgery

treatment, with the median area of the surgical defects in the MMS group being 116.6 mm^2, versus 187.7 mm^2 in the standard surgery group (1b) [11].

A retrospective European study that reviewed 350 cases of head and neck primary and recurrent BCCs treated with MMS with a median follow-up period of 7 years found 3.4% for primary BCC and 4.9% for recurrent BCC; these were similar to the recurrence rates reported in the literature (4) [12].

Although there are no randomized controlled trials comparing MMS and conventional surgery for the treatment of SCC, there is significant evidence supporting its efficacy.

A systematic review of observational studies which assessed outcomes from MMS in a total of 1572 patients with cutaneous SCC found a pooled average local recurrence rate of 3.0% (2a) [13].

In a retrospective study in which 215 patients with 260 high-risk tumors (defined as a site on the ear or lip, or temple in elderly men; size >2 cm; rapid growth >1 cm; perineural involvement; or occurring in the setting of immunosuppression) were treated with MMS, the recurrence rate after almost 4 years was only 1% (2b) [14].

An Australian case series that included 381 patients with primary (n = 229) or recurrent (n = 152) cutaneous SCC followed up for 5 years after MMS found recurrence rates of 3% and 6%, respectively (4) [15].

Melanoma In Situ (MIS) and Melanoma

A long-term outcome study of 882 cases of melanoma in situ (MIS) on the trunk and proximal extremities treated with MMS showed 83% were treated with a 6 mm margin and margins of 9 mm were required to excise 97% of MIS. Only one recurrence occurred in this cohort (2b) [16].

A retrospective review of 662 patients with MIS treated with either (MMS) or wide local exicision (WLE) found no significant differences in the recurrence rate, overall survival, or melanoma-specific survival of patients with MIS treated with MMS compared with WLE (3b) [17].

A retrospective cohort study that evaluated 2114 melanomas in 1982 patients excised using MMS and MART-1 immunostain showed lower local recurrence rates and equivalent or higher Kaplan-Meier survival rates than conventional wide local excision (3b) [18].

A retrospective chart review of 343 head and neck MIS cases treated with MMS found 65% were cleared with a 5 mm margin, but to achieve a 97% cure rate, 15 mm was necessary. This study confirms that MIS on the head and neck can spread significantly beyond the clinical margin and demonstrates the importance of confirming clearance histologically before closure procedures (4) [19].

A Dutch study of 100 lentigo maligna (LM) after micrographically controlled staged surgical excision found four patients with recurrence after a mean follow-up of 60 months (4) [20].

It is widely accepted that MMS for digital melanoma is digit sparing. A retrospective review of 62 digital melanomas over 35 years, of which 57 (91.9%) were primary and 5 (8.1%) were recurrent on enrollment, was performed. Melanocytic antigen recognized by cytotoxic T lymphocytes (MART-1) from melanoma patients and human melanoma black-45 (HMB-45) immunostains were used in 34 (54.8%) and 14 (22.6%) cases, respectively. Five (8.2%) tumors recurred locally during the course of the study, none of which occurred with MART-1 use. Three (60.0%) local recurrences were salvaged with additional MMS. Local recurrence-free survival rates for primary melanomas at 5 and 10 years were 91.8% and 82.6%, respectively. Overall, 55 (96.5%) patients with primary digital melanomas avoided amputation. Five- and 10-year melanoma-specific survival rates for all patients were 95.0% and 81.2%, respectively (4) [21].

Dermatofibrosarcoma Protuberans

A systematic review of the efficacy of dermatofibrosarcoma protuberans (DFSP) treated with MMS found a weak recommendation is given in favor of MMS or similar surgical techniques with meticulous histologic evaluation of all margins as the first-line therapy for DFSP, particularly in recurrence-prone regions. Attention should be given to longer than a 5-year follow-up period. High-quality trials with sufficient follow-up periods should be encouraged (2a) [22].

A retrospective case series review from the Mayo clinic between 1955 and 2012, the largest study from a single institution comparing MMS and WLE for the treatment of DFSP, showed recurrence-free survival rates were higher for MMS with smaller mean postoperative defect size (3a) [23].

A large series of DFSP treated with MMS found the mean minimum margin of 1.34 cm was required to achieve complete clearance for the 74 tumors analyzed. The mean percentages of skin spared using MMS rather than conventional surgery with 2 and 3 cm margins were 49.4% and 67.9%, respectively, confirming MMS can achieve tumor clearance with smaller margins and greater preservation of healthy tissue than conventional surgery (4) [24].

A retrospective case review of 76 cases of DFSP treated with MMS with a mean follow-up of 50 months found recurrence rate of 1.5%, advocating MMS as the treatment of choice for DFSP in all locations (4) [25].

Other Tumors

Extra-mammary Paget's disease (EMPD) The meta-analysis of three observational studies found the treatment of EMPD with MMS resulted in significantly lower recurrence rates than wide local excision and that the current evidence supports the efficacy of MMS in the treatment of EMPD (2a) [26].

Eccrine porocarcinoma (EPC) A retrospective chart review of nine patients with EPC treated by MMS at the Mayo Clinic from 1995 to 2013 with a mean follow-up of 3.3 years showed no recurrence, metastases, or disease-related mortality (4) [27].

Hidradenocarcinoma (HAC) A retrospective review of ten patients in the largest reported

series from the Mayo Clinic of HAC treated with MMS with long-term follow-up showed no recurrences, with mean MMS stages of 1.5 (4) [28].

Sebaceous carcinoma A retrospective case series review of 37 patients with 45 sebaceous carcinoma treated with MMS in a single center reported no local recurrences, metastases, or disease-specific deaths over an average follow-up period of 3.6 years (4) [29].

Preoperative Evaluation

The most appropriate type of biopsy (shave vs. punch) to ensure accurate diagnosis before MMS is debated [30], along with the consequences of biopsy choice on the MMS procedure [31, 32]. A retrospective review of 873 cases found in 23 of 873 patients, the diagnosis changed following examination of the MMS debulk specimen of which 10 of the 23 patients had a diagnostic biopsy prior to referral for MMS, whereas 13 had no diagnostic biopsy performed (4) [33].

A prospective randomized controlled study of pretreatment with Imiquimod 5% cream before MMS showed it significantly reduced the tumor size in primary nodular BCC and reduced the surgical defect size (1b) [34]. Conversely a randomized double-blind vehicle-controlled study of preoperative Imiquimod 5% cream before MMS for nasal nodular BCCs did not reveal any differences in the number of Mohs stages, defect sizes, or costs between the two groups, but the sample size was small (2b) [35].

Several studies have examined the safety of the novel anticoagulants dabigatran, apixaban, and rivaroxaban during MMS [36, 37]. A retrospective chart analysis of 27 patients taking dabigatran and 4 patients taking rivaroxaban during MMS showed no severe hemorrhagic complications during surgery, supporting the strategy of continuing these important medications (4) [38].

An open-label clinical trial of preoperative Vismodegib for 3 months before Mohs surgery for high-risk BCCs showed when taken for 3 months, it appeared to reduce postoperative surgical defect (4) [39], but the authors question whether this made a significant difference in postoperative repair types or sizes.

Best Techniques and Performance

There are great variations in technique among Mohs surgeons regarding tumor debulking, the removal of layers, and the marking of specimens. The common elements for all Mohs procedures include a clinical delineation of tumor margins, removal of the clinical tumor with 1–3 mm margins with a disc or saucer shape, marking of the tumor bed to allow correlation of the surgical site with the excised specimen, and mapping of the specimen. During mapping, the tissue is cut into appropriate pieces and the edges are dyed with different colored inks to identify individual margins. The colors are coded to the corresponding edges on the tissue map. In the pathology phase of the procedure, the tissue is embedded in an appropriate medium in a manner that places the skin edge and the deep/central portion of the specimen in the same plane. The embedded tissue is frozen and sectioned on a cryostat in 2–6 mm sections. Once sections are mounted, they are stained with either hematoxylin or eosin or toluidine blue (T-blue) based on the tumor type and the preference of the surgeon. The sectioning and staining process takes 15–45 min depending on variables such as tissue size, lab volume, and histotechnician technique. After slide preparation, the surgeon examines the slides for the presence of tumor. With the Mohs procedure, the physician can examine the complete deep and peripheral margins of the tissue for the presence of residual tumor. Positive tumor is marked in the appropriate area on the map that is taken back to the bedside where the surgery phase resumes. Using the shape of the defect, the markings made in the wound edges, and the manner in which these correspond to the customized Mohs map created by the surgeon, the area of residual tumor is delineated along with an appropriate margin(s). The excisional and mapping process is repeated until histologically clear, deep, and peripheral margins are verified. Reconstruction of the surgical defect may follow clearance of the tumor with the

Mohs procedure, or the wound may be allowed to heal by second intention (Fig. 4.1).

Although hematoxylin and eosin (H&E) staining for Mohs frozen sections is universal, the utility of metachromatic staining of Mohs sections with toluidine blue (T-blue) has been established in the literature and by the experience of the Mohs surgeons who use it routinely. Toluidine blue highlights the metachromasia associated with BCC tumor stroma, and although retraction artifact is seen with both stains, the magenta staining of acid mucopolysaccharides (MPS) at the periphery of tumor lobules is characteristic of BCC and provides a strong visual clue to the possible presence of tumor [40]. The additional value provided by T-blue lies in its ability to highlight more subtle cords and nests associated with infiltrative neoplasms such as infiltrative BCC, infiltrative SCC, and microcystic adnexal carcinoma [41]. In these tumors, the stromal change can enhance the identification of sparse clusters or cords of cells.

A comparison study of microphthalmia transcription factor (MITF) and melan-A immunohistochemistry during MMS for LM-type MIS and LMM found that although both MITF and melan-A facilitate the identification of tumor during MMS for MMIS and LMM, the apparent melanocyte density on tumor-free chronically sun-damaged skin appears higher with melan-A, but MITF provides a crisp outline of melanocyte nuclei and is a useful alternative stain to melan-A for MMS of melanoma (5) [42].

A prospective cohort study which examined predictors of patient satisfaction with Mohs surgery found higher short- and long-term satisfaction with Mohs surgery is predicted by better preoperative skin-related quality of life and by more intraoperative Mohs stages. The effect of postoperative variables wanes over time, suggesting that factors influencing satisfaction can vary depending on the time frame when satisfaction is measured (2b) [43].

A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and reconstruction found the combination of acetaminophen and ibuprofen is superior to acetaminophen alone or acetaminophen and codeine in controlling postoperative pain after MMS and cutaneous reconstruction (2b) [44].

A randomized prospective study on the use of oral midazolam for perioperative anxiolysis during MMS found it is safe and efficacious in perioperative anxiolysis for healthy patients undergoing outpatient MMS and it offers the benefits of amnesia, reduced alertness, and reduced blood pressure with no clinically significant adverse effects (2b) [45].

A cross-sectional study of practice patterns of early and mid-career surgeons found similarities to remove tumors with similar numbers of stages regardless of their experience, case volume, or geographic location, with the number of stages varying with anatomic location and tumor type (2c) [46].

Safety

MMS is safe, with a very low rate of adverse events, an exceedingly low rate of serious adverse events, and an undetectable mortality rate. Common complications include infections, followed by impaired wound healing and bleeding.

A multicenter prospective cohort study of 23 centers for MMS sought to evaluate intraoperative and postoperative minor and serious adverse events. Among 20,821 MMS procedures, 149 adverse events (0.72%), including 4 serious events (0.02%), and no deaths were reported. The common adverse events reported were infections (61.1%), dehiscence and partial or full necrosis (20.1%), and bleeding and hematoma (15.4%). Most bleeding and wound-healing complications occurred in patients receiving anticoagulation therapy. Use of some antiseptics and antibiotics and sterile gloves during MMS were associated with modest reduction of risk for adverse events. Bleeding and wound-healing issues are often associated with preexisting anticoagulation therapy, which is nonetheless managed safely during MMS. The authors were not certain whether the small effects seen with the use of sterile gloves and antiseptics and antibiotics are clinically significant and whether wide-scale practice changes would be cost-effective given the small risk reductions (2b) [47].

A randomized controlled trial of oral antibiotics versus topical decolonization to prevent surgical site infections (SSI) after MMS showed that in patients with demonstrable carriage of *S. aureus*, topical decolonization resulted in fewer SSI than in patients receiving perioperative oral antibiotics and recommended that antibiotics should be reserved for clinically suspected and swab-proven infections rather than being prescribed empirically (2b) [48].

A multicenter prospective cohort study evaluating the rate of major and minor complications as well as postoperative pain associated with the treatment of skin cancer using Mohs surgery in 1550 patients with 1792 tumors found no major complications occurred during Mohs surgery or reconstruction. A total of 44 (2.6%) minor primary postoperative complications occurred during the study (2b) [49].

A prospective study to evaluate the rate of wound infections in 338 patients undergoing MMS using a single set of instruments found an overall infection rate of 2.1% (7/332). Graft closures had an SSI rate of 3.1% (2/64), and flap closures had an SSI rate of 1.9% (5/268), suggesting savings without harming patients and maintenance of SSI rates within an acceptable range (2c) [50].

Comparison of the prevalence of surgical site infections with the use of sterile gloves (SG) and nonsterile gloves (NSG) during resection and reconstruction during Mohs surgery found the prevalence of infection was 0.50% in the SG group and 0.49% in the NSG group with 3.5 times cost savings (3b) [51].

The findings from a prospective study from nine centers by the UK Mohs and patient safety collaboration group concluded that patients tolerate tumor extirpation and subsequent reconstruction under local anesthesia well, with high levels of patient satisfaction (4) [52].

A prospective study evaluating pain during MMS found postoperative pain after MMS was associated with only mild to moderate pain on the day of surgery and the first postoperative day. Most pain was effectively managed using oral acetaminophen, with a minority of patients requiring prescription analgesics. Surgery on the scalp was significantly more painful than on other sites. Patients can be reassured that MMS and reconstruction are well-tolerated and associated with only mild to moderate discomfort postoperatively (4) [53].

A retrospective study of 214 patients over the age of 90 revealed no deaths within 1 month and median survival of 36.9 months post MMS, concluding this growing section of the population may safely undergo MMS (4) [54].

A prospective study of wound infections in MMS using clean surgical technique in the absence of prophylactic antibiotics found an exceedingly low rate of 0.91% SSIs, underscoring the overall safety of MMS and its performance in the outpatient setting without the use of antibiotic prophylaxis or sterile technique (4) [55].

A recent comprehensive evidence-based review addressing practice gaps in cutaneous surgery sought to address the following key areas: cost effectiveness, anticoagulation, local anesthetic and its administration, patient anxiety, postoperative pain, and topical agents after surgery (4) [56]. It demonstrated that large surgical resections can be done effectively and safely; medically necessary anticoagulant and/or antiplatelet medication should be continued during cutaneous surgery; music and anxiolytic medications are safe and effective ways to prevent patient anxiety; and postoperative opioids and topical antibiotics cause harm to patients and should be avoided.

Postoperative Care and Follow-Up

Patients with a history of NMSC often develop new keratinocyte tumors (KC), but information is limited on the frequency and timing of these subsequent tumors, yet this information is crucial to guide follow-up care. A systematic review and meta-analysis of the risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma found that for BCC patients, the pooled proportion for a subsequent BCC, SCC, or melanoma was, respectively, 29.2%, 4.3%, and 0.5%, and the pooled proportion of a subsequent SCC, BCC, or melanoma in SCC patients was, respectively, 13.3%, 15.9%, and 0.5% (1a) [57]. For

those with a prior melanoma, pooled proportions for a subsequent melanoma, BCC, or SCC were, respectively, 3.8%, 2.8%, and 1.0% (1a) [58].

Alternative Procedures and Modifications

There are no systematic reviews on the effectiveness of MMS in the treatment of NMSC compared with other treatment modalities. A previous systematic review to compare the effectiveness, cost, and complications of MMS and surgical excision in the treatment of periorbital BCCs yielded no reliable conclusions as no studies were found to meet the review's inclusion criteria (2a) [59].

A prospective cohort study of 1174 patients with 1488 tumors of which 24.3% ($n = 361$) were treated with destruction with electrodessication/curettage, 38.3% ($n = 571$) with excision, and 37.4% ($n = 556$) with histologically guided serial excision (Mohs surgery) found the unadjusted recurrence rates did not differ after treatments, 4.9% after destruction, 3.5% after excision, and 2.1% after Mohs surgery, and no difference was seen after adjustment for risk factors. In tumors treated only with excision or Mohs surgery, the hazard of recurrence was not significantly different, even after adjustment for propensity for treatment with Mohs surgery. This data indicates that common treatments for NMSCs were at least 95% effective, and further studies are needed to guide therapeutic choices for different clinical subgroups (2b) [60].

An observational prospective cohort study sought to compare recurrence rates after different treatments in those judged appropriate for MMS found recurrence was less common after MMS than after other treatments, but the absolute difference in recurrence rates was small (3b) [61].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of Evidence
Indications for Mohs surgery	
All high-risk BCCs	B
Recurrent or incompletely excised low-risk BCCs	B
High-risk cutaneous SCCs are those tumors which exhibit clinical or histological features that have been associated with increased risk for aggressive tumor behavior	B
Is the treatment of choice for periorbital BCCs	B
Effectiveness of Mohs surgery	
Creates smaller defects with better cosmetic outcomes for primary aggressive and all recurrent facial BCCs	A
Is tissue sparing for small nodular BCCs	A
Is associated with a lower recurrence rate for cutaneous SCCs especially those that are high risk	B
Mohs for melanoma using MART-1 immunostaining showed lower local recurrence rates than conventional wide local excision	C
Is the treatment of choice for DFSP	D
Is associated with lower recurrence rates for extra-mammary Paget's disease, eccrine porocarcinoma, hidradenocarcinoma, and sebaceous carcinoma	D
Appropriate preoperative evaluation before Mohs surgery	
Imiquimod before Mohs surgery does not affect the outcome	D
Novel anticoagulant use during Mohs surgery is not associated with severe hemorrhagic complications	D
Safety of Mohs surgery	
Is a safe outpatient-based procedure very rarely associated with severe adverse events or major complications	D

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Self-Assessment Questions

1. MMS is recommended for all of the following tumors except
   (a) Radio recurrent basal cell carcinoma on the cheek
   (b) Squamous cell carcinoma of the nose in an organ transplant recipient
   (c) Well-defined nodular basal cell carcinoma on the forearm
   (d) Infiltrative basal cell carcinoma in the post auricular groove
2. MMS for high-risk facial basal cell carcinomas is associated with all of the following except
   (a) Smaller postoperative defects
   (b) Lower risk of postoperative infection
   (c) Better cosmetic outcomes
   (d) Lower risk of recurrence
3. The reported average local recurrence rate for cutaneous squamous cell carcinoma treated with MMS is
   (a) Less than 1%
   (b) Less than 5%
   (c) Between 5% and10%
   (d) Between 10% and 15%
4. The reported recurrence rates after MMS for dermatofibrosarcoma protuberans are
   (a) Less than 2%
   (b) Less than 0.5%
   (c) More than 10%
   (d) Between 5% and 10%
5. Which of the following stains is most commonly used for MMS of melanoma?
   (a) S100
   (b) Mel-5
   (c) MART-1
   (d) HMB-45

Correct Answers

1. c: All the above are indications for MMS except (c). For a primary nodular well-defined BCC measuring less than 1 cm in a healthy adult, excision with a predetermined margin should be considered as the initial management of choice**.**
2. b: All of the above are true except (b). While MMS is a safe, well-tolerated outpatient-based procedure with few risks, there is no evidence supporting the statement it is associated with a lower risk of postoperative infection versus conventional surgery.
3. b: There is significant data to support the statement (b). Several large observational and retrospective studies with up to 5 years of follow-up data report the recurrence rate for primary cutaneous SCC to be less than 5%.
4. a: The largest retrospective case review to date, of 76 patients with DFSP treated with MMS and a mean follow-up of 50 months, found recurrence rate of 1.5% advocating MMS as the treatment of choice for DFSP in all locations. There are no randomized controlled trials comparing Mohs surgery versus conventional surgery, but the evidence for it is robust.
5. c: Several stains have been used to identify melanocytes when evaluating melanoma with MMS, including S-100, human melanoma black-45 (HMB-45), Mel-5, and MART-1 (melanoma antigen recognized by T-cell 1 staining) also known as melan-A.

There are many studies supporting MART-1 as an effective and useful immunostain in the identification of residual tumor in Mohs margins, demonstrating superior sensitivity and specificity compared to other immunostains. Melan-A or MART-1 staining is the most effective single stain used in the evaluation of melanomas with epidermal and dermal components excluding desmoplastic and spindle cell melanoma types.

Advancement Flaps

5

Michael C. Cameron and Mariah R. Brown

Abstract

Local tissue flaps are single-stage procedures that take advantage of adjacent tissue reservoirs for tissue replacement in order to reconstruct cutaneous surgery defects. In dermatologic surgery, local flaps are commonly performed after removal of benign or malignant skin lesions, particularly surgical defects created by Mohs micrographic surgery to treat skin cancer. Other indications include scar revision, correction of congenital abnormalities, and reconstruction after trauma. Advancement flaps are local flaps that utilize the linear movement of incised tissue in a single direction for closure of a tissue defect. Advancement flaps can be used to close a variety of defects in different anatomic sites but are most commonly used in dermatologic surgery for surgical defects on the head and neck. This chapter will review the existing evidence for various advancement flaps and its various for different indications in the field of procedural dermatology.

Keywords

Advancement flaps · Procedural dermatology
Skin cancer · Reconstruction

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Introduction and Indications for Advancement Flaps

Dermatologic surgeons commonly use tissue flaps to reconstruct cutaneous surgical defects that require more complex repairs. Flap closures are divided into local tissue flaps, interpolated or pedicled flaps, and microvascular free tissue transfer. Local tissue flaps are single-stage procedures that take advantage of adjacent tissue reservoirs for tissue replacement. The purpose of a local tissue flap is to achieve a greater degree of tissue movement or to provide a more favorable cosmetic and/or functional outcome than can be achieved by primary closure alone.

Tissue flaps have deep historical roots, but they rose to prominence in the first half of the twentieth century as physicians sought to repair the facial injuries caused by the First and Second World Wars (5) [1]. Advancements in anesthesia, antiseptics, and surgical technique since this time have made local tissue flaps increasingly safe and straightforward to execute. Local tissue flaps are performed by a variety of surgical specialties, including plastic surgery, otolaryngology, ophthalmology, and general surgery. In dermatologic surgery, local flaps are commonly performed after removal of benign or malignant skin lesions, particularly surgical defects created by Mohs micrographic surgery to treat skin cancer. Other indications for local tissue flaps include scar revision, correction of congenital abnormalities, and

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reconstruction after trauma. Dermatologists perform the majority of local tissue flaps in the United States (1b) [2]. Dermatologic surgeons almost exclusively perform these flaps under local anesthesia, and data indicates a low rate of complications (1b) [3].

One of the local tissue flaps frequently used in cutaneous reconstruction is the advancement flap and its variants. Advancement flaps utilize the linear movement of incised tissue in a single direction for closure of a tissue defect. In practical execution, many advancement flaps also have some component of rotation. The tissue movement of an advancement flap is generated by multiple factors, including movement of the flap toward the defect (primary movement), stretching of the flap skin itself, movement of the defect skin toward the flap (secondary movement), and reduced flap travel distance created by the excision of standing cones (Burow's triangles) or by the excision of a crescent. Advancement flaps can be used to close a variety of defects in different anatomic sites, but are most commonly used in dermatologic surgery for surgical defects on the head and neck.

Effectiveness of Advancement Flaps

Advancement flaps can provide tissue replacement for surgical defects and place incision lines in more favorable locations. However, because of their linear movement, advancement flaps cannot redirect tension vectors. As a local tissue flap, advancement flaps have the advantage of recruiting skin tissue of similar texture, thickness, and color. There will be variability in the final outcome of an advancement flap based on the anatomic location and size of the surgical defect, patient factors, and individual surgical technique. The ideal advancement flap will provide optimal functional and cosmetic outcomes at the surgical site, without compromising function or cosmesis at the flap donor site. The majority of evidence regarding advancement flap reconstruction exists in retrospective or case series format without comparison groups (Oxford Centre for Evidence-Based Medicine 2009 Level 4).

Preoperative Evaluation

Preoperative evaluation should include a thorough past medical history and a list of current medications. There are no standard lab or imaging tests required for preoperative evaluation of patients undergoing advancement flaps. As with other invasive dermatologic procedures, labwork may be necessary in certain patient populations to rule out clotting abnormalities, thrombocytopenia, and kidney or liver dysfunction that may worsen intraoperative bleeding. While there are no consensus on critical values, many dermatologic surgeons consider a platelet level below 50,000 platelets/mm^3 and an International Normalized Ratio (INR) level of greater than 3.5 within 1 week of surgery to be relative contraindications to dermatologic surgery (5) [4]. Current literature recommends continuing therapeutic anticoagulation or antiplatelet agents prior to dermatologic surgery, as the risk of thromboembolic events outweighs the risk of bleeding complications (4) [5]. Flap closure has been shown to be associated with an increased risk of bleeding complications after dermatologic surgery (1b) [6]. As a result, dermatologic surgeons may choose in some cases to avoid flap closures in patients with other bleeding risk factors, such as concomitant use of warfarin and clopidegrel [6].

Best Techniques and Performance

In its purest sense, an advancement flap can be visualized as a primary closure with one or both standing cones displaced to a more favorable anatomic location (Fig. 5.1). However, there

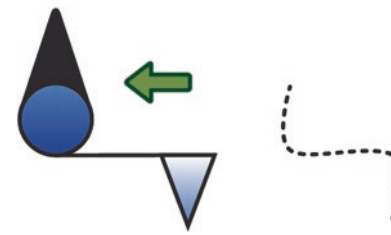

Fig. 5.1 The most basic version of an advancement flap, with linear tissue movement similar to a primary closure and displacement of the standing cones into a more favorable anatomic location. (Diagram by Anne Nichols)

are multiple variations of the advancement flap, including a single rectangular flap (U-plasty), a double rectangular flap (H-plasty), a single triangular flap (O-to-L), and a double triangular flap (O-to-T). Named variants of advancement flaps exist, but all of these variants rely on the same linear geometric principles, with specific modifications dictated by the cosmetic or functional requirements of that anatomic location. A specific type of advancement flap, the V-to-Y advancement flap (previously designated an island pedicle flap), relies on severing the entire cutaneous attachment around the flap and maintaining blood supply through a deep subcutaneous or muscular pedicle. Due to the severing of the entire cutaneous flap attachment, a V-to-Y advancement flap does not typically require the removal of redundant tissue or the extensive undermining of other advancement flaps (Table 5.1).

Advancement Flaps for Reconstruction of the Ear

The use of advancement flaps for surgical defect reconstruction of the ear is limited to case series studies (Table 5.2). *Postauricular cutaneous advancement flaps*, a type of U-plasty advancement flap, have been shown to yield excellent cosmetic results for defects of the helix (4) [7, 8]. The *chondrocutaneous advancement* or *Antia-Buch flap* is another option for reconstruction of helical defects (4) [9] The surgeon has the

Table 5.1 Advancement flap variants

Flap variants	Description
Classic or Burow's advancement flap	Can be visualized as a primary closure with displacement of one or both standing cones Size of standing cones can be varied as needed; standing cone adjacent to defect will most commonly be largest Anatomic variants include: dorsal nasal advancement flap or east-west flap
U-plasty	Rectangular in shape Prone to tip necrosis Standing cone removal reduces the length of flap travel, but can create suboptimal scar lines Variants include: postauricular advancement flap, Rintala flap
H-plasty	Bilateral U-plasty advancement flaps 2 flaps may be sized differently Similar limitations as a U-plasty
O-to-L	Also described as 'A-to-L' or 'L-plasty' Horizontal line is extended along/beyond the base of defect and mobilized on excision of the standing cone at opposing defect edge Large pedicle more favorable to flap survival
O-to-T	Also described as 'A to T' or 'T-plasty' Bilateral O-to-L advancement flaps Often recruits more laxity than a single flap
V-to-Y	Formerly described as an 'island pedicle flap.' This designation is now reserved for V-to-Y flaps that contain a named axial vessel. Random pattern flap with complete incision of cutaneous borders of the flap and maintenance of a vascular pedicle based on the underlying subcutis and/or muscle Minimum of one-third of the flap surface should remain attached to pedicle Reduced need for undermining decreases risk of hematomas/seromas Rarely needs excision of redundant tissue Incision lines often fall outside of cosmetically favorable location
Crescenteric	Variant of an L-plasty Tissue redundancy is removed in crescent shape to increase flap length rather than as a standing cone to decrease the length of the flap recipient side Useful in areas where defects border anatomical regions with a curved border (i.e., nasal ala)
Double O-to-Z	Also described as a 'Burow's triangle flap' Useful for repair of 2 defects of similar size that are in close proximity Two O-to-L flaps, where each defect serves as the Burow's triangle for the other

Table 5.2 Summary of studies of advancement flap for ear surgical defect reconstruction

Reference	Flap variant	Defect location	Sample size	Main findings
Goldberg et al. [7]	Postauricular advancement	Helix	12	Excellent cosmetic results; superficial necrosis in 1 patient
Field [8]	Postauricular advancement	Helix	5	Highly acceptable cosmetic results
Varas-Meis et al. [10] and Fangman et al. [11]	Chondrocutaneous (Antia-Buch)	Helix	2	Excellent aesthetic result with preservation of landmarks/auricle height
Ramsey et al. [12]	Chondrocutaneous (Antia-Buch)	Helix	47	No ischemic necrosis; transient hematomas in 2
Schipper et al. [13]	Modified chondrocutaneous (Antia-Buch)	Helix	1	Good cosmesis; minimal reduction in ear height; preservation of anatomic landmarks
Butler [14]	Modified chondrocutaneous (Antia-Buch)	Helix, scapha, antihelix	2	Minimal alteration of ear contour; slight reduction of vertical height
Zilinsky et al. [15]	Ear-lobe advancement	Helix	13	No complications; cosmesis excellent (76.9%), good (15.4%), fair (7.7%) Axial flap based on cadaver studies
Humphrey et al. [16]	Postauricular V-Y advancement	Helix, scapha, antihelix	2	Excellent cosmetic results
Fader and Johnson [19]	Flip-flop flap	Concha, external auditory canal, antihelix, antitragus	13	Excellent cosmetic results; 11 tumors; two graft donor sites
Patterson et al. [17]	Flip-flop flap	Conchal bowl	41	Cartilage graft donor site two minor postauricular wound dehiscences

option of advancing the superior, inferior, or both helical segments in order to restore helical contour (4) [10–14]. Taking advantage of the increased mobility of a full-thickness helical incision, the *earlobe-based advancement flap* can be used to reconstruct similar helical defects (4) [15]. Based on cadaver studies, this flap is felt to be an axial flap, unlike the majority of advancement flaps [15]. V-to-Y advancement flaps can also be used to reconstruct surgical defects on the ear, in particular as a mechanism to recruit tissue from the postauricular region to repair anterior auricular defects. The *revolving door flap*, also called the *flip-flop flap* or *retroauricular island flap*, can be used to reconstruct the conchal bowl or antihelix of the ear. This flap uses an island of postauricular skin on a subcutaneous pedicle that is then passed through a full-thickness cartilage incision to the anterior ear (4) [16–19]. The flap can also be modified to be tunneled beneath a skin bridge or folded on itself for more versatile applications (4) [20].

Advancement Flaps for Reconstruction of the Nose

The use of advancement flaps for surgical reconstruction of nasal and perinasal defects is similarly limited to case series studies (Table 5.3). Given the risk of free margin distortion, flaps that redirect tissue vectors or use remote tissue donor sites are more commonly used on the nose than advancement flaps.

The *dorsal nasal advancement flap* or *east-west flap* can be used for defects of the nasal supratip off the midline (4) [21–23]. This flap takes advantage of a large superior standing cone along the nasal dorsum or sidewall and a small inferior standing cone along the columella,

Table 5.3 Summary of studies of advancement flap for nasal/perinasal surgical defect reconstruction

Reference	Flap variant	Defect location	Sample size	Main findings
Lambert et al. [21]	Modified dorsal nasal horizontal advancement	Off-midline nasal tip	30	Good to outstanding results; no complications
Love et al. [33]	Columellar advancement	Small, shallow midline nasal tip	2	Excellent cosmesis in all
Zeikus et al. [30]	One-stage simple advancement	Small partial thickness lateral nasal tip or nasal ala	>10	Excellent cosmesis in all; no immediate or long-term nasal valve obstructions or breathing difficulties
Onishi et al. [31]	Rintala and modified Rintala	Middle or distal 1/3 of nasal dorsum	15	Stable blood supply and favorable outcomes with suitable contour in all cases
Rybka [34]	Nasalis-based myocutaneous island	Nasal tip (unilateral for size <1.25 cm, bilateral for size $1.25 < x < 2$ cm)	47	Excellent cosmetic outcomes with no postoperative complications
Constantine [35]	Nasalis-based myocutaneous island	Nasal supratip	24	100% flap survival; excellent cosmetic results
Wee et al. [36]	Nasalis-based myocutaneous island	Nasal tip	19	100% flap survival; no revisions required
Asgari and Odland [41]	Nasalis-based myocutaneous island	Small deep nasal ala	8	Seven of eight with excellent conventional/functional outcome; one with full-thickness vascular necrosis of flap
Willey et al. [38]	Single-sling nasalis myocutaneous island	Nasal tip	61	High aesthetic and functional goals achieved in all patients; complications included hemorrhage ($n = 1$), infection ($n = 2$), and alar notching ($n = 1$)
Krathen et al. [40]	Single-sling nasalis myocutaneous island	Nasal ala	2	Excellent cosmetic results
Husain et al. [24]	Modified perialar crescentic advancement (PACA)	Lower nasal sidewall and mid/lower dorsum	44	Excellent aesthetic/functional results in all cases; six treated with intralesional corticosteroid at postoperative week 3 to improve flap contour.
Borchard et al. [28]	Modified perialar crescentic advancement (PACA)	Lateral nasal sidewall	25	Good cosmetic outcome in all; minor complications restricted to ecchymosis
Zeikus et al. [29]	Dog ear island pedicle	Large nasal ala/sidewall	5	Excellent cosmetic/functional outcomes

but risks nasal tip depression if used for too inferior or too large of a surgical defect. For surgical defects involving perialar skin, the *perialar crescentic advancement flap (PACA)* is a well-established repair option (4) [24–28]. This flap is a variant of an O-to-L advancement that uses a crescent to extend the flap length, rather than removing a Burow's triangle to shorten the donor site length. For defects spanning the alar groove to involve the nasal sidewall and ala, the PACA flap can be modified to use the superior standing cone as a V-to-Y advancement flap to close the alar portion of the defect, referred to as a *dog ear island pedicle flap* (4) [29]. An O-to-L- or O-to-T-type advancement flap has been described for defects of the lateral nasal tip or nasal ala (4) [30], although this flap carries a risk of alar distortion.

For defects of the nasal dorsum, use of the *Rintala* and *Peng* (modified Rintala flap) advancement flaps has been described (4) [31, 32]. The Rintala flap is a superiorly based U-plasty, with the flap pedicle based on the glabella and standing cones removed medially along the alar grooves or at the forehead. The Peng flap adds a component of rotation by removing a central standing cone to create two flap tips that rotate and advance into the defect. Both the Rintala and Peng flap carry the risk of nasal tip elevation. A U-plasty-type flap can also be used to advance tissue superiorly for reconstruction of the nasal tip using a *columellar advancement flap* (4) [33].

V-to-Y advancement flaps, also called *nasalis-based myocutaneous island flaps*, have been used for the reconstruction of nasal defects, most commonly on the nasal tip and supratip (4) [34–36]. This flap is based on the highly vascular nasalis muscle, which can be developed as either a unilateral or bilateral muscular sling to provide flap vascularity (4) [37–39]. The flap limits free margin distortion in studies, but mobilizing the nasalis muscle can be technically difficult. V-to-Y advancement flaps have also been successfully described for alar defects but have some limitations in practice. Superiorly based flaps risk blunting the alar groove (4) [40], while laterally based flaps have more limited tissue mobility and vascularity (4) [41].

Advancement Flaps for Reconstruction of the Perioral Region

Although one randomized controlled trial exists, literature on reconstruction of perioral defects with advancement flaps is primarily limited to case series (Table 5.4). Defects of the upper or lower cutaneous lower lip can commonly be reconstructed with O-to-L advancement flaps (5) [42]. V-to-Y advancement flaps have been described for upper lip defects of varying sizes (IV/C) [43, 44]. Defects that cross the vermillion border can be repaired with double V-Y advancement flaps—one flap for the cutaneous lip and one flap for the mucosal lip (4) [45]. For reconstruction of upper lip defects involving the philtrum, Paniker and Mellette described a modification of the *mucosal advancement flap* (4) [46]. This *Cupid's bow advancement flap* or *gull wing advancement flap* helps recreate the normal anatomy of the philtral crests. Another method for reconstructing the central upper lip involves a V-to-Y flap advanced inferiorly (4) [47].

Table 5.4 Summary of studies of advancement flap for perioral surgical defect reconstruction

Reference	Flap variant	Defect location	Sample size	Main findings
Carvalho et al. [43]	V-Y advancement	Upper lip	25	For aesthetic category, 16 with good and 4 with fair rating
Griffin et al. [44]	V-Y advancement	Upper lip	30	One revision surgery was performed in 14 patients (47%); alar or vermilion involvement, but not defect size, significant factor in revision
Huilgol et al. [45]	V-Y advancement (cutaneous and mucosal)	Upper or lower lip	10	Good or excellent cosmetic outcomes in all; minor hypertrophic scarring in two, small postoperative bleed necessitating takedown of flap
Paniker and Mellette [46]	Modified mucosal	Upper lip involving philtrum	4	Acceptable or very good cosmesis in all cases
Kaufman and Grekin [47]	V-Y advancement involving superior philtrum	Upper lip involving philtrum	4	Excellent cosmetic results with minimal distortion of the vermillion border or obliteration of the philtrum
Sand et al. [48]	RCT of mucosal advancement flap vs. simple primary closure	Lower lip	18	Better patient and surgeon-rated aesthetic outcomes for flap group; side effects rate significantly higher in flap group

For reconstruction of surgical defects of the lower vermilion lip, a *mucosal advancement flap* or primary closure may be used after vermilionectomy. The difference between these two closures is that the mucosal advancement flap uses undermining to increase tissue movement. In a randomized controlled trial comparing primary closure ($n = 8$) to mucosal advancement flap ($n = 10$) for surgical defects of the lower lip, patient-rated mean aesthetic outcome score were 8.4/10 for the advancement flap and 7.5/10 for primary closure (2b) [48]. Surgeon-rated mean aesthetic outcome scores were 7.8/10 and 6.4/10 for advancement flap and primary closure, respectively. However, the rate of side effects, including bruising, swelling, infection, partial flap necrosis, and small wound dehiscence, was significantly higher in the mucosal advancement flap group ($p < 0.05$).

Advancement Flaps for Reconstruction of the Scalp, Forehead, and Brow Region

Reconstruction of surgical defects of the scalp is difficult due to the convexity of the scalp and the inelasticity of the galea aponeurotica, resulting in high-tension defects with a risk of flap necrosis and subsequent alopecia. A limited number of studies have been published detailing the use of advancement flaps for reconstruction of this area (Table 5.5). A *superficial temporal fascia pedicle V-to-Y advancement scalp flap*, supplied by the superficial temporal vessels, has been described as yielding good cosmetic outcomes (4) [49]. Another case series reported no complications using *bilateral H-plasty advancement flaps* for small to medium scalp defects, but had no long term follow-up (4) [50].

Forehead defects can also be difficult to reconstruct due to limited tissue reservoirs, multiple free margins, and prominent relaxed skin tension lines. The *periglabellar advancement flap* has been described to reconstruct central forehead defects by placing standing cones in the superior forehead rhytides and the corrugator creases (4) [51]. Forehead defects can also be closed with *double-opposing rotation-advancement flaps*, in which one flap is designed to close the primary defect and a second flap is designed to close the secondary defect [52]. For surgical defects involving the eyebrow, a variety of closure approaches exist. Gardner et al. described their experiences in using a V-Y advancement flap in

Table 5.5 Summary of studies of advancement flap for scalp/forehead surgical defect reconstruction

Reference	Flap variant	Defect location	Sample size	Main findings
Onishi et al. [49]	Superficial temporal fascia pedicle V-Y advancement	Scalp	7	No complications observed; no baldness seen
Ibrahimi et al. [50]	Bilateral H-plasty advancement	Scalp	69	No long-term follow-up scheduled to evaluate final cosmetic outcome, but no complaints noted during 18 months postoperatively
Ransom and Jacono [52]	Double-opposing rotation-advancement flaps	Forehead	16	Brow position and hairline contour maintained in all cases; one case of cellulitis
Birgfeld and Chang [51]	Bilateral periglabellar Burow's triangle advancement flaps	Central forehead	6	One minor hematoma treated; all scars healed with patients satisfied with results
Boggio et al. [54]	Burow's triangle variant (also called double O-to-Z)	Forehead, mandible (adjacent lesions)	4	Good cosmetic results without postoperative complications
LeVasseur and Mellette [55]	Double O-to-Z	Forehead, temple, cheek, nose, neck	6	Good cosmetic results

reconstruction of medium or large eyebrow surgical defects (4) [53].

Double O-to-Z flaps, also called *Burow's triangle advancement flaps*, have been described for forehead defects but have utility in different anatomic areas, including the temple and cheek (4) [54, 55]. This closure technique is used for two defects of similar sizes that are in close approximation. Each defect is closed with a O-to-L advancement flap, with each defect acting as the Burow's triangle for the other [55].

Advancement Flaps for Reconstruction of the Periorbital and Cheek Region

For reconstruction of cheek-lower eyelid junction defects, a primary concern is ectropion. Table 5.6 reviews studies that reported on periorbital surgical defect reconstructions. The preferred choice for reconstruction in this area has traditionally been a variant of the *cervicofacial rotation-advancement flap* called a *Mustárde flap*, which recruits tissue from laterally. An alternative reconstruction option is a V-to-Y advancement flap recruiting tissue from inferiorly. A retrospective case series compared the Mustárde flap to V-Y advancement flap closure (n = 23) for reconstruction of moderate-size lid-cheek junction surgical defects (2b) [56]. Nine patients (82%) in the cervicofacial group and three patients (18%) in the V-Y advancement group experienced a postoperative complication (p = 0.0002). Three cases of ectropion were observed, including two patients in the cervicofacial group and one in the V-Y advancement group (4%, p = 0.24). V-to-Y advancement flaps have also been applied to medial canthal defects, with the flap donor sites in the medial canthus-glabella area (4) [57] and in the nasal area (4) [58]. A variety of flaps can be used to close cheek defects (5) [42, 59]. In recent years, V-to-Y flaps have been used to close larger cheek defects (4) [60, 61].

Advancement Flaps for Reconstruction of the Extremities

While the majority of the literature on advancement flap reconstruction is devoted to closure of facial defects, advancement flaps can also be used in other anatomic areas. V-to-Y flaps have been described for repair of surgical defects on the leg (4) [62, 63]. For larger defects or to increase flap mobility, fascial perforators can be identified with Doppler ultrasound when performing lower extremity V-to-Y advancement flaps (4) [64, 65]. A variant of the V-Y advancement flap based on fascial perforators, called a *Keystone flap*, can also be used for reconstruction of surgical defects on the extremities (4) [66–69].

Safety

The overall safety and low complication rates of outpatient dermatologic surgery is well established (2b) [3, 70]. There are no studies examin-

Table 5.6 Summary of studies of advancement flap for periorbital surgical defect reconstruction

Reference	Flap variant	Defect location	Sample size	Main findings
Sugg et al. [56]	Cervicofacial rotation-advancement vs. V-Y advancement	Cheek-lower eyelid junction	23	Nine (82%) in cervicofacial group and three (18%) in V-Y advancement group had postoperative complication (p = 0.0002); differences in ectropion development not significant
Skaria [57]	V-Y advancement	Medial canthus	16	Good to excellent results with no cases of web deformation/ectropion at 1-year follow-up
Cecchi et al. [58]	V-Y advancement	Medial canthus	8	Transient trapdoor effect occurred in two patients. No other complications. At mean follow-up of 13 months, very satisfactory functional/cosmetic outcomes in all patients
Gardner and Goldberg [53]	V-Y advancement	Eyebrow	Not reported	Excellent functional and cosmetic results in all patients

ing the complication rates of advancement flaps alone, but they are felt to overall be a safe and reliable reconstructive method. As with all tissue flaps, advancement flaps may develop ischemia and subsequent partial or complete necrosis of the flap. Flap ischemia can be prevented by flap design, undermining depth and suturing technique that minimizes flap tension and maintains an appropriate pedicle width and depth. Other causes of flap ischemia include postoperative complications such as seroma, hematoma, or infection. Care must also be taken when using advancement flaps near free margins to prevent complications such as ectropion or eclabion. Tension vectors should be oriented parallel to free margins to prevent such functional and cosmetic impairment. The dermatologic surgeon should also ideally plan the flap so that final scar lines fall within relaxed skin tension lines, cosmetic subunit borders, or rhytides to yield to most optimal final cosmesis. As with all flaps, advancement flap closure should be avoided if a defect may contain persistent malignancy or infection.

Postoperative Care and Follow-Up

Patients should be discharged after surgery with both verbal and written instructions on how to care for their surgical site. These instructions should include information on the signs and symptoms of complications such as infection, bleeding, and tissue necrosis. Some dermatologic surgeons will see patients back in their clinic for suture removal or assessment of the surgical site within days to weeks after surgery. Longer-term follow-up after advancement flap execution is at the discretion of the individual surgeon.

Alternative Procedures and Modifications

The choice of reconstructive modality will depend on multiple factors, including the size and location of the surgical defect, as well as patient factors, such as skin laxity, comorbidities, and medications. Alternatives to advancement flaps include other local flap procedures, interpolated flaps, and free tissue transfer. Other less complex reconstructive methods include skin grafting and primary closure. In some cases, second intention healing, with or without the aid of skin substitutes, may also be preferred for specific surgical defects.

Observations and Recommendations (Table 5.7)

Table 5.7 Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
The majority of evidence regarding advancement flap reconstruction exists in retrospective or case series format without comparison groups	C
These studies present surgical techniques and anatomic variants of advancement flaps that can greatly benefit reconstructive surgeons	D
The safety and effectiveness of advancement flaps is supported by these studies and a wealth of expert opinions from reconstruction surgeons	C and D

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Self-Assessment Questions

1. An advancement flap cannot:
   (a) Recruit tissue from adjacent tissue reservoirs
   (b) Place incision lines in more cosmetically favorable locations.
   (c) Reorient wound tension
   (d) Avoid encroachment on key anatomic structures
   (e) Prevent distortion of free margins
2. In a randomized controlled trial comparing simple primary closure to mucosal advancement flap for lower lip reconstruction, what did the authors find?
   (a) Higher average patient and surgeon-rated aesthetic outcome scores and significantly lower side effects for flap group
   (b) Higher average patient and surgeon-rated aesthetic outcome scores and significantly higher side effects for flap group
   (c) Lower average patient and surgeon-rated aesthetic outcome scores and significantly lower side effects for flap group
   (d) Lower average patient and surgeon-rated aesthetic outcome scores and significantly higher side effects for flap group
3. V-to-Y advancement flaps require:
   (a) Removal of redundant tissue
   (b) Severing of the entire cutaneous attachment of the flap and maintaining a deep pedicle of subcutis and/or muscle
   (c) Billing as an island pedicle flap
   (d) Extensive undermining
   (e) Reorienting of tension vectors
4. In a retrospective chart review comparing V-Y advancement flaps to the Mustarde variant of the cervicofacial advancement-rotation flap for surgical defects of the cheek-lid junction:
   (a) Both groups had a similar rate of complications.
   (b) Both groups had a similar rate of ectropion.
   (c) The V-to-Y group had a higher rate of ectropion.
   (d) The V-to-Y group had a higher rate of complications.
   (e) The V-to-Y group had better aesthetic outcomes.
5. Advancement flap variants used on the nose include all of the following except:
   (a) Dorsal nasal advancement flap or east-west flap
   (b) Nasalis-based myocutaneous island flap
   (c) Peng flap
   (d) Rintala flap
   (e) Keystone flap

Correct Answers

1. c: Advancement flaps can recruit tissue from adjacent tissue reservoirs, place incision lines in more cosmetically favorable locations, prevent encroachment on key anatomic structures, and prevent the distortion of free margin. However, because an advancement flap only moves tissue in a linear direction, it cannot reorient wound tension vectors.
2. b: A RCT comparing primary closure to a mucosal advancement flap for surgical defects of the lower vermilion lip (after vermilionectomy) found that the mucosal advancement flap has better patient- and surgeon-rated aesthetic scores. However, the primary closure had acceptable aesthetic scores and a lower rate of complications.
3. b: V-to-Y advancement flaps rely on the severing of the entire cutaneous attachment of the flap and maintaining a deep tissue pedicle. V-to-Y flaps do not require the removal of redundant tissue and extensive undermining. They should be billed as an adjacent tissue transfer, rather than an island pedicle flap. Like all advancement flaps, V-to-Y flaps cannot reorient tension vectors.
4. b: This retrospective study found that V-to-Y flaps had a lower rate of complications than the Mustarde variant of the cervicofacial advancement-rotation flap. Both groups had a similar rate of ectropion. No analysis was made of the aesthetic outcome between the two groups.
5. e: All of the above are advancement flaps used for reconstruction on the nose-dorsal nasal advancement flap or east-west flap, nasalis-based myocutaneous island flaps, Peng Flap, and Rintala flap. The Keystone flap is a type of advancement flap based on the fascial perforator used for reconstruction of the extremities.

Transposition Flaps

6

Ian Maher and Ashley McWilliams

Abstract

Transposition flaps facilitate repair of a range of defects in anatomic locations with minimal inherent skin laxity, such as the nose. These flaps have the ability to reorient tension vectors and thus are particularly useful for avoiding distortion of free margins such as the alar rim or eyelid margin. Reservoirs with ample skin laxity are recruited in circumstances where primary closure or a sliding flap is not viable options due to tension at the primary defect. In patients who are at risk for bleeding, transposition flaps are ideal as less undermining is needed compared to sliding flaps. Core principles of successful transposition flap development are elaborated in Fig. 6.1.

Common transposition flaps include:

- Rhombic (single lobed).
- Bilobed.
- Trilobed.
- Nasolabial flaps.

A discussion of the indications, technique, efficacy, and alternatives for each of these transposition flaps will be presented in this chapter.

Keywords

Transposition flap · Rhombic flap · Bilobed flap · Nasolabial flap

Introduction

Transposition flaps facilitate repair of a range of defects in anatomic locations with minimal inherent skin laxity, such as the nose [1, 2]. These flaps have the ability to reorient tension vectors and thus are particularly useful for avoiding distortion of free margins such as the alar rim or eyelid margin. Reservoirs with ample skin laxity are recruited in circumstances where primary closure or a sliding flap is not viable options due to tension at the primary defect [2]. In patients who are at risk for bleeding, transposition flaps are ideal as less undermining is needed compared to sliding flaps. Core principles of successful transposition flap development are elaborated in Fig. 6.1.

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- Rhombic (single lobed).
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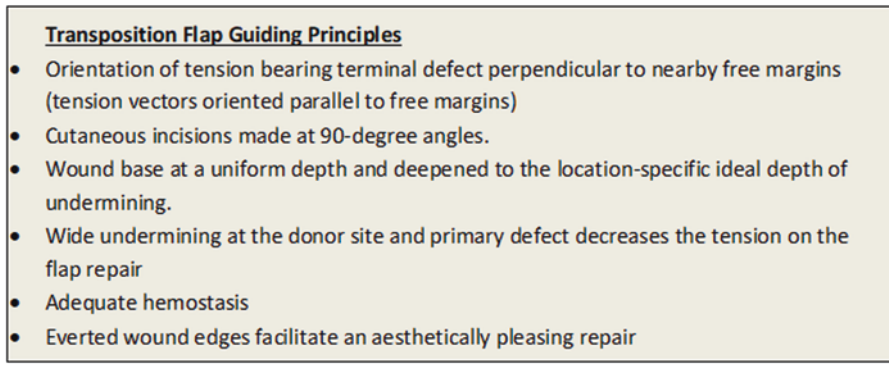

Fig. 6.1 Transposition flap guiding principles. (Summarized from Bolognia [1])

A discussion of the indications, technique, efficacy, and alternatives for each of these transposition flaps will be presented in this chapter.

Preoperative Evaluation

Preoperative evaluation entails accounting for defect size, defect location, inherent elasticity of the neighboring tissue, qualities of the wound bed, and other comorbidities [2–4]. For example, the preoperative evaluation of one version of the rhombic flap, the Dufourmentel flap, necessitates that the tissue reservoir on the nasal sidewall and paranasal cheek is enough to accommodate flap movement without causing alar distortion (4) [5]. This assessment for donor site mobility is common to all flaps, transposition or otherwise. For multilaminar structures such as the distal nose or eyelid, where transposition flaps are frequently used, a thorough assessment of all layers is required: the external covering of the skin, supporting structural appendages, and internal lining and factored into the reconstructive strategy [3]. Additionally, obtaining a relevant history of prior skin cancer, any nearby irradiation, prior surgeries (for nasal defects), and presence of intervening scars will aid in selecting the appropriate reconstruction [2, 6]. Smoking status is also a critical factor. Flap or graft failure may increase with smoking and/or prior radiation exposure. Inconsistences in the survival of flaps or grafts may be due to differences in radiotherapy plan (fractionation, dosage, and timing) [7]. In these populations, raising flaps at the appropriate anatomic level and performing tension-free closures are crucial to reduce the risk of a failed reconstruction (5) [2]. Awareness of comorbidities such as chronic malnutrition, poorly controlled diabetes, uncontrolled hypertension, and bleeding diatheses is pertinent as these disorders increase the likelihood of post-reconstruction complications (5) [8, 9]. Hence, it is prudent to medically optimize the patient prior to any reconstructive surgery. Konofaos adds the optimal reconstructive approach takes into account racial, cultural, socioeconomic factors, and the patient's needs and concerns (5) [10]. Patient factors include age, expectations, and skin redundancy which are also part of the reconstructive preoperative evaluation (4) [11]. However, Shumrick et al. concluded in a study of 15 patients over the age of 80 who underwent nasal reconstruction that elderly age should not be a deterrent to nasal reconstruction as long as the surgery is not a significant risk to the patient's health and the patient has the capacity to appreciate the reconstruction (4) [12]. Additionally, surgeon factors such as experience and preference may also play a role. Assessment of the possibility of collapse of the ala prior to injection of the anesthesia is key (4) [4]. After a comprehensive review of these elements, the dermatologic surgeon should be apt to identify the appropriate repair of the cutaneous defect.

Procedures

Rhombic Transposition Flaps

Indications/Efficacy Classically based on a defect created in the shape of a rhombus or a diamond with four possible flaps drawn perpendicular to the long access of the diamond, the rhombic flap recruits tissue from tissue reservoirs that are immediately adjacent to the primary defect (5) [13]. Rhombic flaps can be used to repair defects in almost any head and neck cosmetic unit, such as the scalp, lateral upper 2/3 of the nose, small defects on the nasal tip, lateral forehead, eyelid, chin, neck, and medial canthus (5) [14, 15]. One case report of an elderly female who sustained a 1.6 × 1.6 cm defect on the nasal dorsum and supratip after excision of recurrent basal cell carcinoma found that bilateral rhombic flaps can be used to successfully repair large (>1.5 cm) central defects (4) [16]. Some reconstructive surgeons have found the bilateral Dufourmentel flap (double rhomboid flap) to be useful for the repair of nasal dorsum defects near or at the midline. These defects can be of any size, including up to 2 cm. Rhombic flaps also may repair defects involving the scalp, neck, and chin [17, 18]. The rhombic flap has successfully repaired deformities over the cheek and temple as well as defects involving the corners and free margins, given the use of adjacent tissue which ensures a tension-free closure. One case report found this workhorse flap is useful even in cheek reconstructions of previously irradiated skin, despite studies demonstrating that radiation can be a risk factor to flap viability (5) [6]. In a case series of 27 ophthalmology patients who underwent Mohs micrographic surgery for basal cell carcinoma (BCC) and underwent rhombic flap repair less than 24 h later, the authors found this flap to be appropriate for older patients with thin, less sebaceous skin. Increased skin laxity in this population decreased or minimized the traction necessary to move the flap into the defect (5) [15].

Technique In its various remunerations (Limberg, Dufourmentel, and Webster), this flap is created so that the corresponding sides and angles, ideally 90° or less, of the defect and flap are equivalent [19]. Measurements should account for facial convexities and concavities (5) [13]. The secondary tension vector perpendicular to the primary defect allows repair of the primary defect to occur without any wound edge tension. Thus, the standing cone and pedicle should be placed toward the side with the greatest tissue reservoir. The flap should then be transferred into the defect by pivoting on a base with movement over normal adjacent skin, creating a standing cutaneous deformity (SCD) at the base [20]. Depending on the location and shape of the defect, the rhombic flap may be duplicated in order to adequately repair a particular wound. When designing the bilateral Dufourmentel flap, the surgeon creates two superiorly oriented rhombic flaps designed from the midpoint of the lateral margins of the defect. Tension vectors are equal and symmetrical, resulting in no nasal tip or alar distortion (4) [5]. Besides offering an identical texture match of the unilateral rhombic flap, the vectors involved in a bilateral rhombic flap repair on the nose prevent twisting of the nose. There may be a slight upward lift of the nasal tip with this repair, but it may be useful in correcting ptosis [16]. Defects up to 1.5 cm in diameter of the inner canthal area or along the superior portion of the nasal sidewall should be approached with a superior-based rhombic flap (4) [21]. When resurfacing canthal defects, using a laterally based flap, with the SCD oriented toward the lacrimal caruncle, minimizes the necessity of excising a SCD, and the redundant tissue from the unexcised SCD helps to resurface the concavity of the medial canthal area (5) [22].

Complications The rhombic repair is a safe procedure given that the literature does not highlight circumstances of functional impairment. Rather, the complications associated with use of the rhombic repair are primarily cosmetic. Like the unilateral rhombic flap, the bilateral Dufourmentel flap has the possibility to introduce alar elevation if the design of the flap is performed incorrectly (5) [5]. Another common complication of the rhombic flap is alar groove blunting (5) [3]. Rhombic flaps have been used to repair skin-only defects of the eyelid; however, inherent to their design, some

of the flap incisions will fall outside of the relaxed skin tension lines (RSTL) (5) [23]. Unintended pivotal restraint, especially in areas of thick skin, may cause well-designed rhombic flaps to fail to reach their intended target in the primary defect. When this occurs, a double Z-plasty may aid in increasing flap movement [24]. Sclafani's case series of 446 Mohs defect repairs identified that rhombic flaps (RR = 1.541, $p = 0.0061$) are a risk factor associated with postoperative complications, especially pincushioning (RR = 4.405, $p < 0.0001$) (4) [25]. In this study, patients with the rhombic flap repair were more likely to need intralesional corticosteroid injections (RR = 2.734, $p = 0.0001$) postoperatively. Other risk factors identified included superiorly based nasolabial flap (RR = 2.153, $p = 0.0144$), bilobed flap (RR = 1.875, $p = 0.0491$), age < 60 years, Fitzpatrick skin type 3, nasal (alar) defect, glabellar flap, full-thickness skin graft (FTSG), and rotation flap [25]. Rhombic flaps are not amenable to repairs of the nasal ala due to the need to orient the repair cephalad with respect to the ala-free margin (5) [3]. The donor site of the flap needs to be on the skin of the nasal sidewall, superior to the alar groove. The tension to close the secondary defect at the donor site can obstruct the nasal valve due to medial deviation of the lower lateral cartilage (5) [3]. Individuals with thin noses or tightly adherent lateral sidewalls are most at risk for alar distortion with this reconstructive option. Hence, another repair should be considered for these patients [5].

Bilobed Transposition Flaps

Indications/Efficacy Compared to rhombic flaps, bilobed flaps are able to recruit donor sites more remote from the primary defect. First described by Esser in the German medical literature in 1918, this double-lobed flap with a pedicle was a fusion of the conventional flaps recruiting skin from the nasal dorsum and the sidewall used to repair nasal tip defects [23, 26]. The primary advantage of this flap is it distributes the tension involved in closure across a broad area, away from the original defect [27]. Additionally, this flap as a single-stage flap with color and texture match to adjacent tissues has a predictable flap viability, pushing movement of the flap toward the free margin, reliable vasculature, and restoration of contour over a convexity (4) [4, 23]. Iddings et al. found this reconstruction to be useful for large cheek defects (5) [28]. The bilobed flap is suited for repair of defects up to 1.5 cm in the distal half of the dorsum, sidewalls, and lateral tip and on the supra-tip that are located ≥5 mm from the free nostril margin (4) [2, 4, 14, 23, 27]. It is most useful for defects that are at the lower eyelid, lower 1/3 of the nose, especially for small-rounded defects at the nasal dorsum and lateral walls, including the anterior and middle nasal alae (4) [3–4, 14]. Reconstruction at these sites minimizes distortion of the ala (5) [2]. Garces et al. report a successful bilobed repair of a full-thickness nasal alar rim defect, a condition commonly corrected with a paramedian forehead flap and the nasolabial flap (5) [29]. The bilobed flaps work well in those with firm alae and is less ideal in those with soft, floppy alae (4) [4]. Bilobed flaps, compared to the skin grafts, are especially useful for defects where the depth extends into and past the subcutaneous fat, as the skin grafts tend to result in visible depressions over the nose in deeper defects and a less than desirable aesthetic result (5) [30]. However, Martinez contends that ipsilateral alar narrowing may result from tertiary defect closure of a laterally or medially placed bilobed flap [31]. As it pertains to eyelids, laterally placed bilobed flaps may be used for large defects on the eyelid. These repairs displace tension to the cheek and/or temple away from the lid margin [32]. However, one study concluded that bilobed flaps are minimally helpful in the repair defects that are larger than 1.5 cm, on the most distal aspect of the nasal tip or ala, or arise on patients with rigid, sebaceous nasal skin. In fact, these features are predictive of bilobed flap failure (5) [33]. Table 6.1 contains a summary of studies evaluating the efficacy and safety of the bilobed repair.

Technique In the design of this flap, the primary lobe is designed at an approximately 45-degree angle to a line bisecting the primary defect and

Table 6.1 Summary of published studies on bilobed flaps

Publication	Study design	Number of subjects	Efficacy	Safety	Level of evidence
Konofaos et al. [10]	Case series, retrospective chart review	419 patients	Bilobed flap for successful repair of 145/278 defects of nasal dorsum, sidewall, lateral tip, and supra-tip	Hypertrophic scar, bulky flap, flap pincushioning, and partial necrosis listed but unclear if these pertain specifically to the bilobed flap	4
Ibrahim et al. [11]	Case series, retrospective chart review	245 patients	Bilobed flap reconstructed 17/42 nasal ala defects, 19/41 nasal tip defects, and 8/25 nasal sidewall defects	No data on complications	4
Jellinek et al. [4]	Case series	6 patients	Bilobed flap for alar rim (<1 cm) defects	No complications listed for these patients, but possible complications include alar contraction, ecnasion, and alar asymmetry	4
Monarca et al. [44]	Cohort study	120 patients (60 patients received the island flap, 60 patients received the bilobed flap)	In the long term, bilobed flaps had nasal distortion. Patient and third-party assessments of island flap repairs were rated more favorably than the bilobed flaps and found to be statistically significant	Island flap: 6 cases of hematoma Bilobed flap: 10 cases of flap congestion, 5 cases of apical flap necrosis of which 2 cases required surgical revision, persistent edema, and 11 cases of trap door deformity	3
Xue et al. [35]	Case series	11 patients	All patients received bilobed flaps, no issues with flap survival or functional deformities	No post-operative complications, such as alar retraction	4

with a size approximately equal to the size of the primary defect. The height of the primary lobe should be equal to the height of the defect (4) [34–35]. The secondary lobe is then designed at an approximately 45-degree angle to the primary lobe giving the bilobed flap a total angle of rotation of about 90 degrees. The addition of a secondary lobe allows for placement of the tension bearing tertiary defect in an area of greater skin laxity, which may be closed easily with a buried, interrupted, absorbable suture (5) [36]. Zitelli found that lengthening of the primary lobe is helpful when there is a large defect (≥1.5 cm) or when the secondary lobe is in tight or immobile skin (5) [37]. This advantage enables repair in sites where tension proximal to the primary defect is excessive or creates an anatomic distortion (5) [38]. When designing this flap, it is important to avoid tension on the lower medial canthus while closing the tertiary defect in order to avoid ectropion. Closing of the tertiary defect pushes the flap toward the primary defect.

Next the primary lobe is positioned, trimmed as needed, and sutured into the primary defect with an absorbable, buried interrupted tacking suture extending from the underside of the primary lobe to the primary defect. The placement of deep sutures that incorporate the deep tissue of the flap and surrounding skin is critical. Improper placement of these key sutures results in distortion of the ala. Thus, one must reassess the position of the primary flap immediately after placement of this first suture and prior to further securing the primary flap [39]. The secondary lobe is trimmed as needed and sutured into the secondary defect with nonabsorbable running or interrupted sutures to approximate the superficial

skin edges of the entire flap (5) [36]. With further improvement of the design, a Burow's triangle next to the primary defect is anticipated and removed, without affecting the base of the pedicle and compromising the vascular supply. Removal of Burow's triangle obviates the need for a secondary procedure in the future to remove the SCD that would otherwise occur at the point of rotation.

Important design principles for this flap include creating a long, thin standing cone defect with a diameter that is 0.75–1.5 times the diameter of the primary defect (5) [37, 40–41] and removing the SCD prior to flap movement (5) [37, 40–41]. The distance between the distal primary defect and the apex of the SCD determines the bilobed's outer arc of rotation. This degree of rotation facilitates less secondary motion at the primary defect and less risk of elevating the alar rim. Incisions for the nose should be carried through the nasalis muscle, periosteum, and perichondrium and the flap is mobilized below the muscle. Wide undermining and meticulous closure decrease the possibility of a trap door deformity [39, 41–43]. In a case series, the author advocated that the bilobed flap may be used for small- to medium-sized defects on the helical rim as the flap may originate from a concealed site such as the posterior rim, and allows for faster wound healing of a defect with exposed cartilage, and provide excellent color and texture match with a one-stage repair. During the design of the bilobed flap, it is important for the surgeon to test airflow through the ipsilateral nostril of the patient and repeat after the first key suture to assess for looming nasal valve collapse due to horizontally oriented tension over the internal nasal valve (4) [4].

Complications The bilobed repair has a number of possible functional and aesthetic complications. For example, nasal obstruction may occur with this type of reconstruction, especially in patients with fragile skin, weak cartilage, and large nasal defects (5) [30]. Internal nasal valve constriction associated with suturing the tertiary defect is a known flaw some surgeons experience (4) [4]. Also, the improper placement of the flap pivot point over the internal nasal valve with these repairs may cause a functional deficit in the nostril (4) [15, 32]. If the nasal valve collapses, a pexing suture at the depth of the alar groove fixed to the sidewall periosteum will help open the valve if the suture is constricted (4) [4, 22]. In a head-to-head trial comparing island pedicle flaps to bilobed flaps for nasal reconstructions, bilobed flaps had statistically significant higher rates of early complications that included hematoma, flap necrosis, and hypertrophic scarring (3b) [44]. The impact of inappropriately designing the lobes can be dramatic. Undersizing of the flap causes contraction of the ala and upward ipsilateral alar retraction, whereas oversizing may result in alar asymmetry and depression (5) [39]. When the secondary lobe is too wide or too long, the tertiary defect cannot be reapproximated and excess skin must be disposed of in order to prevent trap door deformity or push the alar rim inferiorly (4) [29, 35–36]. While the exact etiology of trap door deformity or pincushioning is not definitively known, one hypothesis is that it arises when excess volume of the flap caused by a vascular obstruction at the surgical site creates a poor aesthetic outcome [36]. Sclafani argues that pincushioning is due to the circumferential formation of scars around the flap and the inward vectors produced by scar contractility [25]. It usually appears 3–6 weeks post-surgery (5) [36]. In Sclafani's study of 446 Mohs defects, bilobed flaps were 2.5 times more likely to pincushion ($p = 0.0286$) (4) [25]. Placing this lobe perpendicular to the nasal ala prevents alar displacement or distortion (4) [29, 35, 39]. Excess tension along the flap can result in flap tip necrosis along the free margin.

From a cosmetic perspective, differences in the lobe thickness may also result in visible depressions (5) [30]. Equally concerning, the multiple multidirectional scar lines associated with bilobed flaps, especially in a highly sebaceous rhinophymatous nose, may be difficult to conceal due to some of these lines opposing relaxed skin tension lines (3b) [23, 30, 36, 44]. Dermabrasion sanding with sterile sandpaper or scar revision may help decrease the appearance of scar lines (5) [36]. Wide undermining and

placement of deep sutures that incorporate the deep tissue of the flap and surrounding skin can minimize this complication. Other complications may include distortion of the nasal tip due to elevation of the tip or nasal margin as a result of wound closure. Patients who have a weak nasal structure have a higher likelihood for nasal (ala) distortion and elevation of the nostril free margin (5) [3, 30]. If used in a more cephalad position, the placement of the second lobe at the medial canthus or glabella may distort these structures. The main disadvantage at these locations is that the skin is thin, possibly compromising the viability of the flap (5) [36]. If used for central tip defects, tip contour distortion may occur [10].

Trilobed Transposition Flaps

Indications/Efficacy First described by Esser, these flaps are designed to correct defects of the lower third of the nose that necessitate recruitment of tissue from even more remote sites compared to bilobed flaps. These flaps are ideal for inferomedial alar and distal nasal tip defects (5) [45]. When used on the nose, tissue may be recruited from sites as distant as the nasal root [20]. Given that this is a single-staged flap for large, deep alar and nasal tip defects with possible involvement of cartilage, this is an alternative to the paramedian forehead flap or cheek-to-nose interpolation flap. The latter carries additional risks, costs, and morbidity especially in the elderly [33]. This flap may also be used in the repair of lateral alar defects with a more medially placed design (5) [33]. By displacing the quaternary defect on the nasal dorsum, repairs larger than 1.5 cm may be performed using the trilobed flaps (5) [20]. In a retrospective review of 31 patients, all patients underwent successful reconstruction with the trilobed flap if their defect was >1.5 cm, prominent on the nasal tip or ala, and availability of looser proximal nasal skin was not an option. While there were no reports of flap failure, hematoma, or surgical site infection, one anticoagulated patient required flap takedown after failure to obtain hemostasis through conservative measures. Electrocautery and flap replacement resolved this issue [33]. Finally, the unilateral nature of the trilobed flap creates a less visible scar because less subunits are involved (5) [33].

Technique When creating the trilobed flap, the surgeon begins by creating a vertically oriented dog ear toward the alar crease, allowing the lateral nasal tip to serve as the primary lobe donor. By placing the dog ear along less sebaceous and thinner tissue, this orientation toward the medial canthus reduces bulldozing or depression of the alar rim (4) [33]. The apex of the dog ear is placed within the alar crease, shifting the pivot point into the lower nasal sidewall, freeing up the flap's rotational movement. Additionally, Claiborne and Albertini argue that this dog ear should be designed as small as possible so that any excess tissue from the standing cone deformity at the apex will be inverted and hidden within the crease as an "inverted cone deformity." [45] With a more moveable pivot point, there is a decreased risk of bulldozing and distortion during rotation and insetting of the flap. Moreover, this design minimizes tissue waste, maintains the native ala as much as possible, and preserves the cosmetic subunit (5) [45]. Also, the closure tension vector is transverse across the nasal dorsum and alar distortion is minimized (5) [45]. Like the bilobed flap, each lobe of the trilobed flap rotates 45–50 degrees with an arc of flap rotation of 135–150 degrees (4) [33]. The smaller arc of the rotation in the trilobed flap reduces the Z-plasty like lengthening and thus minimizes the bulldozing of the ipsilateral ala [33]. Since these flaps tend to be in areas with greater skin laxity, the primary lobe should be equal in size to the primary defect. The secondary lobe should have a diameter that is 85–90%, and the tertiary lobe should have a diameter that is 75–80% of the primary defect (5) [45]. The smaller secondary and tertiary lobes help distribute tension, warding off the possibility of pincushioning [33]. Equally, these smaller lobes also allow for primary closure of the tertiary defect, which often lies close to the medial canthus, without distorting important anatomical features. Lobes derived from immobile skin

should not be undersized as the size adjustment is thought to add a small amount of tension, yet decrease pincushioning (5) [45].

Complications Disadvantages of these flaps include more lobes that increase the operating time and increase the risk of a more noticeable scar (5) [38].

Nasolabial (Melolabial) Transposition Flap

Indications/Efficacy Initially described by Dieffenbach for repair of partial nasal alae defects, this repair is the most widely used flap in the nasolabial fold and its adjacent structures (including the lip) due to the flap mobility and its ability to close the secondary defect via primary intention (4) [14, 25, 27]. Additionally, the donor site scar may be concealed within the nasolabial fold. It may be used to reconstruct full-thickness alar defects as large as 2.5 cm, including those on the alar margin (4) [46–47]. In Uzun's case series of 163 patients, the nasolabial flap was one of the preferred reconstruction methods for repair of distal lateral nasal defects involving the alar and domal-alar groove subunits for its reliable blood supply from the medial cheek skin and skin color and texture match of the previously excised tissue (4) [27]. For the nose, this flap facilitates recreation of the nasal ala via simultaneous insertion of cartilage grafts and prevents proximal retraction that may distort a natural-looking contour of the nose (5) [14]. It may be used for reconstruction of large defects or internal lining defects if the flap was turned over when septal mucosal flaps are not available or for large lining defects (4) [48–50]. Defects of the nasal sidewall can be repaired with the ample tissue reservoir of superiorly placed melolabial flaps (5) [3].

Technique Proper execution of the flap entails an excision of Burow's triangle in the direction of the medial canthus. The excised nasal sidewall skin should extend to the nasolabial crease at a 30-degree angle to eliminate the standing cone at the pivot point. For this reconstruction, the medial aspect of the flap begins at the lateral aspect of the defect where a point meets the nasolabial facial sulcus (5) [51]. Incisions may need to be placed into the nasolabial crease, alar crease, and junction between the nasal dorsum and nasal sidewall. The incision is planned to continue along the melolabial crease without entering the hairless triangle where the upper cutaneous lip meets the ala. The lateral incision, which is superior, should be several millimeters above the peninsula formed by the junction of the cheek, upper lip, and ala. The flap is elevated, defatted, and positioned medially over the peninsula of the alar fragment. Wide undermining of the donor site, recipient site, and adjacent tissues of the cheek and nasal dorsum allows a tension-free closure. Placement of buried sutures in the deep aspect of the flap anchored to the piriform aperture helps recreate the nasolabial sulcus and avoids tenting of the cheek onto the nose. A portion of the lateral ala must be present to secure the advancing cheek skin and reapproximate the donor site [3]. Then, the donor site is closed, and the flap is sutured to the recipient site to recreate the alar groove (5) [51].

Complications Careful attention must be made when designing these flaps in the cheek as there is a tendency for the soft supple skin to pincushion or to develop alar groove blunting (4) [10]. In the absence of meticulous suturing, the round scar where the flap insets at the ala tends to invert (5) [3]. Further complications are highlighted in a summary of nasolabial flaps in Table 6.2.

Combined Transposition Flaps

Some investigators used hybrid variants of transposition flaps for unique indications. Fujiwara created a bilobed nasolabial-nasal tip flap to repair a full-thickness defect of the alar rim larger than 20 mm. Besides providing a good texture and color match, this flap also gives the patient a scar concealed in the nasolabial sulcus (5) [52]. Kannan and John also report using a bilobed nasolabial flap for a 2.5 cm left ala defect of the nasolabial fold (5) [53]. Dinehart presents his experience of

Table 6.2 Summary of nasolabial transposition flaps

Publication	Study design	Number of subjects	Efficacy	Safety	Level of evidence
Konofaos et al. [10]	Case series, retrospective chart review	419 patients	69/74 of defects repaired with a nasolabial repair +/−cartilage graft for defects of the nasal ala, dorsum, and nasal sidewall	Flap bulkiness was a complication for some of the repairs	4
Ibrahim et al. [11]	Case series, retrospective chart review	245 patients	Nasolabial flap successfully reconstructed 3/41 nasal tip defects, 12/42 nasal tip defects	No data on complications	4
Carucci [51]	Case series	32 patients	32/32 repairs of the ala with single-staged melolabial flap	No trap door deformity appreciated	4
Han et al. [47]	Case series	17 patients	12/17 repairs of defects ≤2 cm were nasolabial flaps with various aesthetic outcomes from poor to excellent	Alar groove blunting, elevated alar margin, and flap contraction	4

ten patients receiving the rhombic bilobed flap, which produced minimal postoperative complications such as telangiectasias surrounding a spreading scar. No functional deformity resulted (4). A decreased incidence of pincushioning results with this flap due to the sharp angles and dispersion of tension produced by this flap (4) [54].

Postoperative Care and Follow-Up

Immediate postoperative care includes a 24–48-h pressure dressing and daily wound care including gentle cleansing with topical antibiotics or bland emollients. While some surgeons prescribe a short course of oral anti-staphylococcal antibiotics, evidence shows that routine antibiotics are unnecessary (1a) [55].

After reconstruction, some patients develop unsightly scars at the donor site or the site of the primary defect. It is recommended to delay any surgical scar revision for 6–12 months to allow time for scar maturation. Dermabrasion or laser therapy ameliorates this problem and may be used in the early post-operative period to correct for more minor defects in appearance (5) [2, 56]. Dermabrasion may improve the color and texture match of a nasal reconstruction and may be performed as early as 6 weeks after the initial reconstruction (5) [2]. Pulsed dye laser therapy can be safely performed as early as 1 week post-surgery [56].

Alternative Procedures and Modifications

There are alternative repair options that may be reasonably chosen for almost any cutaneous defect. While advancement flaps, rotation flaps, V-to-Y island pedicle flaps, interpolated nasal flaps, interpolated melolabial flaps, and paramedian forehead flaps are covered in more detail in subsequent chapters, this chapter will briefly highlight the indications, advantages, and complications associated with these flaps as alternatives to transposition flaps. Alar advancement rotation flaps are a viable option for 3–4 mm defects in the anterior half of the ala. They offer a fitting color, texture, and thickness match and the scars can be concealed in the alar groove. Closure with this reconstructive option may result in a downward displacement of the free margin, buckling of the alar rim, and obliteration of the alar groove, especially for defects that are too large in the horizontal dimension, if the standing cone is too small or insufficient undermining has occurred (5) [57]. As an alternative to the bilobed flap, the advancement and inferior rotation flap of the nasal sidewall (AIRNS) is a single-stage repair for horizontal defects of the nasal tip or the lower nasal dorsum. Using the upper nasal sidewall and cheek, this flap has less of a tendency to pincushion. However, this repair results in a single curvilinear scar (4) [58]. In

certain circumstances, the bilobed flap remains a better option for certain defects, such as a lateral ala defect (4) [58].

The V-Y island pedicle advancement flap may be used for similar small <0.5 cm in horizontal diameter medial alar defects. Sliding flaps on the ala are only amenable for defects nearer the alar crease and relatively remote from the free margin. Like the transposition flaps, these flaps provide a good color, texture, and thickness match to the native skin. Additionally, the V-to-Y flap has a reliable blood supply, offers ease of harvest, and has a broad pedicle. Compared to the bilobed flap, some authors feel decreased edema results in less chance of a trap door deformity. When this repair is utilized near the free margin, flap movement is limited, and the circulation in this area becomes very much compromised near the margin [3]. The design of the island flap is versatile, able to be crafted into the shape of the defect without disrupting the natural contours of the nasal tip. It can also avoid nostril notching or nasal asymmetry (3b) [44].

For defects that span more than one cosmetic subunit, options include the paramedian forehead flap and composite grafts. Despite its use in providing coverage over large defects, a major drawback of the paramedian forehead flap reconstruction is the creation of a long forehead scar that some patients find aesthetically displeasing (5) [3]. Composite grafts repair large full-thickness defects (defects that involve the skin, structural framework, and the internal lining) of multiple nasal subunits or related to nasal vestibule stenosis (4) [59–60]. It may be used for secondary reconstruction in patients with an unsightly scar resulting from scar contracture or a previous surgery for a congenital defect. However, composite grafts have a high metabolic demand and high risk for necrosis (5) [3].

Full-thickness skin grafts (FTSG) may be used for the repair of alar defects in patients whose comorbidities do not permit them to undergo a long procedure [2]. Full-thickness skin graft is another option that works well in patients with thin skin who require repairs of the cephalic sidewall, dorsum, and infratip lobule. They help to repair superficial defects and provide total nasal coverage in patients with several significant medical comorbidities (5) [2]. However, these grafts are oftentimes a mismatch in the color, texture, and thickness of the native skin (5) [3]. In a retrospective chart review of 186 cases of surgical defects of the nasal ala, FTSG were used to repair defects of at least 1.0–1.4 cm; eight cases involved lesions of 2 cm or greater. With this reconstruction, there was no loss of ala patency, distortion of the free margin, nor complications that may arise with bilobed, trilobed, or nasolabial flaps. Post-operative wound infection occurred with two cases, resulting in antimicrobial use. Two patients had failure of full thickness graft uptake ameliorated with dermabrasion. Dermabrasion was used in 36% of cases to improve the postoperative cosmesis (4) [61].

As an alternative to the melolabial flap for lateral ala defects, the hinge cheek subcutaneous flap is helpful for resurfacing intermediate thickness defects of the lateral nasal ala or sidewall (5) [2].

Additionally, a melolabial interpolated flap can also be used to reconstruct alar defects. As opposed to the cheek transposition flaps, these interpolated flaps are an alternative to the single-staged nasolabial flap for defects that affect the entire nasal ala because of the ample tissue available within the nasolabial fold. The reconstruction is indicated for deep alar defects. It preserves the alar-facial sulcus and offers a close skin and texture match for the ala. It entails the placement of a cartilage batten graft to brace the alar rim against tension vectors that cause flap contraction and the flap provides vascularization of the cartilage graft [2–3]. Key disadvantages of this flap are that the flap, in men, may transfer hair-bearing skin from the donor site to the ala and that melolabial fold asymmetry may result from harvesting broad cheek flaps—limiting the vertical height of the primary defect that the flap is amenable to (5) [62]. Also, there is an apparent extensive pedicle care and a need for a second procedure to detach the flap pedicle and to inset the flap (5) [2].

Nasal defects <1 cm of the middle third of the nose or caudal dorsum and sidewall may be closed primarily (5) [2]. This reconstructive approach is ideal for elderly patients with significant skin laxity that allows tension-free closure (5) [2].

Another alternative for repair of alar defects includes healing by secondary intention. Zitelli found that areas involving the alar crease can be reasonable for healing by secondary intention, whereas other surgeons have found this approach to be useful for small defects (<5 mm) adjacent to the nasolabial sulcus or in the alar-facial crease (5) [3]. For small defects in patients who are poor surgical candidates, healing by secondary intention is a viable option (5) [2]. However, this option is avoided for large, deep defects, particularly those near the alar rim as there is a higher likelihood of alar retraction or nasal valve compromise (5) [2–3]. Concave surfaces may or may not be surfaces amenable for healing by secondary intention. Webbing in concave surfaces is also a well-known complication of wounds that heal from secondary intention (5) [3].

Defects of less than or equal to 2.5 cm of the middle and lower nose involving the nasal dorsum, tip, and sidewall may be repaired with a dorsal nasal flap recruiting ample glabellar skin (5) [2].

Decision Trees on Nasal Reconstruction

While based on surgeon experience, various papers publish decision trees that indicate repair options for specific defects. This information may be helpful for novice surgeons to use until a randomized clinical trial, systematic review, or clinical guidelines develop that validate particular repairs for certain defects. Uzun et al. have an algorithm based on whether the size of the defect and location of the defect are on the nose [27]. Konofaos presents a similar decision tree in his 2014 publication [10].

Conclusion

Transposition flaps are a staple reconstructive tool in the armamentarium of dermatologic surgeons. They are versatile in repairing a multitude of defects as reflected in Table 6.3, which contains various clinical scenarios in which transposition flaps facilitated the re-approximation of tissues

Table 6.3 Summary of studies of multiple transposition flaps

Publication	Study design	Number of subjects	Efficacy	Safety	Level of evidence
Uzun et al. [27]	Case series	163 patients	−31.5% defects of the middle 1/2 of the nose repaired with nasolabial flaps without flap necrosis −39.6% defects of the distal 1/2 of the nose successfully repaired with nasolabial flaps −17.0% of defects of the distal 1/2 of the nose successfully repaired with bilobed flaps −5.48% of defects of the middle 1/3 of the nose successfully repaired with rhombic (Limberg) flaps −7.55% of defects in the distal 1/3 of the nose successfully repaired with the rhombic (Limberg) flap	No complications noted	4
Yoon et al. [50]	Case series	35 patients	3 successful repairs with bilobed flaps, 5 cases of successful repair of nasolabial flaps. No functional impairment	One case of composite free-flap necrosis, tip necrosis of paramedian forehead flap	4

while preserving functional aesthetics. Use of these workhorse flaps is predicated on the proximity of the primary defect relative to the tissue reservoirs. For example, a rhombic flap for a defect on the proximal nose or sidewall with tissue reservoirs immediately adjacent to it may work well as the single lobe of this flap may reach adjacent tissue reservoirs. Defects on the supratip and proximal nasal tip may require a bilobed flap, and very distal defects may require a trilobed flap. Defects of the lateral ala may be addressed with the nasolabial flap. These flaps are overall safe with well-known complications that surgeons have identified strategies to remedy. Further investigation into the indications and techniques for transposition flaps in the future will help generate clinical guidelines that will assist dermatologic surgeons in selecting the most evidence-based approach for addressing the repair of cutaneous defects.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
A thorough assessment of all layers, the external covering of the skin, supporting structural appendages, and the internal lining, must be done and factored into the reconstructive strategy [3]	D
Obtaining a history of prior skin cancer, history of head and neck irradiation, nasal surgery (for nasal defects), and presence of intervening scars helps with selecting the appropriate reconstruction [2]	D
Consider rhombic transposition flaps for virtually any head or neck cosmetic subunit with a defect that is less than 2 cm with adjacent healthy, mobile tissue reservoirs [14–15]	C
The bilobed flap is well-suited for repair of defects up to 1.5 cm in the distal aspect of nasal subunits and lower eyelid [2, 10, 14, 23, 27]	A
Nasolabial transposition flaps are ideal for the reconstruction of defects along the lateral ala, ala margin, and lip in which the donor site scar may be concealed within the nasolabial fold [14, 25, 27]	A
Careful execution in the design, undermining, and suturing of these flaps minimizes the risk of pincushioning, alar retraction, alar elevation, and nasal valve compromise	A
Whereas it is important to base the selection on patient characteristics (especially considering the size and location of the defect), awareness of the complications and best practices in the utility of transposition flaps can be further strengthened through randomized clinical trials, systematic reviews, and clinical guidelines	B

Summary of Observations

- Transposition flaps have a wide range of applications in the repair of cutaneous defects in anatomic locations with minimal inherent skin laxity.
- The decision on which transposition flaps to use is dependent on local tissue characteristics.
- Reconstructions involving transposition flaps are safe.
- These reconstructions do not require discontinuation of anticoagulation or initiation of antibiotics.

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Self-Assessment Questions

1. Compared to rhombic flaps, bilobed flaps are better served for defects in which:
   (a) The tissue reservoir is in a remote location relative to the defect.
   (b) The tissue reservoir is in close proximity to the defect.
   (c) The defect is greater than 2 cm.
   (d) The defect is located on the superior aspect of the nasolabial fold.
   (e) The defect is the result of secondary reconstruction.
2. Optimization of the appearance of scar lines of transposition flaps may entail:
   (a) Dermabrasion only.
   (b) Low or medium potency corticosteroids.
   (c) Dermabrasion and pulsed dye laser therapy.
   (d) Phototherapy.
   (e) Re-exploration of the surgical site.
3. Defects that involve destruction of the internal nasal lining may be repaired with:
   (a) Trilobed flaps.
   (b) Rhombic flaps.
   (c) Bilobed flaps.
   (d) Nasolabial flaps.
   (e) Island pedicle flaps.
4. The type of transposition flap that is most likely to have pincushioning is:
   (a) Bilobed flaps.
   (b) Rhombic flaps.
   (c) Trilobed flaps.
   (d) Nasolabial flaps.
   (e) Advancement flaps.
5. Assessing nasal patency is a critical intraoperative step for this type of repair(s):
   (a) Rhombic and nasolabial transposition flaps of the nasal sidewall.
   (b) Rhombic transposition flaps of the nasal dorsum.
   (c) Rotation flaps on the glabella.
   (d) Advancement and inferior rotation flap of the nasal sidewall.
   (e) Bilobed and rhombic transposition flaps on the lower nasal sidewall or ala.

Correct Answers

1. a: Bilobed transposition flaps are maximally effective when the tissue reservoir is in a remote location. In contrast, rhombic flaps are ideal for repairs of defects in which the tissue reservoir is in close proximity to the defect. The primary flap movement of the rhombic flap is predicated on the free edge of the flap being within a short distance of the primary defect, resulting in minimal pivotal restraint during insetting of the flap.
2. c: Dermabrasion and/or pulsed dye laser therapy may improve the cosmesis of the scar lines of the transposition flaps. They may be used in the early postoperative period to correct for more minor defects in appearance (5) [2, 56]. Dermabrasion may improve the color and texture match of a nasal reconstruction and may be performed as early as 6 weeks after the initial reconstruction (5) [2]. Pulsed dye laser therapy can be safely performed as early as 1 week post-surgery [56].
3. d: Nasolabial flaps may repair defects that have internal nasal lining involvement as these flaps may be turned over when septal mucosal flaps are not available or large lining defects are present.
4. b: Despite dogma that posits that flaps with rounded edges are more likely to pincushion, Sclafani's case series reviewing the complications from 446 Mohs defect repairs found that rhombic flaps were 4.4 times ($p < 0.0001$) more likely to pincushion than bilobed flaps (RR = 2.488, $p < 0.0286$) flaps [25]. The study did not comment on the likelihood for pincushioning with other types of transposition flaps or advancement flaps.
5. e: Jellinek and Cordova assert that it is critical for the surgeon to test airflow through the ipsilateral nostril of the patient in bilobed reconstructions and repeat the assessment after the first key suture to assess for looming nasal valve collapse due to horizontally oriented tension over the internal nasal valve (4) [4]. For rhombic defects, the tension to close the secondary defect at the donor site can obstruct the nasal valve due to medial deviation of the lower lateral cartilage [2]. Hence, it is prudent to check nasal patency for rhombic defects as well. Reconstruction of defects over the bony nasal skeleton that are more proximal on the nose should not affect the nasal valves.

Rotation Flap

7

Farhaad R. Riyaz and David M. Ozog

Abstract

A rotation flap is a procedure carried out in cutaneous surgery in order to close a defect in the skin by recruiting cutaneous tissue from a nearby reservoir (5) (LoPiccolo, Dermatol Surg 41(Suppl 10):S247–S254, 2015). Akin to many other flaps, rotation flaps are reputable workhorse flaps first described in 1978, (5) (Albom, J Dermatol Surg Oncol 4(12):906–907, 1978) often used to repair defects on the head and neck but can also be useful for bodily sites such as the hand, forearm, and nail bed (5) (O'Neill, Litts, Clin Plast Surg 31(1):113–119, 2004). They are performed in a single stage and are widely regarded as highly reliable, efficient, and straightforward (2c) (Moore et al, Head Neck 27(12):1092–1101, 2005). They are executed in a sliding fashion but are distinguished from other sliding flaps, such as advancement flaps, by moving at an angle about a pivotal point, and are therefore useful for redirection of tension vectors. They recruit tissue from adjacent sites. This distinguishes them from transposition flaps, where recruited tissue is transferred over another portion of skin.

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Keywords

Rotation flap · Cheek · Cheek rotation · Flap reconstruction · Plastic surgery

Indications for Rotation Flaps

A rotation flap is a procedure carried out in cutaneous surgery in order to close a defect in the skin by recruiting cutaneous tissue from a nearby reservoir (5) [1]. Akin to many other flaps, rotation flaps are reputable workhorse flaps first described in 1978, (5) [2] often used to repair defects on the head and neck but can also be useful for bodily sites such as the hand, forearm, and nail bed (5) [3]. They are performed in a single stage and are widely regarded as highly reliable, efficient, and straightforward (2c) [4]. They are executed in a sliding fashion but are distinguished from other sliding flaps, such as advancement flaps, by moving at an angle about a pivotal point, and are therefore useful for redirection of tension vectors. They recruit tissue from adjacent sites. This distinguishes them from transposition flaps, where recruited tissue is transferred over another portion of skin.

When used in dermatology, a rotation flap consists most often of the epidermis, dermis, and subcutaneous fat but also can contain underlying muscle. The rotation flap is known to have a rich vascular pedicle and usually is a random pattern

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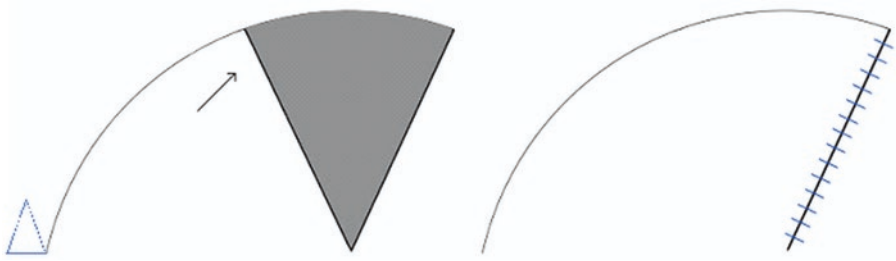

Fig. 7.1 The simplified movement of a rotation flap, closing a triangular defect

flap with no named artery to supply blood, although in a few case reports there are named arteries recruited as a blood supply with an unknown difference in outcomes (4) [5].

Rotation flaps can be used to hide incision lines within curved relaxed skin tension lines or at the border of cosmetic subunits and can move standing cones anywhere along the arc of the flap or even retroauricularly (2a, 5) [6, 7].

Rotation flaps were classically described as arcuate flaps used to repair triangular defects (Fig. 7.1). They can be used for small or full-face defects. Other than being used for facial reconstruction, they have been used in all age groups to repair pilonidal sinuses and are considered superior to primary closure for this purpose (1b) [8]. They have also been used to repair sacral pressure ulcers but may have higher rates of complication than perforator flaps when used for this purpose (2b, 3b) [9, 10]. Also, rotation flaps are used to recruit the laxity of the ulnar forearm toward the radial forearm in children with radial longitudinal deficiency (2b) [11].

Modifications of the rotation flap include bilateral rotation flaps used for large forehead wounds or chin defects (2c) [12], "O to Z" rotation flaps used for defects of the scalp (5) [13], dorsal nasal flaps used for defects of the distal nose (4) [14, 15], and Tenzel and Mustarde flaps for lower eyelid reconstruction (4, 5) [16, 17]. A lateral eyelid rotation flap has also been described in one case for reconstruction of full-thickness eyelid defects (2b) [18]. In three reported cases, one rotation flap has been used to repair multiple adjacent defects on either the cheek or nose (4) [19–21]. Finally, a modification of the rotation flap called the "reverse Yu flap" has been studied in a cohort fashion with good oral competence and aesthetic outcome at a mean of 20 months of follow-up (4) [22].

Effectiveness of Rotation Flaps

One of the largest case series of rotation flaps described effectiveness in closing circular defects in 178 patients after removal of malignant neoplasms (4) [23]. The widespread use of rotation flaps and their resilience to major change over time are a testament to their effectiveness and reliability (5) [24]. Despite this, there is a paucity of data on this subject. Experts consider them effective for the repair of defects with an adjacent tissue reservoir, sitting in an area with curved relaxed skin tension lines or a curved cosmetic subunit within which to hide incision lines. The effectiveness of rotation flaps is not believed by many experts to be markedly affected by patient demographics such as age, comorbidity, or smoking status (5, 3a) [1, 25].

As with all scars, their appearance can be expected to improve over the first 6–24 months, but unfortunately there is no data comparing this property in rotation flaps with other types of surgical scars.

Preoperative Evaluation

Preoperative evaluation for this procedure is anecdotal and begins with assessing the size, location, shape, and depth of the wound that requires repair and finding an appropriate adjacent reservoir of tissue. Adjacent reservoirs of tissue can be pre-

dicted by assessing the laxity and movement of the skin surrounding the defect. Identification of nearby cosmetic subunits and relaxed skin tension lines is also helpful in determining patient suitability for a rotation flap (3a) [25].

As rotation flaps typically have broad vascular pedicles, there is believed to be low risk of ischemia and high survival of the flaps even in patients who have vascular comorbidities, are elderly, are on blood thinners, or who smoke (5) [1]. Although there is no evidence to support these claims, the authors believe it is widely understood that rotation flaps, as with other flaps, will survive when placed directly over exposed bone or cartilage (5) [26]. There does not appear to be any evidence regarding the appropriateness of a rotation flap in patients with active infection, though chronic infections such as HIV or hepatitis C do not appear to be contraindications. As flaps create geometric scars, it is reasonable to consider other options before carrying out a rotation flap in patients with a tendency to form keloid scars.

A reconstructive differential is often discussed to compare reconstructive techniques and their predicted outcome for the defect at hand. The appropriate closure may be selected from options including primary closure, advancement flap, rotation flap, transposition flap, full or split thickness skin graft, and healing by secondary intention. These techniques have not been evaluated side-by-side, likely due to their nuanced use depending on size, shape, and position of the defect, variation in training and reconstructive choice among surgeons, and difficulty in obtaining long-term follow-up.

Best Techniques and Performance

The first step in performing a rotation flap is to remove any beveled edges of the defect if created during Mohs surgery or other excisional techniques. Some surrounding skin in the vicinity is removed as well to create a triangular defect (3a) [25]. This can be drawn and performed as one of the initial surgery steps or the tissue can be rotated into place and the redundancy identified/removed.

Classically, the recommended ratio of length to width of a given rotation flap was around 2:1 (2b, 5) [27, 28]. The flap should also be designed with length around four times the width of the base of the triangular defect. This ratio is thought to allow for redistribution of tissue along unequal lengths of the arc and can eliminate the need to remove a standing cone by using the rule of halves. Depending on the situation, the flap may be shortened for better concealment or lengthened in cases of limited mobility, but it may be beneficial for the leading edge of the flap to extend beyond the distal edge of the defect to reduce tension on the flap and enable it to rotate into place without force (2c) [4]. Mathematical models suggest flaps are best if they have ¼ circle arc, because too much or too little of an arc hypothetically creates unwanted tension on the flap (5,2b) [17, 27]. In the case of cervicofacial rotation flaps, a small study of 13 patients showed that rates of flap loss were similarly low whether the flap was rotated in a forward fashion or a reverse fashion (4) [29].

For optimal flap motion, experience dictates that the pivotal area of restraint must be undermined (5) [7]. The subcutaneous plane is preferred by experts over a deep plane because it has comparable tip necrosis rates and potentially lower ectropion rates (3b) [30] and is thought to preserve nerves such as the supratrochlear, supraorbital, and facial nerves (3a) [25]. This is in contrast to earlier opinions that the blood supply and reliability of cervicofacial rotation-advancement flaps could be improved significantly by dissecting the flap in a deeper plane (4) [31]. An exception to this is the expert opinion that scalp flaps should be dissected in the subgaleal plane and that cheek flaps should be dissected below the SMAS (5) [26, 32]. A back cut into the body of the flap can improve motion as well. It is not known whether this compromises the vascular supply of the pedicle, but it is anecdotally useful in freeing restraint (2b) [33]. This classical back cut has not been compared in a systematic fashion to the modified "crescentic" back cut, which is designed to minimize the scar line (4) [34]. Other techniques designed to increase the motion of rotation flaps, including pivot point modification, cyclic loading, galeal scoring, and skin stretching, have also not been studied in a controlled, comparative, or outcome-oriented fashion (2b) [35]. A series of nine patients

with limited cheek skin laxity were treated with "Yin-Yang" modifications of the Mustarde flap for infraorbital defect repair. This counter-rotation of the temporoparietal scalp in a direction opposite to the Mustarde flap for increased movement showed good aesthetic quality at 36 months (4) [16].

When closing the wound, dermal vertical mattress sutures are placed first, starting with the first stitch at the advancing edge of the flap as classically recommended for all advancement and rotation flaps, using 4-0 polydioxanone or polyglactin 910. Unfortunately, this dogmatic principle has no published evidence to support it (5, 3a, 5) [1, 25, 28]. And in some cases, it is appropriate to begin suturing at the base of the flap to advance tissue and minimize stress on the leading edge. Another adjunct, particularly in large facial flaps, is to place plication sutures in fascial planes to support the flap and transfer tension vectors. Afterward, more dermal sutures are placed approximately every 8 mm along the flap using a size 5-0 suture. Periosteal suspension sutures can be used to prevent ectropion, but it is uncertain how effective this technique may be. The optimal epidermal layer of sutures and technique for placement have not been outlined in the literature.

Safety

Likely due to the wide pedicle, properly designed rotation flaps have good blood supply, and distal tip necrosis rates across all sites are reported in the range of 0–23% (3b) [30, 36].

In one study of 33 patients who underwent cervicofacial and cervicothoracic rotation flaps, minor wound complications occurred in 11 patients, most commonly epidermolysis of the distal skin flap. There was no statistically significant association between wound complications and a history of smoking, diabetes mellitus, peripheral vascular disease, or preceding radiation therapy (2c) [4]. However, this is not sufficient evidence to conclude that these factors do not affect flap survival.

In another study of 30 patients undergoing lateral cheek rotation flap, the overall complication rate was 23%. Thirteen percent of all patients had hematoma formation and 10% had partial flap necrosis. Two-thirds of patients who had partial flap necrosis were active smokers. No patient developed a wound infection, and there was no complete flap loss. Ten percent of patients had transient facial nerve branch palsy and all recovered spontaneously. Twenty-eight of 30 patients had a final reconstruction that was functionally satisfactory, and the same number had a reconstruction that was cosmetically satisfactory to both patient and surgeon. Two patients underwent revision of Burow's triangle to improve cosmesis. There was no periprocedural mortality (2c) [37]. It is unlikely that the closures also had suspension/plication sutures, which in our opinion would reduce these complication rates. In a separate study of nine lateral cheek rotation flaps combined with z-plasty to enhance movement and decrease tension, all flaps survived without any developing hematoma, wound infection, distal flap necrosis, or lower lid ectropion (4) [38]. There is a known increased risk of postoperative lower lid ectropion if eyelid skin is involved in a defect covered by a rotation flap as shown in an evaluation of 31 patients undergoing periorbital reconstruction by a cheek rotation flap (2b) [39].

The frequency of complications such as bleeding, pain, nerve damage, wound dehiscence, wound infection, persistent Burow's triangle formation, hypertrophic scar development, ectropion, and functional or cosmetic skin restriction due to scarring is not discussed further in the available literature. When widely undermining any flap, these risks are present.

Postoperative Care and Follow-Up

Compression dressings should be placed for 24–48 h and that the wound be examined at that time to ensure no hematoma has developed. Suture removal at 5–7 days for facial flaps and 10–14 days for cervical and scalp flaps is appropriate if nonabsorbable superficial sutures are used (3a) [25].

Residual standing cones may be excised immediately at the time of procedure but may also be managed with an intraoperative z-plasty or monitored for 6 weeks. Deformities that do not flatten after 6 weeks may necessitate excision. These methods have not been studied or compared with each other specifically for rotation flaps (3a) [25].

If trap-door deformity occurs, physical massage or injection of the area deeply with triamcinolone may encourage resolution. Expert opinion is that surgical revision should not be considered for 9–12 months following the flap surgery (3a) [25].

Alternative Procedures and Modifications

Experienced surgeons believe that rotation flaps have their greatest utility on the scalp, temple, cheek, and nose. On the scalp, rotation flaps must be quite long due to poor skin mobility but are widely believed by experts to be next in line for defects that cannot be closed primarily (5) [40]. On the temple and medial cheek, the large reservoir of skin from the lateral cheek can be recruited (5) [17]. Rotation flaps performed to reconstruct the lateral and central cheek, however, may pull hair-bearing skin of the sideburn medially onto the malar eminence.

Aside from the dorsal nasal flap, most small dorsal nasal defects are better repaired with other flaps such as the bilobed or rhombic flap because the skin of the nasal tip is inelastic. Despite this, a case report shows good results with a bilateral version of this versatile flap on the nasal tip (5) [41]. Rotation flaps recruiting cheek skin to repair nasal sidewall defects can create unfavorable and conspicuous distortion of the nasolabial fold. The same principle applies for defects of the lateral lip and obstruction of the melolabial fold (5) [28].

A "dog-ear rotation flap" has been described for large defects wherein the surgeon attempts to perform a linear repair from one end of a wound and creates a rotation flap out of the standing cone left at the other end when the two edges can no longer be approximated. This method has not been compared to the standard rotation flap, but the authors claim that it creates a low-tension repair with extremely low rates of flap necrosis (5) [42].

In the repair of cleft lip, the rotation-advancement repair has been studied in comparison to the philtral ridge repair with respect to the height and symmetry of Cupid's bow, width and height of the nasal vestibule, height of the vermilion, and alar base position. Both the rotation-advancement and philtral ridge techniques produced outcomes with a comparably high degree of facial symmetry in a study of 26 patients who were analyzed with facial points mapped out by imaging software (1c) [43].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Rotation flaps can be used to close cutaneous defects on the head, neck, and other bodily sites	D
Rotation flaps are widely regarded as highly reliable, efficient, and straightforward	D
Rotation flaps require an adjacent tissue reservoir in order for proper execution	D
Standing cones may be placed anywhere along the arc of the flap	C
The effectiveness of rotation flaps is not believed to be markedly affected by age, comorbidity, or smoking status	B
Identification of nearby cosmetic subunits and relaxed skin tension lines is helpful in determining patient suitability	A
It may be beneficial for the leading edge of the flap to extend beyond the distal edge of the defect	C
The recommended ratio of length to width of a given rotation flap is around 2:1	D
For optimal flap motion, experience dictates that the pivotal area of restraint must be undermined	C
Residual standing cones may be excised immediately at the time of procedure but may also be monitored	D
If trap-door deformity occurs, physical massage or triamcinolone injection of the area may encourage resolution	C

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Self-Assessment Questions

1. Expert opinion suggests that rotation flaps are useful for defects on all of the following parts of the body except the:
   (a) Nasal dorsum
   (b) Nasal sidewall
   (c) Temple
   (d) Medial cheek
   (e) Medial lip
2. Rotation flaps:
   (a) Recruit tissue from distant locations to close wounds
   (b) Are often performed in more than one stage
   (c) Require a named artery to supply blood
   (d) Have narrow vascular pedicles
   (e) Can be placed over exposed cartilage
3. The defect shape that is most suitable for repair by rotation flap is:
   (a) A circle
   (b) A square
   (c) A triangle
   (d) A rectangle
   (e) An ellipse
4. Which of the following risk factors have been established as exclusion criteria for undergoing a rotation flap?
   (a) Current smoker
   (b) History of insulin-resistant diabetes mellitus
   (c) Hypertriglyceridemia
   (d) Elderly age
   (e) None of the above
5. Which of the following is not true regarding rotation flaps?
   (a) Z-plasty can be used to extend the rotation of the flap into the defect.
   (b) Standing cones do not have to be excised at the time of surgery.
   (c) c. Mathematical models state that 90° of rotation arc is ideal for rotation flaps.
   (d) High-level evidence has shown that back cuts may damage the vascular pedicle of rotation flaps.
   (e) Ectropion is more likely in patients who undergo rotation flaps if their defect requiring repair has a portion which sits on the lower eyelid.

Correct Answers

1. b: The nasal sidewall is believed to lack the laxity necessary for a rotation flap, and skin rotated from the cheek to the nasal sidewall can blunt the nasolabial fold.
2. e: Experts say that most skin flaps have the necessary vascular supply to survive on top of exposed cartilage.
3. c: Geometrically, a triangular defect is the ideal wound to be repaired by rotation flap.
4. e: None of the listed factors has been shown to be significantly detrimental to the survival of rotation flaps.
5. d: Only expert opinion has suggested that a broad vascular pedicle is preventative against adverse complications, such as distal flap tip necrosis.

Pedicle Flaps

8

H. William Higgins II and Jeremy Bordeaux

Abstract

Skin cancers of the head and neck treated by Mohs micrographic surgery often leave wound defects requiring advance reconstruction. Interpolation flaps, including the pedicled melolabial, paranasal, and retroauricular, are sophisticated and reliable options for large defects in facial areas. The paramedian forehead flap is a classic example of an interpolation flap, and it will be discussed in another chapter. The melolabial flap, also known as the cheek-to-nose interpolation flap, is a two-stage flap classically utilized for defects involving the nasal ala, inferior nasal tip, or columella. One limitation to the use of this flap is the resulting asymmetry of the melolabial folds. The paranasal flap overcomes this pitfall and is an excellent option for small to medium alar defects. Both flaps are generously vascularized by tributaries of the angular artery. The retroauricular flap is useful for full-thickness defects of the ear. Classically, this flap is used for defects on the middle third of the ear. However, it can also be utilized for defects on the inferior aspect of the ear, closer to the earlobe. These interpolation flaps, when utilized skillfully, can provide excellent cosmetic results and offer viable options for repair of defects of the nose and ear.

Keywords

Interpolation flap · Paranasal interpolation flap · Cheek-to-nose interpolation flap · Postauricular interpolation flap · Mohs surgery · Reconstruction · Melolabial interpolation flap

Introduction

Skin cancers are commonly located on the head and neck, and surgical removal still remains the gold standard for the majority of these tumors. Many cutaneous head and neck tumors will be treated by Mohs micrographic surgery (MMS) , which involves tumor extirpation, confirmation of clear histologic margins, and, if necessary, surgical repair of the resulting tissue defect. When repairing defects on cosmetically sensitive locations of the head and neck, the surgeon must have a broad knowledge and essentially algorithmic approach to the various repair options in order to provide the optimal esthetic and functional outcome.

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Options for repair range from second-intention healing to complex surgical reconstruction. Depending on the size and location of the defect, particularly in relation to surrounding anatomic structures, a flap repair or tissue rearrangement may be employed. A well-designed and properly executed flap provides reconstructive advantages in that it ensures a cosmetically optimal tissue match, maintains function, and ideally allows for a well-camouflaged donor site.

The caudal third of the nose and the ear are areas with complex topography given the intricate interplay of convexities and concavities. In addition, these sites lack apposite neighboring donor tissue often necessitating the use of more distant tissue reservoirs when repairing medium- to large-sized defects. Interpolated flaps are staged repairs that have long been utilized to overcome the unique features of these anatomic locations. These sophisticated flaps are generously supplied by a named artery or its immediate branches and have a donor site separated from the defect by an intact bridge of skin. Patient preoperative education and assessment of social support are prerequisite. Counseling regarding the extent of wound care, the need for multiple visits, activity limitations, and simply the mental preparation for having a pedicle in place for weeks are key to a smooth postoperative course.

Repair options vary from minimalistic to complex. Second intention requires no surgical reconstruction, but involves an extended healing process. Complex surgical reconstruction requires an understanding of head and neck anatomy, as well as limitations of the skin. When chosen properly, flaps offer superb cosmesis and outcomes (4, 2c, 4) [1–3]. An appropriately designed and well-executed flap offers reconstruction advantages, as flaps often offer a source of richly vascularized tissue to repair the wound (1b, 2a) [4, 5].

This chapter will discuss the use and proper execution of pedicled melolabial, paranasal, and retroauricular flaps with step-by-step recommendations for optimizing their outcome (4) [6]. The forehead paramedian flap is a classic example of an interpolation flap. It will be discussed in Chap. 10.

Interpolation Flap Considerations

In contrast to advancement flaps, the interpolation flap pivots into the defect. In contrast to transposition flaps, the base of the interpolation flap is located a significant distance from the defect that it is repairing. As such, the pedicle, or viable tissue of the flap, often passes through intervening tissue. For pedicles that pass over intervening tissue, a takedown stage is often required, necessitating a second surgical procedure. This feature of interpolation flap results in a longer postoperative period and requires extensive patient counseling on what to expect between each stage of the flap and after let-down of the second stage of the flap.

Melolabial Interpolation Flap

With its densely sebaceous texture, inelasticity, and elaborate contour, the nasal ala can be a unique and challenging region to reconstruct. Moreover, its conspicuous location and important functionality provide higher stakes when choosing the appropriate repair. The dearth of immediately adjacent donor tissue limits options for linear closure and adjacent tissue rearrangement. Graft repair, while reasonable for shallow defects, may not provide the optimal tissue match or structural support achieved with other reconstructive options. Interpolated flaps are valuable tools for overcoming the inherently challenging features of the ala in that they allow the recruitment of well-matched skin from a more distant donor site.

The melolabial interpolation flap, also known as the cheek-to-nose interpolation flap, is primarily used for medium to large defects of the nasal ala that do not involve the alar-facial sulcus. It can also be utilized for defects involving the inferior nasal tip or columella. This two-staged repair provides tissue akin in color and sebaceous texture to the native skin of the caudal nose while hiding the donor scar within the natural valley of the melolabial fold. In addition, the cheek-to-nose interpolation flap maintains the natural concavity of the alar-facial sulcus, which can be

blunted with other repair options such as the melolabial transposition flap.

While the melolabial interpolation flap is traditionally regarded as an axial pattern flap, the pedicle does not contain a named artery. It is instead supplied by perforating branches of the angular artery, making its vascular network more random than axial (3b, 3b) [7, 8]. Consequently, the blood supply is less robust than an axial pattern flap but still generous enough to reliably perfuse the flap during the healing period (Fig. 8.1a–d).

Description of Technique

For alar defects, any remaining tissue of the cosmetic subunit needs to be first excised to provide a more esthetic resurfacing of the entire alar lobule. Ideally, a 1 mm margin of skin should be left on the lateral-most aspect of the ala to preserve the natural contour of the alar-facial groove.

The nasal ala is composed of firm fibrofatty tissue, essentially devoid of cartilage, and functions as the external nasal valve. When repairing a medium to large soft tissue defect in this region, cartilage grafts are often used to maintain the complex contour of the nasal ala and prevent collapse of the nasal valve. These grafts also counter against contraction of scar tissue resulting from the overlying flap (2b, 4, 4) [9–12].

For defects with loss of nasal mucosa, restoration of the nasal lining is often required. However, this subject is beyond the scope of this chapter (2b) [13].

For defects with cartilage loss, cartilage grafts are typically harvested (2b, 2b) [14, 15]. Oftentimes, the conchal bowl or the antihelix of the ear can serve as a source of cartilage for this

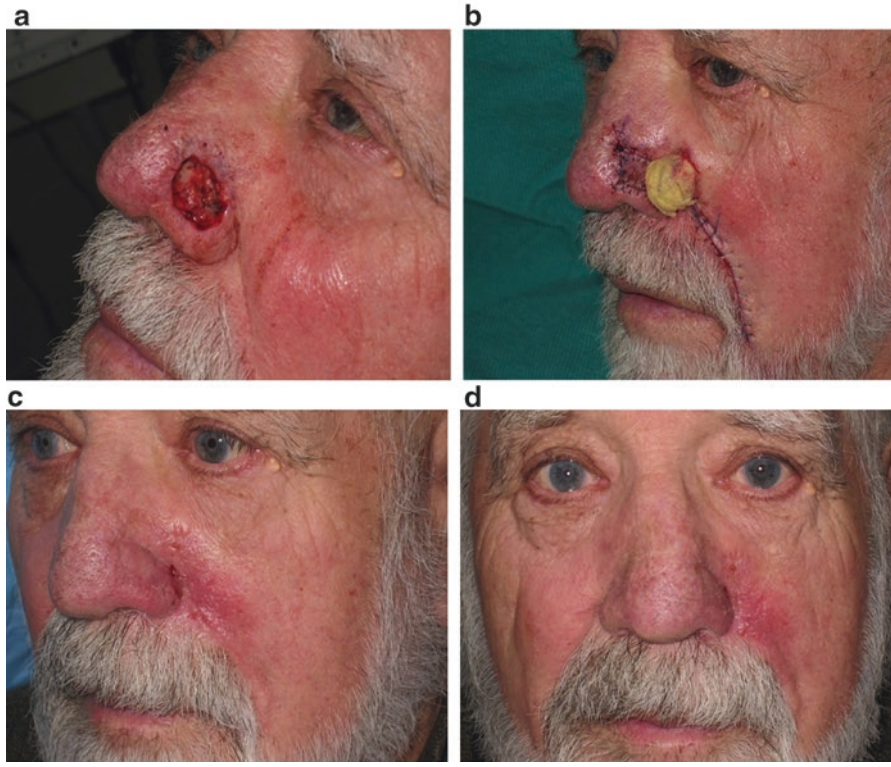

Fig. 8.1 (**a**) Defect of the left ala after Mohs surgery. (**b**) Interpolation flap sutured in place with emollient-impregnated dressing wrapped around the pedicle. (**c**) Left-sided view of patient after pedicle takedown with nice preservation of the natural concavity of the lateral nose and medial cheek. (**d**) Frontal view of patient after pedicle takedown

purpose. Conchal bowl cartilage can be harvested via an anterior or posterior approach and are ideal for larger defects that require more restoration of curvature and structural support. The conchal bowl contralateral to the defect is often chosen given it better mimics the bowed contour of the contralateral alar rim. Cartilage from the antihelix is useful for defects that may require a less curvilinear strut for contour restoration. Small tissue pockets are incised on the medial and lateral aspect of the defect, and the graft should be slightly oversized by 3–5 mm on either end to fit into these pockets. Non-absorbable sutures are then placed in a horizontal mattress or figure-of-eight fashion to secure the graft into the medial and lateral pockets as well as the inner alar lining. Because of the avascular nature of cartilage, the vascular supply provided from the overlying flap is essential for healing (3b) [16]. For more detailed description of cartilage grafting, see Chap. 11.

After placement and securing the cartilage graft, the contralateral alar subunit is then measured. A template can be made with various materials, such as using foil from a suture packet or a small sheet of a non-stick dressing such as Telfa. This template is then inverted and traced along the melolabial fold ipsilateral to the surgical defect. The inferior border of the template, which will eventually be transferred to the anterior aspect of the alar defect, should be positioned just superior to the oral commissure. The inferomedial border of the template, which will be mobilized to meet the superior aspect of the alar defect, should run along the valley of the melolabial fold. The larger flap pedicle is then designed, incorporating the templated area, as either an elliptical island, detached from all surrounding cutaneous tissue, or as a peninsula with a superiorly based cutaneous pedicle. When using the elliptical island design, the superior most border of the pedicle should be no higher than the inferior border of the alar-facial sulcus to minimize distortion of this natural concavity. With the peninsular design, the superior border of the pedicle may be as high as the alar crease to allow for adequate pivoting motion of the flap. The superior end of the island design will taper like the end of an ellipse, whereas the superior end of the peninsular design will have a wider width matching that of the alar template. With either design, a rolled piece of gauze may be employed to mimic desired flap motion, which will be a clockwise pivot from the left cheek and counterclockwise from the right, and ensure adequate flap length.

The inferior tissue cone of the pedicle is then excised and discarded allowing for easier closure of the donor site. Starting distally, the remainder of the pedicle is then elevated. The plane of dissection for the peninsular variant is more superficial, leaving a thin 3–4 mm layer of subcutaneous tissue on the undersurface of the flap. For the island design, the plane of dissection becomes progressively deeper toward the flap's pivot point. There the depth of dissection should reach the surface of the levator labii superioris alaeque nasi and zygomatic major muscles. Some advocate including fibers of the levator labii to ensure adequate blood supply from the perforating branches of the angular artery (5) [17].

The remaining steps of the first stage are essentially the same regardless of which design variant is used. The cheek donor site is widely undermined and closed in a layered fashion to help push the flap superomedially toward the ala. The primary defect may be undermined and debeveled to ensure even apposition of the flap edges with the recipient site. Subcutaneous tissue may also be trimmed from the flap to better match the depth of the primary defect. The flap is then meticulously sutured in place with 5-0 or 6-0 cutaneous sutures [16]. Buried dermal sutures are not typically utilized. The pedicle is then wrapped with Vaseline-impregnated gauze or Xeroform, and a pressure dressing may be placed.

At 3 weeks, the patient will return for the second stage, division and inset of the pedicle. The pedicle is severed at the base and the cheek defect may be closed primarily for the island design pedicle or in a V-shape for the peninsular design pedicle. For the nose, the lateral aspect of the flap is debulked of subcutaneous tissue and excess skin is trimmed to match the size of the defect. The flap may then be secured in place with interrupted cutaneous sutures.

On occasion, the patient may return for a contouring procedure in 3 months to thin the flap and/or further refine the natural concavity of the alar-facial sulcus. Minor trapdooring of the flap can often be addressed with intralesional steroid injections. Pain is often controlled with local anesthesia or by performing nerve blocks.

The island design may offer certain advantages over the peninsular design. The island design's deeper pedicle incorporates more tributaries from the angular artery and therefore has a more robust blood supply. In addition, the island's lack of cutaneous attachment allows for easier mobility when pivoting the flap to the recipient site. Lastly, the island's tapered superior pole allows for simpler closure of the superior aspect of the donor site during takedown. Ultimately, both designs provide reliably good results and the variant chosen will hinge on surgeon preference and comfort level with the technique.

Paranasal Interpolation Flap

While the melolabial interpolation flap is a mainstay for alar restoration, there are limitations to its use. One potential shortcoming is consequent asymmetry of the melolabial folds, which may detract from an otherwise excellent esthetic outcome on the ala. A limitation in males is that the flap pedicle typically incorporates terminal hair-bearing skin which may then be transferred to the ala (2b) [18].

The paranasal interpolation flap circumvents these potential pitfalls and is a reliable reconstructive option for alar defects that are small to medium in size. It also allows for a shorter donor scar and may avoid resurfacing of the entire alar subunit. Like the melolabial interpolation flap, the paranasal interpolation flap is a random-pattern flap generously vascularized by tributaries of the angular artery. The donor site provides an excellent color and texture match for the ala with the added benefit of not having terminal hair (Fig. 8.2a–h) [18].

Description of Technique

Before committing to using the paranasal interpolation flap for surgical repair, adequate laxity of the medial cheek must be assessed in order to avoid distortion of the nose, medial cheek, or ipsilateral lower lid when closing the donor site. When designing the flap, the vertical diameter of the defect must match the width of the flap [18]. The paranasal pedicle rotates 90° toward the primary defect, and this measurement ensures an appropriate fit for the flap at the recipient site.

If structural support is needed, a cartilage strut may first be placed and secured in the manner previously described above in the section on melolabial flaps. Two vertical and essentially parallel incisions are made that continue superiorly along the nasofacial sulcus and then meet at a 30° taper. The medial incision line should begin immediately adjacent to the alar-cheek junction, and the lateral incision line should originate at a distance equal to the vertical diameter of the alar defect. Starting superiorly, the flap pedicle is elevated along a subcutaneous tissue plane. The plane of dissection becomes progressively deeper moving inferiorly toward the flap's pivot point. The pedicle tip should be trimmed to be marginally thinner than the depth of the alar defect, and its diameter should equal or be slightly less than the recipient site diameter to reduce the risk of pin-cushioning. After wide undermining, the medial cheek donor site is closed in a layered fashion. Absorbable buried vertical mattress sutures are placed to secure the flap to the recipient site followed by a layer of epidermal sutures.

Flap division is performed at 3 weeks. If the entire alar subunit was not replaced, the flap pedicle is incised along the lateral aspect of the defect, thinned, and sutured in place in a layered fashion. In cases where the entire cosmetic subunit is resurfaced, pedicle division is performed and appropriately sized to replace the larger surface area of the entire alar lobule. In cases where the entire cosmetic subunit is resurfaced, pedicle division and inset may be more involved [18].

Once the remainder of the cosmetic subunit is removed, the pedicle is divided to match the size of the larger primary defect. The lateral aspect of the pedicle and the primary defect may both be generously thinned to match in thickness and depth. The flap edges are then appropriately trimmed and inset with layered closure. Similar

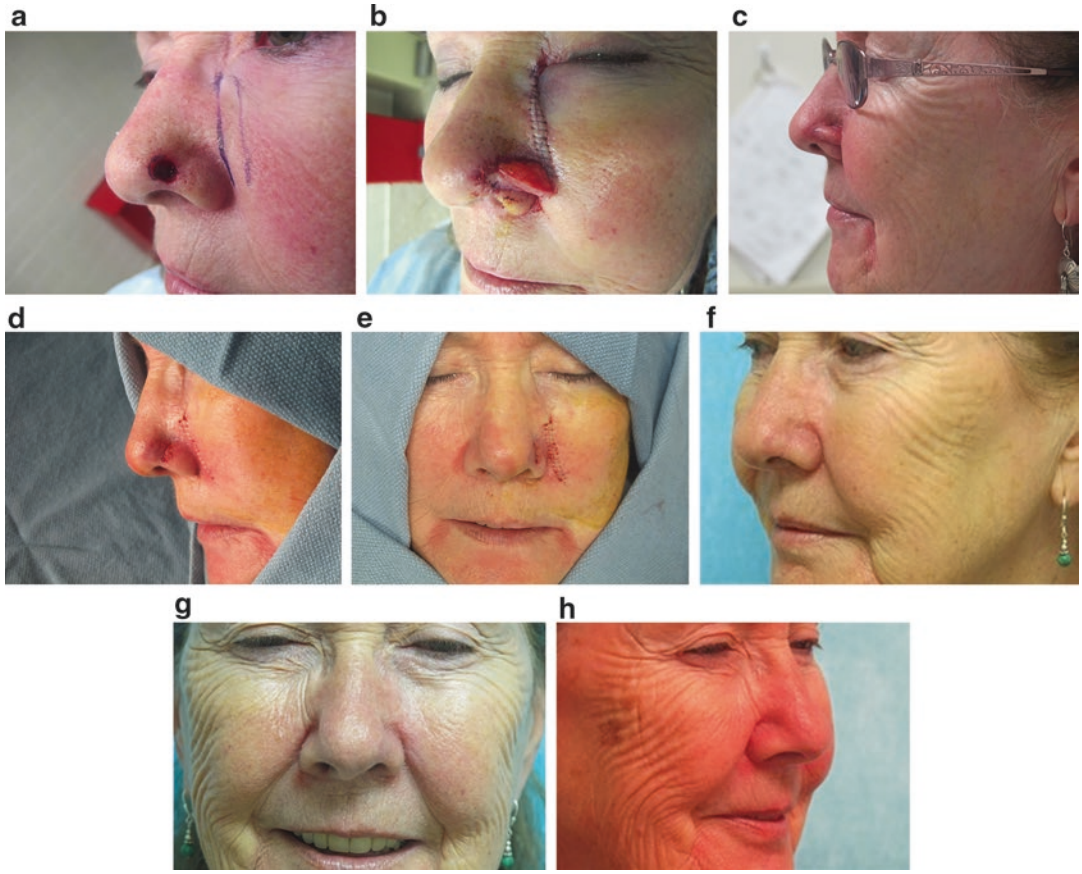

Fig. 8.2 (**a**) Defect of the left ala after Mohs surgery. The proposed flap pedicle is marked to hide closure of the secondary defect between the nasal sidewall and medial cheek. (**b**) Interpolation flap sutured in place. (**c**) Well-healed pedicle along the left ala prior to takedown. (**d**) Lateral view after takedown of pedicle from the left ala. (**e**) Frontal view after takedown of pedicle from the left ala. (**f**) Left-sided view of patient showing excellent color and contour restoration of the left ala. (**g**) Frontal view of patient after repair. (**h**) Contralateral view for comparison

to the melolabial interpolation flap, some patients may require further contouring procedures or intralesional steroid injections for further refinement. Limitations to this flap include alar defects with a larger vertical diameter and patients with poor laxity of the medial cheek donor site (2b) [19]. In these cases, the melolabial interpolation flap may be a better repair option.

Retroauricular Flap

The staged retroauricular flap is a useful and reliable option for large full-thickness defects of helix. This repair is classically used for defects on the middle third of the ear but may also be utilized for defects located more inferiorly near the lobe. This random-pattern flap is based on the plentiful blood supply of the postauricular scalp and provides excellent restoration of the rounded contour of the lateral ear (Fig. 8.3a–d).

Description of Technique

In designing this repair, the width of the flap's leading edge should be equivalent or slightly larger than the vertical axis of the primary defect. The flap is elevated along the adjacent skin of the posterior ear and extends to the retroauricular sulcus and neighboring scalp. When further structural support is needed, a cartilage graft may be taken from the conchal bowl of the opposing

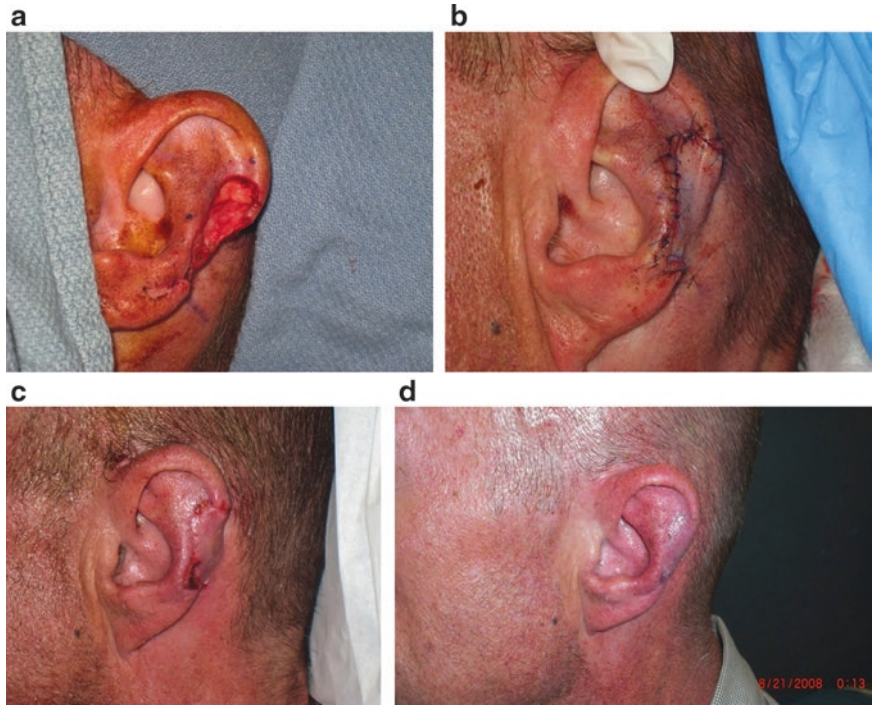

Fig. 8.3 (**a**) L helix with defect after Mohs surgery. (**b**) Interpolation flap sutured in place. (**c**) Pedicle prior to take down. (**d**) Well-healed flap restoring natural contour of the ear

ear and anchored to the intact auricular cartilage of the primary defect with absorbable sutures.

The flap is then dissected along the subcutaneous tissue plane, advanced to cover the primary defect, and secured in place via layered closure. Ideally, the flap length should be three to four times the width to ensure sufficient mobility while maintaining adequate perfusion. The exposed portion of the retroauricular pedicle is usually dressed with emollient-impregnated gauze.

Flap division is performed at 3 weeks. The pedicle is incised at the base and the medial aspect of the flap is rolled to cover the cartilage graft and native cartilage of the posterior ear. The retroauricular donor area may be closed primarily, grafted, or allowed to granulate.

A variation of this design may be performed in which the flap is elevated more posteriorly from the retroauricular scalp and mobilized to close the helical defect while leaving the skin of the posterior ear and sulcus intact. Division and inset is done at 2–3 months at which time a cartilage graft may be placed if additional support is needed. Potential benefits of this design are less exposed tissue of the posterior ear between the first and second stages of repair and a smaller secondary defect to resurface at flap division. However, the obvious trade-off is significantly longer time to takedown. This design may be used for large defects of the mid or inferior helix.

Conclusion

Staged pedicle flaps are invaluable tools in the reconstructive surgeon's assemblage of repair options. The interpolation flaps, when executed properly, offer safe and effective options for reconstruction of Mohs defects (2b) [20]. Major complications are exceedingly rare, and minor complications fall in the realm of the expected: minor bleeding, infection, dehiscence, and flap necrosis.

Careful planning, measurement, and methodical execution are required for flap success. An

understanding of skin texture, anatomy, and the patient's comorbidities is also essential. Preoperative patient counseling and detailed framing of the postoperative course cannot be overlooked and work in concert with excellent technique to provide the best patient outcomes. Postoperative patient instructions are also essential to minimize flap necrosis or infection. Given the potential bulkiness of these flaps, there should be a low threshold for employing cartilage support. The generously vascularized pedicle ensures survival of the cartilage graft as well as overlying multilayered flap. This versatile flap allows the surgeon to restore the patient's natural skin topography after procedures related to tumor extirpation.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Interpolation flaps have a demonstrated record of safety.	B
Interpolation flaps offer excellent cosmetic results for repair of nasal defects.	B
Complications of interpolation flaps include bleeding, infection, necrosis, dehiscence, and pin-cushioning/hypertrophic scar.	B

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Self-Assessment Questions

1. Which of the following statements regarding cheek-to-nose interpolation flaps is false?
   (a) For alar defects, remaining tissue of the cosmetic subunit may be first excised for better cosmetic outcome.
   (b) A 1 mm margin of skin should be left on the lateralmost aspect of the ala to preserve the natural contour of the alar-facial groove.
   (c) At baseline, the nasal ala is essentially devoid of cartilage.
   (d) Cartilage grafts can be used in conjunction with a pedicle flap to prevent collapse of the nasal valve and counter contraction of scar tissue.
   (e) Takedown is usually performed 4 weeks from the first stage of the repair.
2. The paranasal interpolation flap is supplied by:
   (a) The dorsal nasal artery
   (b) The facial artery
   (c) Perforating branches of the angular artery
   (d) Perforating branches of the ophthalmic artery
   (e) The angular artery
3. The pedicle of the cheek-to-nose interpolation flap may be carried out in an island or peninsular design. What advantages are offered by the island design?
   (a) The island design's deeper pedicle incorporates more tributaries from the angular artery and therefore has a more robust blood supply.
   (b) The island's lack of cutaneous attachment allows for easier mobility when pivoting the flap to the recipient site.
   (c) The island's tapered superior pole allows for simpler closure of the superior aspect of the donor site during takedown.
   (d) (a) and (b)
   (e) All of the above
4. Which of the following is not an example of a pedicle flap?
   (a) Melolabial interpolation flap
   (b) Paranasal interpolation flap
   (c) Peng interpolation flap
   (d) Retroauricular interpolation flap
   (e) Paramedian forehead flap
5. What best describes the vascular supply pattern for the retroauricular interpolation flap?
   (a) It's an axial pattern flap based on a named blood vessel.
   (b) It's a random-patterned flap.
   (c) It's supplied by the cartilage of the recipient defect site on the ear.
   (d) (a) and (c)
   (e) None of the above

Correct Answers

1. e: Takedown and inset of a cheek-to-nose interpolation flap is typically performed at 3 weeks from the first stage of repair.
2. c: While commonly thought of as an axial pattern flap, the paranasal interpolation flap is actually supplied by the perforating branches of the angular artery and not the artery itself.
3. e: While the island design offers the advantages above, both designs provide reliably good results, and the variant chosen will hinge on surgeon preference and comfort level with the technique.
4. c: The Peng flap is not an interpolation flap. Rather, it is a sliding flap and is commonly used on the nose. There is no such thing as a Peng interpolation flap. The addition of the word "interpolation" is a distractor.
5. b: The staged retroauricular flap is a random-pattern flap based on the plentiful blood supply of the postauricular scalp.

Forehead Flaps

9

Agnieszka K. Thompson and John A. Carucci

Abstract

The forehead flap has been a staple in nasal reconstructive surgery dating back to 700 B.C. and continues to serve as a workhorse for sizeable nasal defects. Its roots trace back to India, where the rudimentary version of today's forehead flap was employed as a reconstructive modality following nasal amputations as a form of punishment. Over the centuries, the forehead flap has evolved and been refined by reconstructive pioneers. The current version serves as an effective, reliable, reproducible flap providing a robust blood supply and excellent texture and quality match for nasal defects. Herein, we review the forehead flap and describe the scientific evidence supporting this flap as well as modifications, variations in execution and design, and complications. We will focus on recent advances in the literature in this area.

Keywords

Blood supply · Forehead flap · Nasal reconstruction · Paramedian forehead · Flap

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Introduction

The forehead flap has been a staple in nasal reconstructive surgery dating back to 700 B.C. and continues to serve as a workhorse for sizeable nasal defects [1, 2]. Its roots trace back to India, where the rudimentary version of today's forehead flap was employed as a reconstructive modality following nasal amputations as a form of punishment [2–4]. Over the centuries, the forehead flap has evolved and been refined by reconstructive pioneers [1, 5]. The current version serves as an effective, reliable, reproducible flap providing a robust blood supply and excellent texture and quality match for nasal defects [4, 6]. Herein, we review the forehead flap and describe the scientific evidence supporting this flap as well as modifications, variations in execution and design, and complications. We will focus on recent advances in the literature in this area.

Indications for Forehead Flaps

The forehead flap is a reliable and predictable reconstructive technique used for sizeable nasal defects. Generally, this flap is used for defect size larger than 1.5–2 cm and/or for full-thickness defects requiring multilayered reconstruction, nasal lining, and structural support (5) [5, 7–9]. The forehead flap is an excellent option in cases where local flaps are insufficient and where

reconstruction requires a flap with its own blood supply (4) [8]. Forehead flaps can also be used in periocular reconstruction, particularly when there is a concomitant nasal defect (4) [10, 11]. Reconstruction following exenteration is another indication for forehead flap use (4) [12].

This flap can be used in all demographic groups but most commonly is employed in adults with nasal defects of various etiologies. In the majority of cases, nasal defects of this size are secondary to nonmelanoma skin cancer (NMSC) surgery (generally Mohs micrographic surgery) but less commonly can be caused by removal of other malignancies such as melanoma [8, 13–15]. In other scenarios, the forehead flap can be a reconstructive tool in traumatic nasal defects [16, 17]. Forehead flaps can be performed on pediatric patients; however, this is a small proportion of patients [17]. In the pediatric population, the need for forehead flap is most commonly due to malformations, benign tumors, and traumatic injury (4) [17].

History and Efficacy

From its inception in ancient India, nasal reconstruction using the forehead flap was brought to Europe in the 1500s and to the United States in the 1800s [5]. The modern version of the forehead flap was popularized in the United States in the 1930s by Kazanjian using a midline approach involving paired supratrochlear arteries [5, 16]. Since then, the techniques have been fine-tuned and finessed by aesthetic masters such as Millard, Gillies, Converse, Menick, and Burget to arrive at the current state of unilateral forehead flap for nasal reconstruction, most commonly termed the paramedian forehead flap [5, 6].

The forehead flap is the most dependable and aesthetically acceptable reconstructive option for large nasal defects, particularly of the lower nose (5) [6, 7]. Due to the robust blood supply, this flap is extremely reliable and provides excellent restoration of function and cosmesis due to the comparable texture and adnexal composition of the forehead skin as compared to the nasal skin (5) [4, 7]. Since the forehead flap is the superior choice in appropriate defects by expert consensus, there is a paucity of data on relative efficacy of the forehead flap as compared to other reconstructive options (second intention healing, grafting, local flaps, etc.). The forehead flap is generally reliable, although certain factors can lead to suboptimal results in the form of vascular compromise [4, 18]. This includes excessive flap thinning, inadequate time between the first stage and takedown, and strangulation of the flap due to excessive torsion of the base of the pedicle. Aesthetically, inadequate results can be noted from insufficient distal flap thinning resulting in a bulky appearance, insufficient undermining of the recipient site leading to pincushion deformity, or inadequate structural support and nasal lining [19, 20]. Patient factors that lead to suboptimal outcomes include poor nutritional status, tobacco use, and inability to properly care for the surgical site prior to takedown [4, 16, 20].

Preoperative Evaluation

The preoperative assessment before consideration of forehead flap first involves determination if this reconstructive technique would be appropriate for the given patient. Generally, health status, age of the patient, and ability to receive appropriate postoperative care are at play. The forehead flap is a relatively rigorous surgery that necessitates multiple stages and thus requires commitment on the part of the patient. Additionally, the forehead flap is an excellent choice in situations where local nasal flaps or skin grafts would provide unacceptable cosmetic and functional outcomes (5) [4].

Prior to operating, patient health status should be optimized. Tobacco users should be counseled regarding the deleterious effects of nicotine on wound healing and flap viability [8, 9, 14, 20, 21]. Diabetics are at risk for tissue necrosis (3b) [1, 9, 22] and thus should be counseled to maintain tight glucose control. Individuals on anticoagulants or with hematologic disorders should be forewarned regarding bleeding risks, and internataional normaliszed ratio (INR) should be in reference range for warfarin users preoperatively. Doppler ultra-

sound may be utilized to confirm the supratrochlear artery location and path for traditional paramedian forehead flap design; however, this is typically not necessary and can be accomplished using anatomic landmarks (4) [15]. The use of Doppler might be of added benefit in cases where pedicle design approaches a 1 cm stalk, to assess blood supply when forehead scars are present, and in suspected abnormalities in vasculature (5) [4].

Relative contraindications for the forehead flap include anatomic issues that might compromise the blood supply to the flap. For example, presence of deep horizontal scars across the base of the forehead might impede adequate perfusion in a forehead flap (5) [4]. Interestingly, due to the robust collateral blood flow of the glabellar and mid-forehead region, previous history of a forehead flap is not a contraindication, as the contralateral side can be used. Lastly, as in the case of all therapies, comorbidities must be considered and risks and benefits weighed to deem appropriateness for forehead flap.

Best Techniques and Performance

The forehead flap, originally derived as a median forehead flap and now performed as a more streamlined and advanced paramedian forehead flap, is well-described in the literature. The basic techniques and execution of this reliable flap are rather consistent; however, numerous variations exist, which will be described herein.

Approaching the Defect

The first step involves addressing the extranasal portions of the defect. For example, if a defect extends onto the medial cheek, cheek advancement might be considered prior to performing a forehead flap to maintain and respect cosmetic subunits (Fig. 9.1) [4, 6]. Next, the defect to be repaired should be optimized prior to flap insertion. This involves creating a uniform base of the defect (generally dissected down to perichondrium or periosteum) and cleaning wound edges to debevel and create more squared off edges. Angular defects are less likely than curvilinear defects to result in trapdoor deformity through concentric scar contraction (5) [23]. The defect should also be adequately undermined to allow plate-like scar formation and further decrease risk of trapdoor or pincushion phenomenon (5) [4].

The principle of defect only versus subunit reconstruction is another consideration. If a defect involves great than half of a cosmetic subunit (Fig. 9.2), it might be prudent to excise the

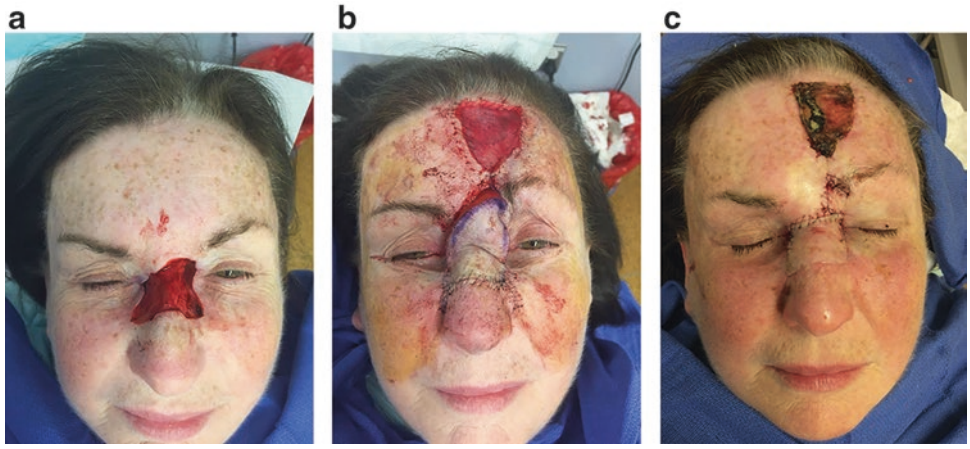

Fig. 9.1 An example of paramedian forehead flap design and execution. (**a**) A defect of the nasal bridge and bilateral medial cheeks following Mohs micrographic surgery for removal of basal cell carcinoma. (**b**) Bilateral cheek advancement and paramedian forehead flap were used to close the defect, addressing distinct cosmetic subunits. (**c**) Excellent contour achieved at takedown

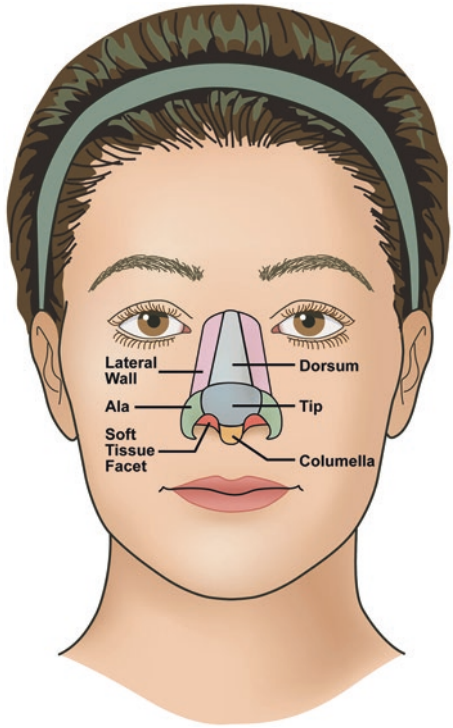

Fig. 9.2 An illustration of the subunits of the nose

remainder of the cosmetic subunit so that the entire subunit is replaced by the forehead flap (4) [3, 9, 24, 25]. This strategic control of the shape of the defect, the flap shape, and the resultant scars allows for favorable and inconspicuous results (5) [4]. However, the alternative perspective cautions against removal of excessive amounts of healthy skin and formation of larger defects (5) [8]. Randomized data is lacking on this topic given the variable and subjective nature of reconstructive surgery.

Addressing Nasal Lining

Next, nasal lining should be reconstituted in the case of full-thickness defects. If small, this can be closed primarily. In the case of larger defects, several techniques can be employed. Turndown flaps, such as the "hinge flap" or "bucket handle flap," have been described (5) (Fig. 9.3) [4, 26]. For defects that do not involve the free margin, split- or full-thickness skin grafts can be used.

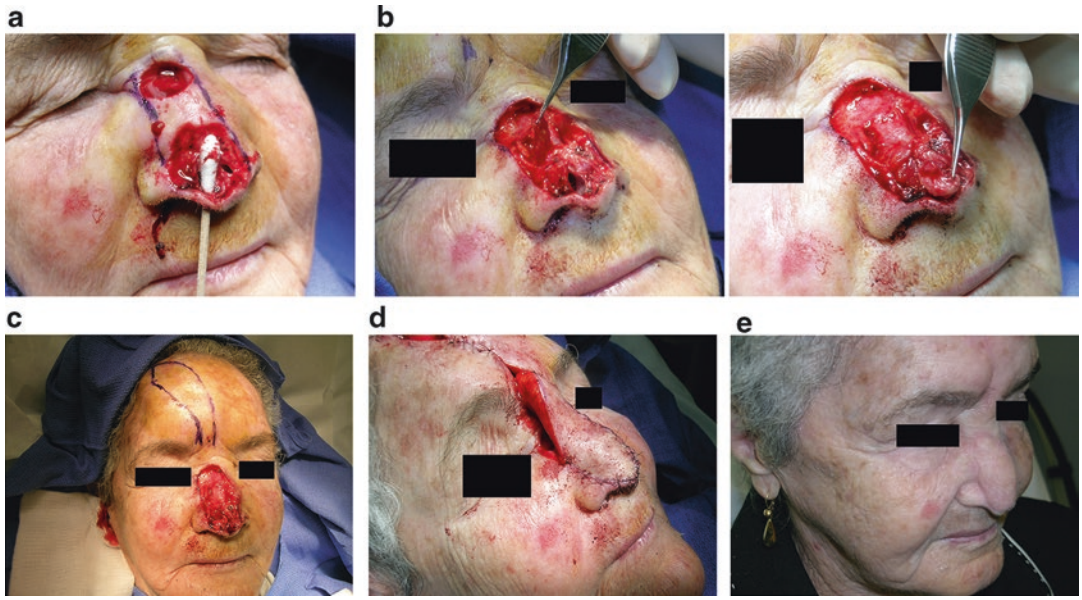

Fig. 9.3 An example of paramedian forehead flap design and execution addressing nasal lining, structural support, and cutaneous cover. (**a**) Following Mohs micrographic surgery for multiple basal cell carcinomas, patient left with full-thickness defect on the nasal root and a through and through defect on the nasal tip. (**b**) Hinge flap performed using "page of book configuration" to address nasal lining. (**c**) Following cartilage graft from conchal bowl, forehead flap design is illustrated. (**d**) Paramedian forehead flap sutured in place. (**e**) 8-month follow-up showing excellent functional and cosmetic outcome

Split-thickness skin grafts have a risk for contraction and nasal collapse, while full-thickness skin grafts carry a high risk of necrosis [26]. Full-thickness skin grafts should thus be ideally used when the forehead flap is placed directly on the graft's deep surface in the same stage to optimize contact and thus survival (5) [26]. A folded forehead flap may also be used to assist with reconstitution of nasal lining (5) [5].

Structural Support

Once nasal lining is restored, the framework and structural support must be addressed [6]. In the case of nasal reconstruction, this generally involves cartilage grafting (Fig. 9.3). The septum can be used as a donor site if exposed; alternatively, auricular cartilage is ideal with the use of templates for precision (5) [4, 9]. Of note, cartilaginous struts must be secured carefully to surrounding tissue so that they maintain adequate vascular supply. In the case of alar structural support, stab incisions allow for creation of pockets and use of tongue in groove placement [4, 9]. In more substantial defects, rib cartilage might be needed to recreate structural support [5].

Anatomic Considerations in Flap Design

The forehead flap design is considered next, and in this step, great variability exists. Despite the variations in technique, the premise of the forehead flap based in the robust vasculature of the medial forehead is the unifying element. Traditionally, the forehead flap has been deemed an axial flap based off of the supratrochlear artery [1, 6, 7, 9]. Shumrick et al. studied the supratrochlear artery and showed that the artery routinely exits the orbit at 1.7–2.2 cm from midline (3b) [2]. Further study has demonstrated that the supratrochlear artery lies directly beneath the glabellar frown line in nearly 50% of cases and within 6 mm lateral to the frown line in the remainder (3b) [27]. This provides another reliable landmark; stalk design can thus center around this anatomic landmark, with a total width of 1–1.2 cm (average, 10.9 mm) [27]. As mentioned previously, Doppler ultrasound is not necessary for confirmation of supratrochlear artery location and path for traditional paramedian forehead flap design [15, 26].

While long-standing dogma exists that the forehead flap is based off of the supratrochlear artery, multiple studies have shown the complex and vessel-rich nature of the medial forehead, including supraorbital, supratrochlear, infratrochlear, dorsonasal, and angular arteries (Fig. 9.4) [28–31]. McCarthy et al. [32] demonstrated filling of the dorsal nasal arteries after ligation of the supratrochlear and supraorbital arteries; these were felt to be terminal branches of the facial artery and of sufficient quality to supply vertically oriented forehead flaps (3b). An extensive central forehead cadaveric study in 2007 performed on 60 hemiheads confirmed localization of the supratrochlear artery 5 mm medial or lateral to the medial canthal line (3b) [28]. Additionally, medial to the supratrochlear artery, numerous axial vessels were identified that supplied the central forehead and glabellar region, termed the central and paracentral arteries [28]. Faris et al. [22] subsequently studied three forehead flap designs (classic paramedian, glabellar paramedian, and central artery flap design), finding that the central artery forehead flap was as reliable in terms of vascularity as the glabellar and classic paramedian forehead flap (3b). This more midline approach is associated with less transposition of frontal hair than its more laterally based counterparts [22]. Further supporting the success of variably localized forehead flaps, Stigall et al. [15] reported equivalent outcomes in paramidline versus Doppler-based paramedian forehead flaps, with no significant difference in flap survival or complication rates (3b). Interestingly, in both groups, small arteries predominated, with large arteries infrequently identified; number and size of arteries did not correlate to flap survival. Ultimately, this study deemed that the complex vascular plexus of the glabella was responsible for the success of the flap rather than a single axial vessel [15].

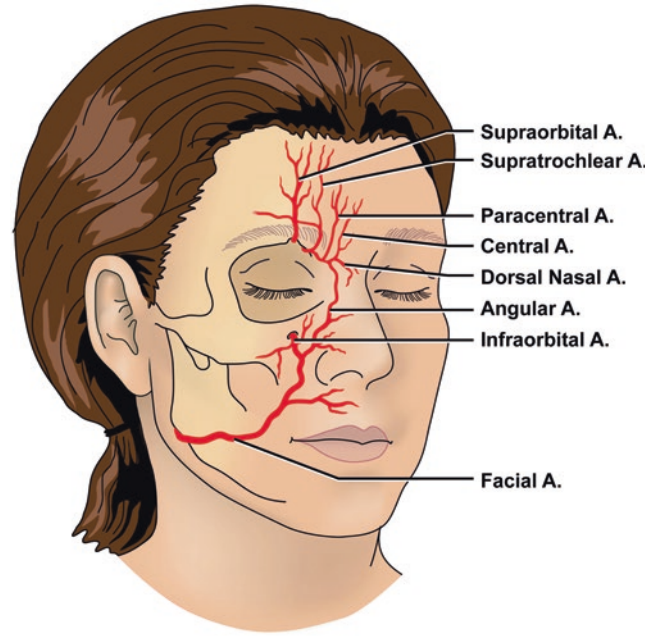

Fig. 9.4 The vasculature of the glabellar complex. The anastomoses of the supraorbital, supratrochlear, paracentral (angular artery (AA) continuing superiorly medial to the medial canthus), central, dorsonasal, and angular arteries create a vascular plexus that allows for reproducible reliability of the forehead flap

Flap Elevation and Insetting

Once the path of the forehead flap has been established, the defect is templated to the upper forehead, ideally avoiding hair-bearing skin, and distance is measured to achieve adequate reach of the flap. Incisions are made using the rule of thirds. The distal third is maintained at the level of the superficial fat plane, and the middle third dives to the plane between fat and pre-muscular fascia, while the proximal third plunges superficial to the periosteum. Careful dissection to the orbital rim, in addition to maintaining a narrow pedicle stalk, allows for adequate reach and decreased risk of torsion (5) [4]. The base of the pedicle ranges from 1 to 1.5 cm (5) [4, 6]. Generally, midline defects can be repaired from either left- or right-sided stalks. Lateral defects are optimally repaired with ipsilateral pedicles, to decrease the reach of the stalk (5) [33]. Nevertheless, other surgeons prefer a contralateral approach in an effort to decrease torsion on the base of the pedicle; these two principles of reach and torsion are in opposition of one another and are generally dependent on the surgeon's preference and the patient scenario. Variations on the traditional vertically oriented forehead flap include those that cut transversely once the upper forehead has been reached or slant across the forehead; the benefit is added length, while the downside is decreased vascular reliability and thus increased risk of necrosis [33]. Frequently, the benefit of added length can lead to flap design into hair-bearing skin; in this case, the benefit of greater reach for optimal flap design outweighs the hair's presence on the nose. At the time of flap incision, these hair bulbs can be individually cauterized or postoperatively removed using laser, shaving, or plucking [16, 33].

After elevation of the flap and adequate distal thinning, the flap can be sutured in place using well-placed dermal and epidermal sutures. The superior portion of the nasal defect is not sutured to allow adequate blood flow to the distal flap. The forehead defect is closed in a layered fashion as much as possible following undermining in the submuscular plane [4]. Excessive tension may result in a higher risk of necrosis [13]. Many times, the superior aspect of the defect is left to heal by second intention [4, 16]. Alternatively, a porcine xenograft may be used to facilitate wound healing of the forehead defect and assist in hemostasis. It is important to avoid excessive

suturing inferiorly on the forehead as to avoid impingement on the vascular pedicle [13].

A novel technique was recently published by Ullmann et al. [34] in which a subcutaneous forehead lift was performed to allow direct visualization of the supratrochlear vessels resulting in a thinner flap as well as ability to more easily close the donor site. This technique involves incision along the hairline and subcutaneous dissection of the forehead skin. The flap is tailored by turning the forehead onto the nasal defect. The donor site is closed with rotation and advancement of the remaining lateral portions of the forehead flaps toward midline (4).

Takedown

The takedown of the pedicle classically occurs 3 weeks following the initial stage in a traditional two-stage procedure (4) [6]. This duration generally allows for adequate neovascularization from the recipient nasal tissue to the flap. The various stages of the forehead flap are illustrated in Figs. 9.1, 9.3, and 9.5. Modifications in the takedown and number of stages have also been discussed at length. In high-risk individuals, such as smokers and poorly controlled diabetics, a three-stage flap may be more seriously considered, with final takedown at 6 weeks (4) [22]. Other suitable candidates for this technique include repairs requiring complex contouring or major defects involving multiple subunits (3b) [6, 33]. In this situation, the forehead flap may be elevated with all its layers, including frontalis, to maintain maximal vascular viability. Then, thinning occurs at 3 weeks after the initial stage. This involves elevation of the skin of the flap with minimal subcutaneous fat and subsequent debulking of the fat and frontalis to optimally contour the nasal topography. The skin is then inset and sutured in place, with the additional benefit of quilting sutures.

Some research shows that pedicle division can occur even at 1 week after the initial stage, particularly in young, healthy patients who would be

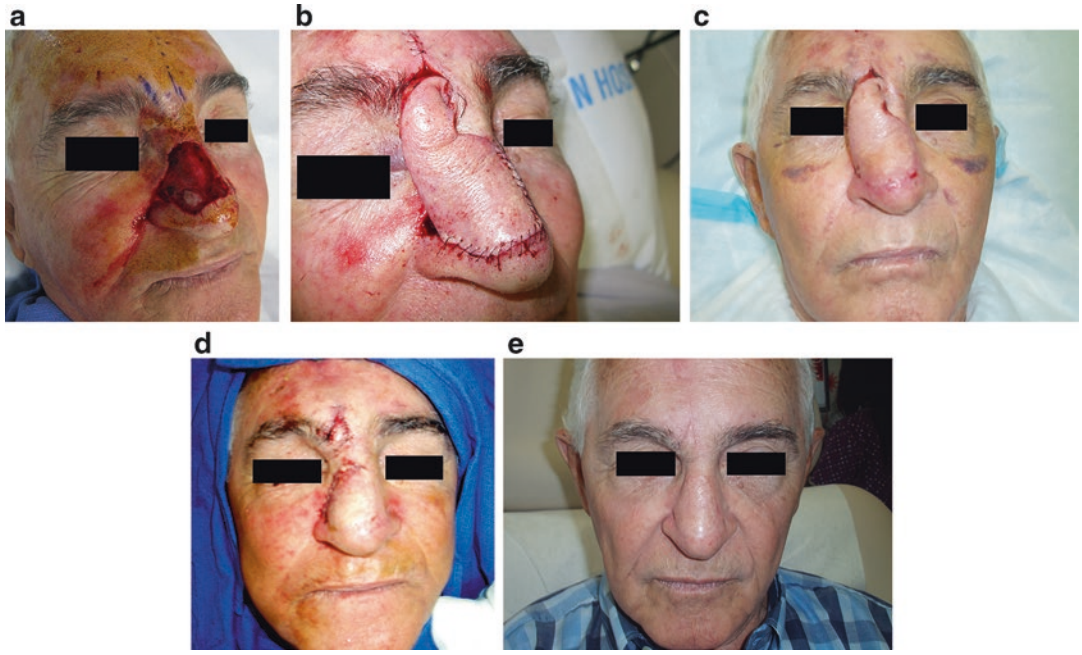

Fig. 9.5 An example of paramedian forehead flap design and execution. (**a**) A defect on the right nasal sidewall and dorsum from Mohs micrographic surgery. (**b**) Paramedian forehead flap was sutured in place in the first stage, with good results at 1-week postoperative visit (**c**). (**d**) Takedown was performed at 3 weeks following the first stage, with favorable long-term cosmetic and functional outcome (**e**)

negatively affected by prolonged presence of the external trunk (4) [18, 35]. In these cases, takedown occurs at 1 week, with subsequent debulking and contouring at 3 weeks; therefore, this becomes a three-stage procedure. During the third stage, the superior portion of the flap might require debulking to achieve a more appropriate match of thickness. The base of the pedicle is excised during the second stage, with goals to reposition the eyebrow after its medial and downward displacement. The use of laser-assisted indocyanine green (ICG) angiography to assess flap perfusion has also been reported with takedown performed 2 weeks after the first stage. In this report, an ischemic threshold of 25–30% was used intraoperatively, together with surgical judgment, to allow earlier pedicle division in low-risk patients, thus reducing the morbidity of eyebrow displacement (3b) [36].

Single-stage forehead flaps can also be considered in certain occasions. This procedure is generally employed in unique patient populations, such as mission work that does not allow multiple repeated procedures, elderly patients, or those who do not tolerated a pedicle (4) [37, 38]. Originally, this was performed by tunneling a flap pedicle under dorsal nasal skin (4) [39]. Side effects of venous obstruction were noted. Modification of this technique included transection of the procerus muscle and wide undermining of the glabellar complex (3b) [40]. Single-stage procedures can also avoid skin tunneling and be performed as transposition flaps (4) [37]. The benefit is avoidance of the burdens of an external pedicle, such as bleeding, inability to wear glasses, and more challenging dressing changes [37].

Safety

Overall, the forehead flap is successful due to its excellent blood supply. The most common complications include bleeding, postoperative pain, infection, and, less likely, superficial necrosis or epidermolysis [14, 19]. Flap edema and vascular congestion can also be noted in the short-term postoperative period [9, 13]. Flap failure in the form of necrosis is rare given the robust blood supply of the forehead flap. A study of 290 paramedian forehead flaps at a single center quoted the most common complication of bleeding among 33 patients, all within 24 h of the procedure, and not requiring hospitalization (3b) [14]. This same study identified 11 cases of necrosis (3.8%), ranging from total full thickness in 2 cases to 6 cases of partial thickness of the flap; 8 of these 11 were tobacco users [14]. Paddack et al. [20] reported an overall paramedian forehead flap failure rate of 6.1% among 82 patients, with a complete failure rate of 1.2% (4), similar to Little et al.'s [41] overall and complete failure rate of 4.9% and 1%, respectively, in a series of 205 patients (4). While Little et al. [41] did note statistical significance between smoking and flap failure, Paddack et al. [20] did not replicate these findings, although five of six failures were in smokers. Rohrich et al. [8] reported 1.7% necrosis risk among 532 paramedian forehead flaps (4). In another large retrospective study of 187 paramedian forehead flaps, partial necrosis rates of 3.4% and 5% were identified in two-stage and three-stage flaps, respectively (4b) [42]. In other studies, tobacco use is commonly implicated in partial flap loss (4) [8, 20, 21].

Long-term complications include pincushioning and trapdoor deformity resulting from inadequate thinning of the distal flap or insufficient undermining of the recipient site [13, 20]. Furthermore, contracture causing retraction or notching of the ala can be noted. The maintenance of nasal patency is of utmost importance as well, to maintain a clear nasal pathway through the nasal valve; this is greatly facilitated through the use of cartilage struts to preserve structural support of the nose [16]. Nevertheless, complications of nasal obstruction are occasionally observed [9, 20].

Lastly, while the emphasis is placed on the aesthetic outcomes and complications associated with the nasal defect and its repair, patients should also be made aware of associated sensory changes due to forehead incisions that disrupt the supratrochlear neurovascular bundle. Patients can be counseled that these deficits are usually temporary.

Postoperative Care and Follow-Up

Postsurgical cares for forehead flaps involve achieving adequate hemostasis, frequent follow-up, and excellent wound care. Once hemostasis is successfully obtained, the pedicle should be wrapped with nonstick gauze, and a 24-hour postop check should be performed. The use of porcine xenografts has been advocated to optimize pedicle care in interpolated flaps (4) [47]. The xenograft is sutured in place around the exposed pedicle taking care to avoid compromising the vascularity of the pedicle [47]. Gelatin sponges can also be applied directly to the unepithelialized surface of the pedicle as a hemostatic tool (4) [48]. In cases of suspected vascular compromise, topical nitroglycerin paste every 4–6 h can be used, although benefit has not been shown in the literature (4) [9].

Postoperative and/or preoperative antibiotics are recommended in the case of forehead flaps [4, 14, 16]. Flap takedown generally occurs at 3 weeks. However, time range of takedown varies from 1 to 6 weeks [22, 36]. Some surgeons prefer to perform a flap refinement at 3 weeks with takedown at 6 weeks [6, 49]. The details of the various takedown modifications are outlined above.

Follow-up occurs over several months, in addition to suture removal 1 week after each stage. Several months following takedown, the patency of the nasal airway can be assessed. Revisions can be considered on a case-by-case basis. Excessive bulk of the flap can be addressed with surgical revision. Intralesional corticosteroids can also be used to minimize pincushioning or excessive flap thickness [9, 14, 19, 21]. Nonsurgical options for scar revision include resurfacing procedures and/or vascular lasers [1]. Dermabrasion and fractionated CO_2 laser can reduce hypertrophic scarring (4) [14, 50].

Alternative Procedures and Modifications

Alternatives to the forehead flap include grafting and local skin flaps. However, when considering sizeable defects of the nose, none of these options are comparable in quality to the paramedian forehead flap [5]. The melolabial interpolation flap can be considered for laterally based smaller alar defects in patients with good cheek skin laxity [8, 43].

Modifications

While there are no excellent alternatives to the forehead flap, various subtle modifications exist in forehead flap design. One such modification, named the cross-paramedian forehead flap, provides a smoother arc of rotation, increased length, and avoidance of any eyebrow distortion. The flap begins axially, but as it traverses across the forehead, the distal portion is random pattern. The pedicle is based on the contralateral side to decrease the arc of rotation (4) [21].

For extensive nasal defects encompassing the majority of the nose, bilateral paramedian forehead flaps can be used. The initial forehead flap is used for recreation of the nasal lining, with a subsequent stage involving the opposite side paramedian forehead flap for the external nasal repair in a later stage (4) [44]. This is particularly useful when intranasal local flaps are not favorable or in the case of patients with extensive tobacco abuse history, where the reliable axial blood flow of the forehead flap creates an advantageous vascular environment [44].

The principle of vascular delay can also be employed in forehead flaps, particularly in high-risk populations, such as heavy tobacco abusers, poorly controlled diabetics, and patients with history of irradiation (4) [1, 8, 9, 16, 45, 46]. This involves an intermediate phase prior to flap transfer aimed at improving blood flow into transferred tissue. Technical execution involves elevation of the flap with vertical incisions, and subsequent epidermal suturing back into the native bed, producing relative ischemia to the flap with sustained axial blood flow. The proximal and distal ends of the flap are left intact until the flap is transferred 7–14 days later (4) [45, 46]. The mechanism of action is felt to involve development of a hyperadrenergic state upon severing sympathetic innervation, creating relative ischemia of the tissue and metabolic changes allowing for increased flap survival. Additionally, neovascularization is

observed through angiogenesis [1, 45, 46]. In the indicated situations, the benefit of higher chance of flap success can outweigh the additional surgeries and time.

Conclusions

For reconstruction of large and complex nasal defects, the forehead flap is frequently the optimal choice. Although this flap requires multiple stages, its reliability and texture match provides consistent and cosmetically pleasing outcomes for patients. With numerous modifications, variations, and nuanced techniques, the forehead flap can be fine-tuned and tailored to address the depth and extent of nasal defects in each unique patient situation. By understanding the anatomy, flap design, and execution, as well as acknowledging patient-specific challenges, facial reconstructive surgeons can confidently achieve excellent function and aesthetics through the forehead flap.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
The forehead flap is the optimal reconstructive option for medium to large defects of the nose and can also be used for periocular defects.	C
The forehead provides an excellent texture and adnexal quality match for nasal reconstruction.	C
The rich vasculature of the medial brow and central forehead is responsible for the high success rate of this flap. The supratrochlear artery has traditionally been felt to be the main blood supply to the paramedian forehead flap; however, collateral axially oriented vessels allow for reinforced blood supply and ultimate reliability of this flap.	B
This interpolated flap is generally performed in two to three stages. Three stages are utilized in higher-risk patients, such as tobacco users, or in more substantial nasal defects.	C
The use of vascular delay can be a valuable tool for forehead flap reconstruction in patients who are considered high risk for flap necrosis.	C
Disadvantages include need for multiple stages, alteration of medial brow placement, and donor site scarring.	C
Complications include postoperative bleeding, flap necrosis, pincushion deformity, and impaired nasal valve function.	C
Doppler ultrasound is not necessary for forehead flap planning; anatomic landmarks can be used with success.	B
The subunit principle can allow for more strategic defect control and more favorable reconstructive outcomes.	D
The forehead defect can be closed primarily; any portion that remains can be left to heal by second intention.	D
Takedown ranges from 1 to 6 weeks following the first stage.	C
Flap necrosis is rare due to the excellent blood supply of the forehead flap and ranges from 3% to 6%.	C

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Self-Assessment Questions

1. What technique and flap modification can be utilized in cases considered at high risk for flap necrosis?
   (a) Hinge flap.
   (b) Postoperative porcine xenograft surrounding pedicle.
   (c) Subunit principle.
   (d) Takedown at 1 week.
   (e) Vascular delay.
2. What is the approximate rate of flap necrosis in paramedian forehead flaps?
   (a) 0%; the flap never fails
   (b) 5%
   (c) 10%
   (d) 15%
   (e) 20%
3. What is the current presumed role of Doppler ultrasound in paramedian forehead flap design?
   (a) Doppler can be beneficial in certain cases, but is not necessary for flap design or success.
   (b) Doppler is necessary for confirming flap viability and course.
   (c) Doppler is used to identify the supraorbital artery in paramedian forehead flap design.
   (d) Doppler provides no benefit in forehead flap design.
   (e) Doppler use increases the width of the forehead flap.
4. What is the most appropriate reason for creating a slanted forehead flap extending diagonally rather than vertically?
   (a) To access skin of greater adnexal quality match.
   (b) To avoid disturbance of vertically oriented nerves.
   (c) To create a more appealing and aesthetic scar.
   (d) To follow the path of the supratrochlear artery.
   (e) To increase flap length.
5. What is the typical width of the stalk of the forehead flap?
   (a) Less than 0.5 cm.
   (b) 0.5–1 cm
   (c) 1–1.5 cm
   (d) 1.5–2 cm
   (e) Greater than 2 cm.
6. Which patient factor puts the forehead flap at greatest risk of necrosis?
   (a) Diabetes.
   (b) Hematologic malignancy.
   (c) Hypertension.
   (d) Poor nutrition.
   (e) Tobacco use.

Correct Answers

1. e: Vascular delay. Although the mechanism is not entirely understood, adrenergic response, angiogenesis, and changes in tissue metabolism are felt to contribute to increased viability of flaps using vascular delay. The other answer choices are modifications in technique used in forehead flaps. A, B, and C are not generally associated with increased or decreased risk of tissue necrosis. D is not generally utilized in patients at risk for necrosis; rather a longer interval between stages would be elected.
2. b: 5%. Reports range from approximately 3% to 6% rate of necrosis.
3. a: Doppler can be beneficial in certain cases, but is not necessary for flap design or success. Doppler ultrasonography can be used to trace the path of the supratrochlear artery and verify its localization on the forehead, but is not necessary in forehead flap design. Recent studies have shown that using anatomic landmarks is sufficient in creating a reliable forehead flap. Additionally, the vascular plexus and anastomoses of various axial vessels, including supratrochlear, supraorbital, and dorsal nasal arteries, are responsible for the reproducible success of the forehead flap.
4. e: To increase flap length. Other reasons for slanting or diagonally orienting the forehead flap are achieving a smoother arc of rotation, avoidance of eyebrow distortion, and avoiding transfer of hair-bearing skin.
5. c: 1–1.5 cm.
6. e: Tobacco use. While the evidence is mixed and some studies do not show statistical significance, tobacco use is most associated with risk of both partial- and full-thickness necrosis.

Cartilage Transfers

10

Julie Jefferson and David Zloty

Abstract

In dermatologic surgery cartilage transfers are widely used in auricular, nasal, and eyelid reconstruction in both children and adults (2a) (Liu and Cao, Chapter 20: Repair, grafting, and engineering of cartilage. In: Neligan PC (ed) Plastic surgery: volume 1, principles, 3rd edn. Elsevier, New York, p 398–424, 2013; Otley and Sherris, J Am Acad Dermatol 39:982–992, 1998). Other indications for use include nipple reconstruction, rhinoplasty, and chin contouring (Liu and Cao, Chapter 20: Repair, grafting, and engineering of cartilage. In: Neligan PC (ed) Plastic surgery: volume 1, principles, 3rd edn. Elsevier, New York, p 398–424, 2013). Experience with cartilage grafting is extensive in reconstructive surgery, complications are uncommon, and results are typically excellent (Otley and Sherris, J Am Acad Dermatol 39:982–992, 1998). Cartilage grafts serve two primary purposes: to restore natural contour and architecture to a site of cartilage loss and to preserve a free margin position against the contractural forces of wound healing (Otley and Sherris, J Am Acad Dermatol 39:982–992, 1998). Both structure and function of key free margins can be optimized with well designed and executed cartilage grafting (Otley and Sherris, J Am Acad Dermatol 39:982–992, 1998).

Keywords

Cartilage · Graft · Composite grafts · Costal cartilage · Septal cartilage · Cartilage transfers

Indications for Cartilage Transfers

In dermatologic surgery cartilage transfers are widely used in auricular, nasal, and eyelid reconstruction in both children and adults (2a) [1, 2]. Other indications for use include nipple reconstruction, rhinoplasty, and chin contouring [1]. Experience with cartilage grafting is extensive in reconstructive surgery, complications are uncommon, and results are typically excellent [2]. Cartilage grafts serve two primary purposes: to restore natural contour and architecture to a site of cartilage loss and to preserve a free margin position against the contractural forces of wound healing [2]. Both structure and function of key free margins can be optimized with well designed and executed cartilage grafting [2].

Cartilage is classified into three types: (1) elastic cartilage, (2) fibrocartilage, and (3) hyaline cartilage [1, 3]. Elastic cartilage is primarily found in the structure of the outer ear and also in

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the larynx and epiglottis [1, 3]. It is characterized by high elasticity and great flexibility that can withstand bending owing to its large network of elastic fibers intertwined with collagen fibers [1, 3]. It is surrounded with perichondrium [1, 3]. Fibrocartilage, composed of thick bundles of collagen fibers along with intervening unicellular islands, has high tensile strength and serves to support structures that are subjected to frequent stress such as intervertebral discs, menisci, symphyseal joints, and joint portions of bone, tendon, and ligaments [1, 3]. Hyaline cartilage is built to withstand compressional loading and is characterized by stiffness as it is rich in glycosaminoglycans [1, 3]. It is the most common type of cartilage and is found in nasal, costal, articular, and tracheal cartilage [1, 3]. Hyaline cartilage is covered with perichondrium with the exception of articular cartilage [1, 3].

Partial- or full-thickness nasal alar defects that compromise the rigid alar form can result in medial sagging due to contractural wound healing [2]. Indeed, even modest nasal valve constriction can cause objectionable airway obstruction without appropriate cartilage support [2]. The need for cartilage support can be assessed by compressing the contralateral ala with a finger while the patient inspires deeply in supine position. If the ala exhibits increased collapse relative to the contralateral ala on deep inspiration, cartilage grafting should be considered to avoid issues with both form and function. Similarly, if airway obstruction of a nasal sidewall defect is apparent, cartilage grafting should be considered to avoid nasal valve obstruction.

Indications for cartilage repair of large auricular defects include cosmesis as well as providing support for the purpose of eyeglasses, or hearing aids [2]. Partial-thickness lower eyelid defects with tarsal plate loss but preservation of the conjunctiva are at risk for contraction and ectropion without cartilage grafting [2]. Pulling down on the eyelid skin to gauge lid laxity can be performed to assess the need for possible cartilage grafting.

Demographics Very little demographic data is available in the literature concerning patients treated with cartilage grafts. From our personal experience, patients requiring cartilage transfers are typically elderly (mean age 67) with Fitzpatrick 1–3 skin and advanced tumors extending through cartilage on the nose or ear. More specifically, no data is available correlating age to success of cartilage transfer. Given the broad range of applications for cartilage transfer, all age and ethnic groups can benefit from the procedure.

Effectiveness of Cartilage Transfers

The first autologous cartilage graft was reported in 1896, but cartilage grafting has only gained the favor of dermatologic surgeons over the past 20 years [2, 4]. Notably, cartilage has a low metabolic rate owing to its relatively sparse cell population and avascular structure [1]. The tissue is primarily sustained through diffusion and its oxygen consumption and glycolytic activity nears anaerobic levels [1]. Hence, cartilage grafts can be associated with long-term survival rates of up to 95% after 20 years (2a) [2, 5]. In addition, covering a cartilage graft with a microvascularly transferred interpolation flap, which provides a robust blood supply to the graft, can increase graft survival to greater than 97% (4) [1, 6].

Beyond what has been outlined above, the cartilage and skin survival percentages for the different clinical uses of cartilage transfer are not available in the literature. Within the author's own surgical center, survival rates have been estimated by careful photographic assessment of almost all of their cartilage transfers over the past 20 years. Cartilage used as a support for a wound healing by secondary intention or as a structural support under transposition or interpolation flaps have demonstrated greater than 95% survival. Cartilage used to support or provide volume under a full-thickness skin graft has exhibited approximately 90% survival, while the overlying skin has a greater than 80% survival in 75% of the cases. Composite grafts of skin and cartilage harvested from the ear and used to correct full-thickness nasal tip/ala defects have shown 80% survival of cartilage and 70% survival of associated skin (5).

Preoperative Evaluation

The preoperative consultation is integral to the success of a potential cartilage graft. Obtaining a thorough medical history, assessing the cartilage donor site for necessary characteristics including degree of memory and pliability, assessing the recipient site for size and necessary contour, and discussing the surgery in detail with the patient can reduce surgical complication risk and improve the physician-patient relationship. The patient should be informed of the possible treatment options, complications, and the expected postoperative course (2a) [7, 8].

A preoperative questionnaire inquiring about past medical and surgical history, allergies, medications, responses to prior procedures, and social and family history completed by the patient prior to the consultation can facilitate the visit and provide useful information in a concise manner. The questionnaire can also help the physician allocate the appropriate amount of visit time to addressing potential complications and prevention planning [7].

Patients with diabetes can be assessed for disease control with a random or fasting blood glucose level and hemoglobin A1C. Diabetics, smokers, and patients with ischemic heart disease have compromised microvasculature and are at an increased risk of delayed wound healing, wound dehiscence, and wound necrosis particularly of flaps or grafts [7, 8]. It is important that disease is under good control. For diabetes, the physician should also be keen to monitor for signs of hypoglycemia throughout the procedure [8]. Sweetened juices or glucose tablets should be on hand at the time of the procedure [8]. Ideally, patients should discontinue smoking prior to surgery and during wound healing. If they are unwilling or unable to completely discontinue smoking, consumption should be decreased to less than 1 PPD for 1 week prior to surgery and for 3–4 weeks afterward [7]. Sublingual nitroglycerin should be readily available for patients with a history of ischemic heart disease or angina [7].

Hypertension is another disease that should be well managed at the time of the procedure. When under poor control, hypertension can lead to an increased risk of intraoperative and postoperative bleeding (2b) [8, 9]. The patient's blood pressure should be checked prior to the procedure on the operative day and it may be necessary to postpone the surgery for systolic pressures over 180 mmHg and diastolic pressures over 100 mmHg [7].

In general, medically necessary anticoagulants should be continued (2a) [7, 10]. However, it is important to note that guidelines cannot adequately address the particulars of all patient scenarios, and clinical judgment has a key role in the consideration of all patient care factors. If the patient is on warfarin per physician order or due to history of myocardial infarction (MI), angina, or transient ischemic event, an INR should be obtained [7]. An INR between 2 and 3.5 is acceptable for surgery [7]. Patients who are on aspirin for pain control or to prophylactically prevent an MI or stroke can discontinue the medication 7 days prior to the procedure [7]. Similarly, NSAIDs should be discontinued 3 days prior to the procedure [7]. Both aspirin and NSAIDs may be resumed 3 days postoperatively [7]. It is important to note that patients on aspirin with a normal bleeding time appear to have no increased risk of complications [7].

It is recommended that patients who drink socially discontinue consumption 48–72 h prior to surgery to prevent unnecessary bleeding [7]. Patients who suffer from alcoholism should be asked to decrease their consumption if possible, but not discontinue completely, as this may precipitate life-threatening alcohol withdrawal symptoms [7].

Best Techniques and Performance

An auricular cartilage graft composed of elastic cartilage is quite versatile as it can be easily contoured into different shapes for a variety of purposes [1]. In addition, auricular cartilage is easily accessible, and the distinct contours of different portions of the ear can be quite useful for certain reconstructions [1, 2]. The conchal bowl and antihelix donor sites are used most

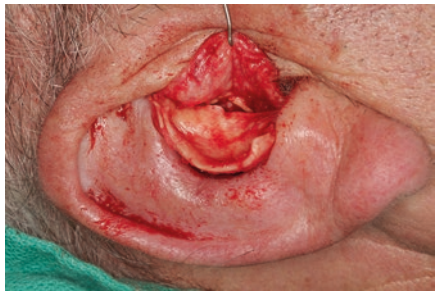

Fig. 10.1 Conchal bowl cartilage harvested using an anterior approach

commonly [2]. An anterior or posterior approach can be taken when harvesting cartilage from the ear (Fig. 10.1) [1, 2]. Local anesthesia should be injected into the perichondral plane both anteriorly and posteriorly, and then the skin hydrodissected off the cartilage [2]. When harvesting conchal bowl cartilage anteriorly, the incision should be made along the inner aspect of the antihelical fold to expose the conchal cartilage [2]. The cartilage can be harvested using either a No. 15 or 11 blade or fine scissors [2]. Auricular cartilage should be harvested gently as it can be susceptible to fracture with excess tension [2]. When harvesting antihelix cartilage, care must be taken to leave adequate residual cartilage to prevent helical distortion [2]. Composite chondrocutaneous grafts are harvested by performing a wedge excision from the helical rim and closed primarily [10]. In particular, the junction of the anterior helical rim adjacent to the cheek is ideal for alar composite grafts [2]. After the cartilage has been harvested, accurate and precise hemostasis should be obtained and the incision site sutured [2].

Other cartilage donor sites include nasal septal cartilage and costal cartilage [2].

In dermatologic surgery, septal cartilage harvesting is primarily an option in instances of full-thickness nasal defects that provide direct access to the septum [2]. Septal cartilage can also be harvested as a free graft after elevating a mucoperichondrial flap [2]. In order to perform a mucoperichondrial flap, a unilateral mucosal flap is elevated and cartilage is harvested directly from the septum with a scalpel through the nostril [2]. The mucoperichondrial flap is sutured through and through to the residual contralateral mucosa [2]. One centimeter of both caudal and dorsal septal cartilage should be left intact to provide adequate nasal support and prevent morbidities such as saddle-nose deformity and columellar retraction [2].

Costal cartilage harvesting is rarely performed by dermatologic surgeons and comes with increased risks of morbidity when compared with septal and auricular harvest sites [2]. Risks include pneumothorax and postoperative atelectasis, which must be excluded by a postoperative chest x-ray (2b) [1, 2, 11]. Costal cartilage does provide a large cartilage reservoir that can be utilized when performing complete auricular reconstruction [1, 2], as well as reconstruction of significant saddle-nose deformity (4) [12], nipple reconstruction (2b) [13], septorhinoplasty(4) [14], tracheal reconstruction (4) [15], and treatment of maxillonasal dysplasia (Binder's syndrome) (4) [16]. Cartilage is typically harvested from the sixth, seventh, eighth, or ninth ribs through an oblique incision made superior to the desired costal margin [2]. Muscular attachments must be freed from the cartilage prior to removal [2].

Following the harvesting of the cartilage graft, excess soft tissue should be removed [2]. There is no general consensus on whether or not to remove perichondrium, but we prefer to leave it in place as does Otley and Sherris [2]. However, tumefactive graft proliferation was noted by Reiter et al. in four cases, and they recommend that the perichondrium be removed to avoid this complication (4) [17]. Grafts can then be shaped carefully to fit [2]. Grafts can be crushed with a cartilage press or nicked at the lateral edges to improve pliability although this may increase the risk of fracture and/or graft viability [2].

Nose

Cartilage grafts for nasal alar defects can be placed in 2–3 mm-deep recipient pockets that can be made with a scalpel (or undermining scissors depending on surgeon preference) for each of the distal ends [2]. After inserting the tips of the graft into the

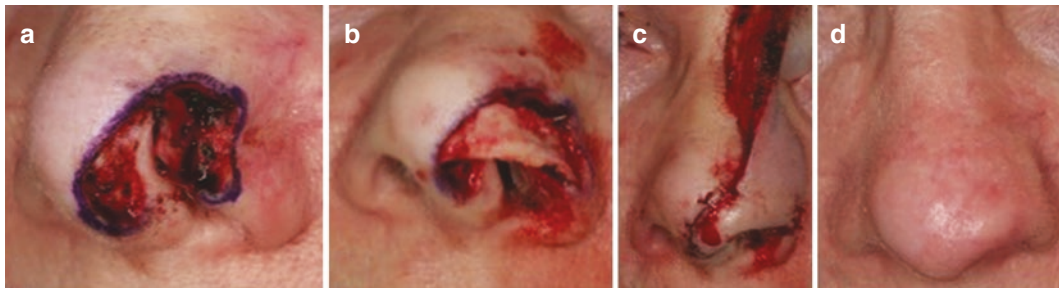

Fig. 10.2 (**a**) Nasal defect following Mohs surgery. (**b**) Placement of cartilage graft. (**c**) Placement of paramedian forehead flap atop cartilage graft. (**d**) Surgical outcome after 1 year

recipient pockets, the graft should be secured into place with absorbable suture [2]. Preferably the graft is then covered with a transposition or interpolation flap. Less desirable is coverage with a skin graft, which when placed over avascular cartilage is prone to necrosis (Fig. 10.2) (4) [2, 18, 19]. When using cartilage grafts to repair full-thickness alar defects, it is important to repair or reconstruct a vascularized mucosal lining to improve the chances of the cartilage graft survival [2]. Full-thickness composite grafts from the anterior helix can be used to reconstruct some full-thickness alar rim defects, but given their bulk and complex composition, these grafts have high metabolic demands (4) [2, 20]. It is recommended that these composite grafts not exceed 1.5 cm in diameter to minimize the risk of ischemia and necrosis [20]. For nasal sidewall defects, cartilage grafts should generally extend from the dorsal septal cartilage to the maxillary bone or soft tissue of the nasofacial sulcus [2]. Another option to repair small- to medium-sized defects of the alar subunit that do not involve the alar margin is a free cartilage graft followed by secondary intention healing (4) [21].

Reconstruction of the nasal tip can include several cartilage grafts which can be secured to one another for enhanced stability with absorbable suture [2]. Bilateral lateral nasal cartilage batten grafts can be placed proximally and secured between the maxillary bone and dorsal septal cartilage [2]. A dorsal nasal cartilage graft is often placed to provide the nose with a smooth contour [2]. Distal structural support can be provided with a columellar strut graft secured to the anterior nasal spine and between the medial crural feet, or to the caudal end of the septum when medial crural feet have been resected [2]. Atop the columellar strut graft, a tip graft is often employed to improve the aesthetic projection of the nose [2]. Alar batten grafts secured from recipient pockets created in the lateral alar soft tissue as described above can be secured medially to the columellar strut graft [2].

Ear

Large helical defects can be repaired with cartilage grafts followed by overlay with a cutaneous flap, or less commonly, by the use of composite grafts (4) [20, 22]. As with composite grafts of the alar rim, the maximum recommended diameter is 1.5 cm [20].

Eyelid

Full-thickness defects of the lower eyelid are frequently repaired with a tarsoconjunctival flap from the apposing eyelid rendering cartilage grafting unnecessary. However, placement of an auricular cartilage graft with attached perichondrium in contact with conjunctiva followed by a vascularized cutaneous or musculocutaneous flap is another option that works well (4) [23]. The cartilage graft should be sutured to the free edges of the remaining tarsal plate with buried absorbable suture. Reepithelialization of any exposed perichondrium can take up to approximately 3 weeks depending on size.

Other reconstruction options include auricular chondrocutaneous composite grafts, but again, given the high metabolic demands, composite grafts are susceptible to ischemia and subsequent necrosis [20].

Safety

Complications of cartilage grafts are rare [2]. Risks associated with cartilage grafting include resorption, deformation, or displacement of the graft after placement and extrusion [2]. Recipient sites such as the ear that are frequently subject to trauma or movement are at an increased risk of resorption [2]. Depending on recipient site, resorption can result in helical notching, ectropion, alar retraction, or nasal collapse [2]. Placing a cutaneous flap with good vascularity overtop of a cartilage graft is currently thought to improve cartilage graft survival [2].

If cartilage grafts are not sufficiently anchored into place, they can migrate when exposed to the constant force of contractural scarring [2]. Hence, it is recommended that they be anchored with either a slowly absorbing or permanent suture [2]. Cartilage grafts should be of sufficient thickness, length, and stiffness to prevent deformation during contractural wound healing [2]. Extrusion is an uncommon complication, and risk can be minimized by providing adequate, well-vascularized cutaneous flap coverage [2]. Tumefactive cartilage graft proliferation has also been reported with rhinoplasty in the otolaryngology literature [17]. The authors believed that the presence of perichondrium increases the likelihood of this complication, citing an unpublished observation that irregular, unpredictable growth of rabbit auricular cartilage occurs when implanted with its perichondrium intact [17]. They also believed that tumefactive proliferation was also due in part to trauma [17].

All cartilage donor and recipient sites are susceptible to infection, but this is uncommon. The avascularity of cartilage can impair the delivery of systemic antibiotics, and infections of cartilaginous structures can become serious [2]. Gram-negative bacteria such as *Pseudomonas* are often present in the external auditory canal and should be considered when selecting empiric antibiotic coverage for conchal donor sites [2]. Septal cartilage harvesting is most often complicated by *Staphylococcus* infections [2].

Location-specific complications of cartilage transfer can include septal perforation, auricular distortion, sterile chondritis, and pneumothorax [2]. Sterile chondritis may be symptomatic for up to a year postoperatively and can be managed with trauma avoidance, NSAIDs, cool compresses, and time [2].

Other Complications Complications can arise when performing total distal nasal cartilage reconstruction with auricular cartilage [2]. While the nasal grafting is reliable, the auricular restoration following the harvesting of the donor cartilage can often result in loss of auricular definition [2]. Alar and lower eyelid cartilage grafting using auricular donor sites can sometimes appear too thick and require thinning [2]. The positioning of the conjunctival/cutaneous junction during lower eyelid restoration with cartilage may sometimes also require revision [2].

Postoperative Care and Follow-Up

There is no consensus on postoperative wound care and follow-up visits. In our office, we apply a pressure dressing directly after surgery for 24 h at which time it can be removed and the wound gently cleansed with sterile saline twice daily. We typically see patients back in 1 week. During this visit, we assess both donor and recipient sites for infection, stability of graft location, and presence/severity of any perichondritis. Should these complications occur, they are treated as outlined within the safety section. Barring any complications, patients are assessed again in 3–4 months, and then as needed.

Alternative Procedures and Modifications

Alternatives to autologous cartilage transfers that currently exist include alloplastic implants composed of silicone, polytetrafluoroethylene,

polyethylene, metals, and calcium phosphate ceramics [2]. However, these implants can be complicated by foreign body reactions, infection, and/or extrusion [2]. In addition both basic and applied research are ongoing in regard to cartilage engineering. Few preliminary clinical trials have been conducted to date in this area and much work remains in order to offer cartilage engineering as a realistic option in clinical practice [1].

The volume of chondrocytes that can be harvested from auricular, nasal, and costal cartilage is limited and the ability to develop cartilage from stem cells would have great utility [1]. Using adult mesenchymal stem cells derived from bone marrow and adipose tissue, chondrogenic differentiation can be achieved with co-culture with chondrocytes (2b) [24], growth factor induction (2b) [25], or chondrogenic matrices (2b) [26]. In order to facilitate chondrogenic differentiation and cartilage formation, researchers are aiming to mimic the molecular signaling and histoarchitecture of the cartilage microenvironment [26].

Cartilage can develop both in vivo and in vitro. In vivo cartilage engineering uses the human body as the bioreactor. Once the cartilage block has formed, it is harvested, shaped, and then implanted into the desired site. In vivo engineering requires patients to undergo at least two operations and they must also take proper care of the developing cartilage block (2b) [27]. In vitro cartilage engineering is preferred because it requires less surgery and patient suffering. However, in vitro-engineered cartilage is relatively weak compared to in vivo-engineered cartilage owing to differences in the surrounding microenvironment (2b) [28]. The in vivo-engineered cartilage microenvironment promotes further maturation of cartilage with differential expression of collagen IX and pyridinoline, providing it with enhanced mechanical strength [28]. While the exact mechanism has not been fully elucidated, researchers have found that dynamic loading of articular cartilage increased Young's modulus and the production of cartilage oligomeric matrix protein and collagens II and IX (2b) [29].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Cartilage grafts serve to preserve both form and function and are commonly used in auricular, nasal, and lower eyelid reconstruction in dermatologic surgery [1, 2]	A
Cartilage grafts can be associated with long-term survival rates of up to 95% after 20 years (B) given the tissues' low metabolic rate, sparse cell population, and avascular structure (A) [1, 5]	B, A
Donor sites for cartilage grafts include the auricular cartilage, nasal septal cartilage, and costal cartilage [1, 2]	A
Composite grafts have a higher metabolic demand and should be restricted to 1.5 cm in widest diameter to decrease the risk of ischemia [20]	B

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Self-Assessment Questions

1. Cartilage transfers can be used in reconstruction of the following areas except:
   (a) Nasal defects
   (b) Auricular defects
   (c) Eyelid defects
   (d) Nipple defects
   (e) Lip defects
2. Long-term survival rates of cartilage grafts approximate:
   (a) 95%
   (b) 85%
   (c) 75%
   (d) 65%
   (e) 55%
3. Cartilage donor sites used in dermatologic surgery include all of the following except:
   (a) Conchal
   (b) Costal
   (c) Septal
   (d) Articular
   (e) Helical rim
4. For patients on coumadin, an INR between what two values is considered acceptable for surgery?
   (a) 1–2.5
   (b) 1.5–3.0
   (c) 0–1
   (d) 2–3.5
   (e) 1–2
5. Given high metabolic demands, the diameter of a composite graft used in auricular or nasal reconstruction should not exceed what length to avoid ischemia?
   (a) 0.5 cm
   (b) 1 cm
   (c) 1.5 cm
   (d) 2 cm
   (e) 2.5 cm

Correct Answers

1. e: Cartilage transfers are not used in the reconstruction of lip defects.
2. a: Long-term survival rates of cartilage grafts approximate 95%.
3. d: Articular cartilage is not typically used in dermatologic reconstructive surgery.
4. d: An INR between 2 and 3.5 is considered acceptable for dermatologic surgery.
5. c: Composite grafts have a higher metabolic demand and should be restricted to 1.5 cm in widest diameter to decrease the risk of ischemia.

Skin Grafts

11

Shauna Higgins and Ashley Wysong

Abstract

Skin grafts have become a mainstay of the reconstructive ladder with primary subtypes being full-thickness, split-thickness, composite, and free cartilage skin grafts. Full-thickness skin grafts (FTSGs) contain the complete epidermal and dermal layers of the skin. Split-thickness skin grafts (STSGs) comprise the epidermis and a portion of the dermis and are characterized as thin, medium, or thick, based on the amount of dermis they contain. Composite grafts comprise two types of tissues, usually skin and cartilage, and free cartilage grafts are exclusively composed of cartilage. Here we discuss the indications, techniques, and outcomes associated with each of the skin graft subtypes.

Keywords

Full-thickness skin grafts · Split-thickness skin grafts · Composite skin grafts · Free cartilage skin grafts · Mohs Micrographic Surgery · Reconstructive surgery

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Introduction

Skin grafting was first performed in India approximately 3000 years ago, with widespread interest emerging only after the nineteenth century [1]. Ollier and Thiersch first described the use of split-thickness skin grafts (STSGs) in 1872 and 1886, respectively. In 1942, Brown and McDowell used the STSG to treat burn wounds [2]. Today, skin grafts have become a mainstay of the reconstructive ladder with the primary subtypes being full-thickness, split-thickness, composite, and free cartilage skin grafts.

Full-thickness skin grafts (FTSGs) contain the complete epidermal and dermal layers of the skin. This includes all dermal adnexal structures, which have important surgical and aesthetic considerations. Split-thickness skin grafts (STSGs) comprise the epidermis and a portion of the dermis and are characterized as thin (0.005–0.012 inches), medium (0.012–0.018 inches), or thick (0.018–0.030 inches), based on the amount of dermis they contain [2, 3]. Composite grafts comprise two types of tissues, usually skin and cartilage, and free cartilage grafts are exclusively composed of cartilage [4].

Procedures

Full-Thickness Skin Grafts

The earliest record of FTSG use is by J. Mason Warren in 1843 with modern aspects developed

predominantly by J. Staige Davis and V.P. Blair [5]. Full-thickness skin grafts (FTSGs) contain numerous nutrient-requiring structures in the dermis such as sebaceous glands, sweat glands, nerves, hair follicles, and the arrector pili muscle. They consequentially require a sufficiently vascular bed to meet their metabolic demands and are therefore indicated in smaller repairs. Thin grafts are typically taken from the eyelid or post-auricular sulcus, medium grafts are taken from the preauricular cheek or cervical regions, and thick grafts are taken from clavicular or preauricular areas [4, 6]. The grafts from these areas are often utilized to reconstruct facial defects after definitive skin cancer removal; however, they should not be used if there is elevated risk for recurrence. Other indications include clinical scenarios in which cosmesis is prioritized as FTSGs typically have better cosmetic outcomes when compared to STSGs. In addition, FTSGs are also considered in patients with tissue reservoirs surrounding the defect that is insufficient for local flap reconstruction. The literature details a variety of additional uses including head and neck reconstructions, reconstruction status post-degloving injuries, release of burn scar contractures, and reconstructions after excisions for a variety of other cutaneous pathologies [4].

The general technique begins with creation of a template for the graft. An outline of the defect is typically drawn at the donor site. To accommodate for graft shrinkage, a graft 3–5% larger than the template is usually harvested. Grafts used for lower eyelid reconstruction should be harvested to allow for a greater amount of shrinkage to allow for contraction and to avoid possible ectropion. Once the donor site is marked, anesthesia should be injected. Injection prior to marking may distort the shape and size of the graft. The graft is then excised, typically at the level of the subcutaneous fat. The donor site is customarily closed primarily with a layered closure. Although it is best to use the graft immediately, it can be held for up to 1–2 h if placed in a dish with normal saline or saline-soaked gauze. Prior to placement in the recipient site, the graft should be trimmed and defatted down to the white glistening dermal surface (Fig. 11.1). Surgeons should avoid excessive thinning that may destroy adnexal structures and have

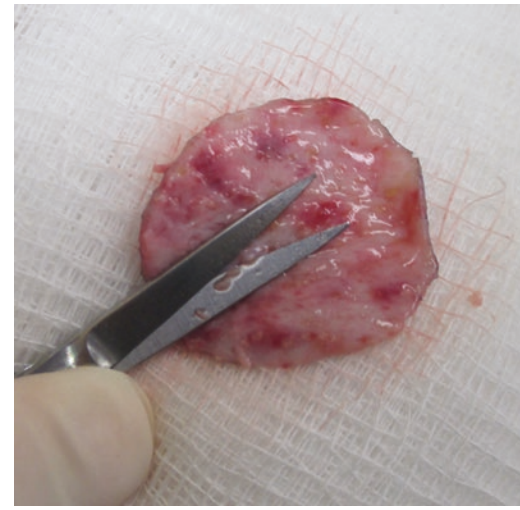

Fig. 11.1 A FTSG is defatted with iris scissors. The yellow fat should be removed to expose the intact white and glistening dermal surface

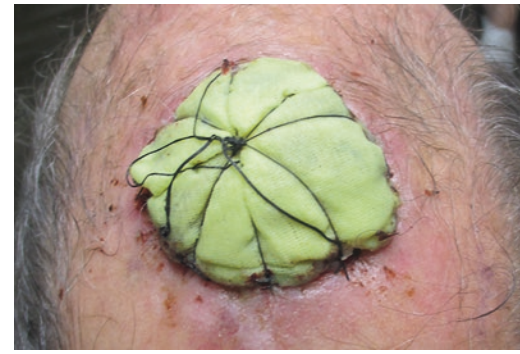

Fig. 11.2 Bolster consisting of antibiotic ointment, petrolatum-impregnated gauze, and moistened cotton balls anchored with tie-over suture

cosmetic implications. Once the graft is placed in the defect, it can be anchored with sutures around the perimeter. Bolsters may then be used to further anchor the graft to the recipient bed (Fig. 11.2). After bolstering, a light dressing and pressure dressing are applied. The pressure dressing usually remains for approximately 24–48 h. The bolster is left in place for approximately 1 week [7].

One of the main head and neck applications of the FTSG is nasal reconstruction. The nose is a unique reconstructive quandary in that it is a three-layered structure comprising the skin, cartilage or fibrofatty tissue, and mucosa. Replacement of each

tissue layer is indicated for an optimal cosmetic and functional result. Different techniques are utilized to achieve this, and they depend on the type of defect and patient. For enhanced structural support, a variety of flaps have been reported in combination with overlying FTSGs. Fader et al. described a muscle hinge transposition flap with overlying local FTSGs for repair of deep nasal defects in a single-stage procedure (4) [8]. In a separate study of 12 patients, basal cell carcinomas were excised by Mohs micrographic surgery (MMS), and a template was cut to mirror defect dimensions; it was then placed superior to the defect and outlined to incorporate it into the anticipated defect. The outlined area was excised down to subcutaneous fat. The muscle flap is then incised and elevated above the periosteum or perichondrium with the inferior base at the superior margin of the defect. The muscle flap is then transposed and secured into the defect with the graft secured on top of the flap. The donor site is closed primarily. This method is most effective in small to medium, 1–2 cm soft tissue defects of the nasal dorsum, sidewall, supratip and ala lobule, and in areas of sufficient skin laxity superior to the defect but which lack a sufficient adjacent tissue reservoir for a single-stage local flap procedure. This method resulted in no cases of infection or necrosis. Cosmetic and functional outcomes were graded from good to excellent by both patients and surgeons with cosmesis provided by similar color, thickness, texture, and sebaceous density similar to the excised tissue [8]. A similar combination of a muscular hinge flap with an overlying FTSG has been reported for reconstruction of the complex oral commissure area (5) [9]. In this case report, a 73-year-old male had a recurrent squamous cell carcinoma of the right oral commissure excised to leave a deep, vertically oriented defect measuring 4.0 by 1.5 cm. Given the complexity of the anatomy and a resulting paucity of reconstructive options, authors opted for a turnover muscular hinge flap with a Burow's FTSG for best possible cosmetic and functional results. To achieve this, an incision was made through the skin and subcutis at the inferior aspect of the defect, creating a Burow's triangle from the junction of the inferior aspect of the oral commissure to the medial edge of the defect. This skin was saved as a Burow's graft. An incision was then made through the orbicularis oris and depressor anguli oris muscle, undermining the area below the muscle to create a triangular hinge flap. The flap was draped over the commissure and upper lip defect and sutured into place while the defect was advanced laterally and closed primarily. The Burow's STSG was defatted, trimmed, and sutured over the muscular hinge flap to recreate the right upper cutaneous lip and right upper oral commissure. Excellent cosmetic and functional results were obtained at 1-, 3-, and 6-month follow-ups with the overall oral aperture being minimally reduced and no functional compromise being reported [9].

In addition to muscular hinge flaps, FTSGs have also been reported in combination with mucosal and dermal hinge flaps. Bickle and Bennett reported use of a combined mucosal hinge flap and FTSG for a through-and-through non-rim nasal defect with no other adverse effects other than persistent erythema treated with pulsed dye laser (5) [10]. A dermal flap with overlying FTSG can also be used in the reconstruction of nasal defects. In cases of burned nasal ala, using rolled dermal flap with overlying FTSG provided reliable reconstruction (4) [11]. In these cases the lateral surface of the nose was used as the dermal flap donor site and was de-epithelialized. An incision was then made 6–10 mm above the free edge; the distal skin was detached and then inverted to constitute the internal aspect of the nostril. The inferior pedicle dermal flap was then detached from the deep plane, rolled, and sutured to nostril margin. A FTSG was then used to cover the reconstruction and dermal donor site. Of the seven patients, one developed necrosis of the tip of the nose and another developed retraction of the nasal ala during growth. Both cases required surgical revision [11].

In 2013, Zopf and colleagues evaluated the utility of a FTSG overlying a separately harvested auricular cartilage graft for nasal alar reconstruction (4) [12]. In this case, cartilage augmentation was indicated due to deep cutaneous defects of the ala that made retraction or collapse probable. The cartilage graft helps resist contraction, improve contouring, enhance volume, and stabilize the external nasal valve [12]. This technique can also be utilized in a delayed

fashion whereby the cartilage graft is placed and followed by the FTSG 1–2 weeks later.

Forehead defects can have various etiologies including skin cancer resection, trauma, or iatrogenic causes such as the creation of a paramedical forehead flap. These are historically closed primarily or allowed to heal by secondary intention (5) [13]. These approaches, however, may result in significant downtime and may provide a suboptimal aesthetic outcome, particularly in large defects. In a recent report, Osorio et al. report on a technique to reconstruct the forehead using a frontalis-pericranial flap and a FTSG. In the case, a patient was left with a 3x3 cm defect extending to the bone on the midline forehead after MMS for a sarcomatoid SCC. The cortex of the bone was drilled to improve the eventual graft recipient bed. After a 5-week attempt at granulation, a frontalis-pericranial flap was performed. An excision was made posteriorly into the hair, and the flap was exposed via elevation of the skin and subcutaneous tissue in a plane above the frontalis muscle and deep to the hair follicles. Supraorbital and supratrocheal vascular pedicles were maintained and the flap was transposed into the defect. The scalp was then closed with subsequent placement of a FTSG from the supraclavicular fossa over the flap. The bolster dressing was removed 1 week postoperatively with good functional and cosmetic outcomes. Alternatives include a local flap, which may have led to alteration of the hairline. A free flap would have also been a viable option in this case, but the patient refused [13].

Full-thickness skin graft donor sites are generally numerous given the relatively small surface areas required. In 2005, Dimitropoulos et al. detailed a novel donor site for nasal reconstructions utilizing a FTSG harvested from the forehead (4) [14]. While nasal defects are often repaired with tissue from the preauricular, post-auricular, supraclavicular, clavicular, conchal bowl, melolabial fold, and upper eyelid skin, forehead grafts may be a thicker and more appropriate match for deeper nasal defects than traditional graft sources (Fig. 11.3). It may also provide apt camouflage of donor site in forehead rhytids if present. In the three patients presented, function and cosmesis were reported to be excellent at follow-up (>6 months). The three patients had minimal scarring with no secondary revision or dermabrasion [14]. Surgical considerations for all FTSGs but particularly for thicker grafts include a requirement for a well-vascularized recipient bed. Thus, these should not be considered as first-line therapy for diabetics, smokers, and vasculopaths.

Finally, methods to decrease the size of the defect and therefore increase the clinical situations in which the FTSG can be utilized and improve the viability of the grafts in cases in which they are already being used include a purse-string assisted closure (Fig. 11.4) [15].

Split-Thickness Skin Grafts

Split-thickness skin grafts have much broader applications than FTSGs and can be utilized for significantly larger defects. This is by way of their thinner nature and therefore smaller metabolic and vascular demands. The larger harvest area brings with it several surgical considerations to be cognizant of in addition to several possible adverse effects. The STSG results in a second

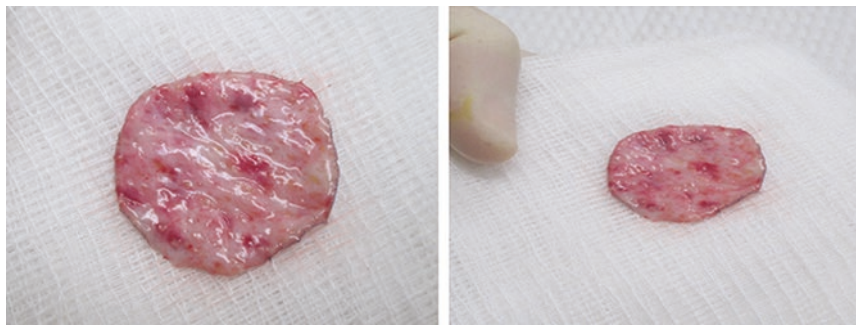

Fig. 11.3 Dermal surface of a FTSG collected from the supraclavicular region

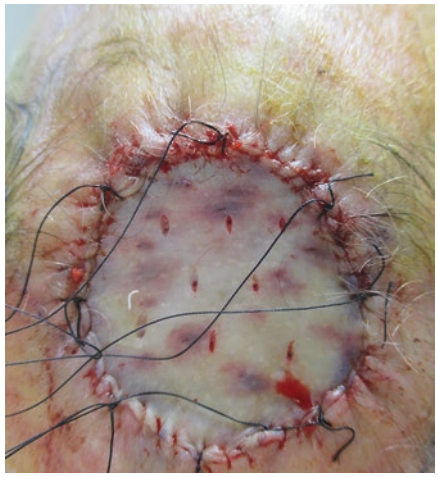

Fig. 11.4 FTSG on the scalp with delayed purse-string closure

defect that can result in fluid loss, excessive pain, a prolonged period of healing and immobilization, hypertrophic scarring, and undesirable pigmentation (1) [16]. Because the STSG is thin and somewhat fragile, they usually do not suitably withstand subsequent stressors such as radiation. Additional considerations include that they contract quite a bit, tend to be hypo- or hyperpigmented, have texture irregularities, and lack hair growth. Thus, these grafts are indicated for cases in which a large coverage area is required and when function is prioritized over cosmesis.

The general technique for the STSG begins with harvesting the graft with either electric dermatomes or freehand devices such as a scalpel, razor blades, or Weck knife (Figs. 11.5 and 11.6). The order comprises marking, anesthetizing, and

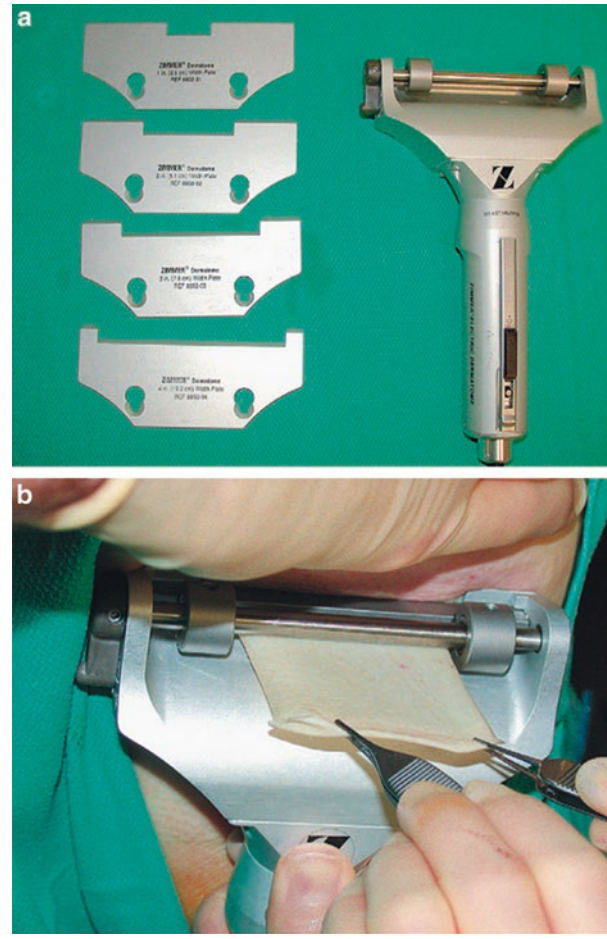

Fig. 11.5 (**a**) The Zimmer electric dermatome and its four-width blades and (**b**) harvesting a graft with the Zimmer electric dermatome [17]

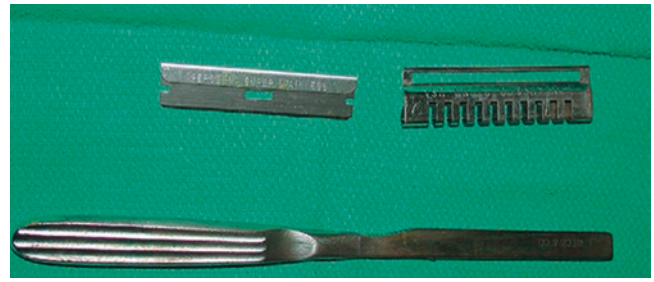

Fig. 11.6 Weck blade components including the knife handle, blade, and a template to control the STSG [17]

then harvesting. Although the harvest technique varies with the instrument used, the electrically powered dermatome has gained popularity. Prior to dermatome-assisted harvest, the donor site should be lubricated typically with mineral oil to ensure a smooth pass over the skin. While an assistant applies traction, the surgeon gently glides the machine over the skin at a 30°–45° angle to the donor site with depth determined by the desired graft thickness. As the graft emerges, it is gently lifted away with forceps or hemostats. Once completed, the machine is removed and the graft is placed in saline. If additional surface area is required from the STSG, such as in burn patients with extensive surface area involvement, the graph can be scored to create a meshed appearance prior to being placed at the recipient site. The meshing of the graft allows release of serosanguinous fluid that would interfere with graft take if allowed to accumulate between the graft and its recipient bed. After the graft is placed at the donor site, it is secured with peripheral sutures. Basting sutures are also recommended to ensure central adherence, particularly in larger grafts. A bolster with pressure dressing is then applied. The sutures are typically removed after 7–10 days [7].

Uses reported in the literature include reconstruction of head and neck wounds including scalp wounds and oral defects, reconstruction of abdominal wounds, genital defects, degloving injuries, burn injuries, and other extremity defects [18–48]. Scalp reconstructions can be challenging for a variety of reasons. Reconstructive options include second-intention healing, primary closure, local flaps, tissue expansion with subsequent flap repair, FTSG, STSG, or free-tissue transfer (4) [18]. Second-intention healing is noted as the simplest wound management method, but this has several drawbacks including the need for prolonged downtime and wound care. Resulting scars may also be atrophic or telangiectatic, hair-bearing areas will usually be alopecic, and contraction may limit use in the periocular region. The scalp is also relatively inelastic and lacks substantial surrounding tissue reservoirs making primary closure difficult, although it can be performed for defects under 3 cm with galeal undermining. This inelasticity also makes local flaps difficult for larger defects; however, closure of the donor site with the STSG can address this problem [18]. In addition, STSGs may be utilized on the bone with limited periosteum given the lower metabolic demand in comparison with FTSGs. This method has been reported to be effective for defects up to 150 cm^2 with complications in 3.4% of cases [18]. Disadvantages of the combined flap and graft technique include a predictable area of cicatricial alopecia associated with the placement of a hairless graft [18].

Additional applications of the STSG in the head and neck region include management of helical and non-helical defects, mastoid, mandible, and maxilla reconstruction. Helical rim defects are typically reported to be repaired with FTSGs or advancement flaps. Helical rim defects for which STSGs may be indicated include large keloids (4) [43]. The combination of the pathology and location makes these cases particularly challenging. Keloids are large and disfiguring. In addition, the helical rim is a three-dimensional and easily deformable structure. In a series of five patients with moderate (4–10 cm) and large (>10 cm) keloids, Rasheed and Malachy report the use of excision followed by STSG. In their

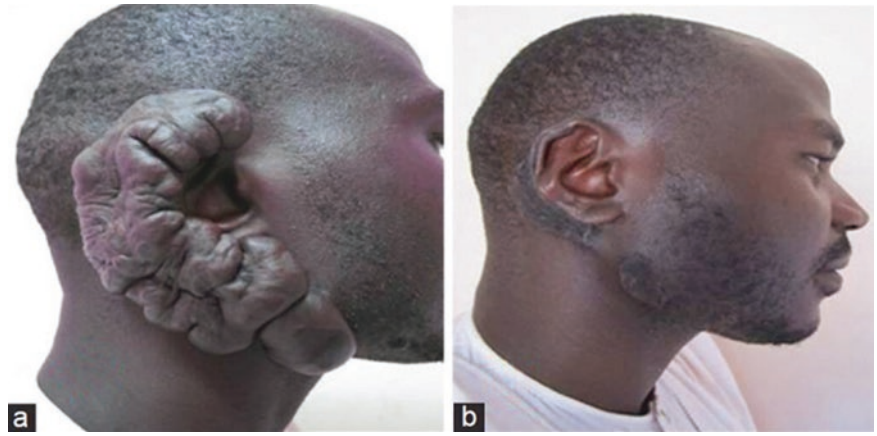

Fig. 11.7 (**a**) Helical rim keloid before treatment and (**b**) helical rim keloid after treatment [43]

series, the periphery of the keloid was anesthetized followed by full-thickness excision with a thin rim of the lesion remaining. A STSG was then applied over the defect with edges sutured. Forty milligrams of triamcinolone were injected into the residual rim of the keloid at 2 weeks status post-operation and this was repeated every two weeks for a total of six injections. All grafts survived although there was evidence of keloid recurrence in two patients. Aesthetic results were reported to be satisfactory with no secondary surgical revision required to improve the contour of the reconstructed helical rim (Fig. 11.7) [43].

Defects of the non-helical rim and ear defects devoid of perichondrium may also be challenging to reconstruct. These include locations of antihelix, crura of antihelix, scaphoid fossa, triangular fossa, antitragus, and the posterior surface of the ear. Full-thickness skin grafts may be too thick for these regions. Two-staged flap procedures are time-consuming, and second-intention healing may not be ideal due to risk of cartilage desiccation and webbing of the contoured surface of the ear. This leaves the STSG as the ideal option to treat non-helical defects of the external ear (5) [30].

In utilization of the STSG, final cosmesis can be reportedly optimized with slight softening of the cut angle. Traditionally, cutaneous lesions are excised with the scalpel held at a 90° angle when local skin flaps or primary closure is possible. In the context of STSG, however, a more pleasing

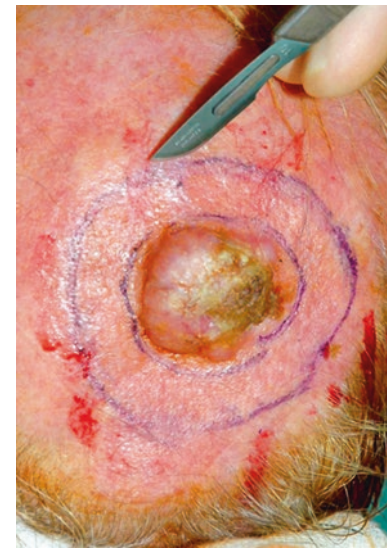

Fig. 11.8 Scalpel at a 45° angle to produce a beveled excision [20]

cosmetic result may be attained when the edge of the skin is beveled up to 45° to create a saucer-shaped defect, resulting in several distinct advantages (Fig. 11.8) (4) [20]. Among these is the ability of the beveled graft edge to better adapt to the edges of the wound by draping over the wider soft tissue defect and decreasing the propensity for poor take that may occur at right angles [20].

The STSG also has wide-reaching applications in the genital region both in males and in females. A recent 2016 case study responded to the paucity of data on pediatric penile reconstruc-

tion by evaluating the use of the STSG in this regard (5) [24]. Traditional approaches to this reconstruction include the use of excess preputial skin and rotation skin flaps from areas of redundancy. In cases in which there exists no excess or redundant skin, however, the STSG may present a good option. The donor site utilized for this procedure was the lateral thigh due to its glabrous skin and proximity to the genitals. Outcomes were promising with good penile graft elasticity and sensation at 7 months [24].

Further applications of the STSG in the penile area come from data on the treatment of concealed penis in young males (4) [28]. Concealed penis most commonly seen in neonates and moderately obese prepubertal boys can exist with varying severities and etiologies. Thus, the surgical approach differs accordingly. In this case, the authors used a transverse suprapubic incision to excise fat or loose elastic tissue and anchor the base of the penis to the periosteum of the pubis. Alternative procedures include freeing the abnormal dartos attachments and covering the penile shaft with inner preputial skin or using multiple Z-plasties to rearrange and lengthen the penile skin. Additional options for patients with denuded penis after excess circumcision include vascularized flaps, scrotal flaps, multiple Z-plasties, and skin grafts. In the case of patients who have insufficient skin to resurface the penile shaft, the STSG proves to be a good option. In these cases, the graft is anastomosed to the glans margin. There were no cases of lymphedema in the STSG patients. Important surgical considerations include an assessment of the cause of concealment and the appropriate timing of the surgery. In this series, the procedure was performed before the patient reached school age. Recovery of sensation will need to be prospectively followed, although most adults recover adequate to completely normal sensation in the treated area [28].

The STSG can further be utilized status postglansectomy for squamous cell carcinoma or other penile carcinoma (4) [38]. After glansectomy, a 1.2–1.5-mm-thick skin graft was harvested from the thigh and transplanted to cover the tip of the distal corpora cavernosa. The graft was then sutured proximally to the neurovascular bundles. This series reported two patients with early partial loss of the graft, one of them requiring surgical re-grafting. Two late complications occurred, one being meatal stenosis and the other being postoperative phimosis. Functional results were extremely satisfactory at 36 months. Preserved orgasm and ejaculation and reduced glans sensitivity were reported by all patients. No local recurrences were noted [38].

For females, the STSG has been utilized often in vulvo-vaginal reconstruction. In 22% of these cases, however, infection and sloughing may occur with the standard techniques that are used, especially at irradiated recipient sites. To address this, the authors of a 2005 study report on a novel method of vulvo-vaginal reconstruction comprising the use of fibrin tissue adhesives and vacuum-assisted closure (VAC) devices to improve the viability of the grafts (4) [23]. Fibrin tissue adhesives were first used with skin grafts in 1944. It was reported that surgeons coated the graft with fibrinogen containing plasma and coated the recipient bed with a thrombin solution. Improved wound healing occurs via stronger initial mechanical bond. Fibrin tissue adhesives typically comprise a highly concentrated, autologous fibrinogen with albumin, fibronectin, plasminogen, aprotinin, and factor XII along with thrombin and calcium chloride. The combination converts fibrinogen to fibrin monomers that polymerize and form an adhesive fibrin matrix. The wound VAC devices have been reported to improve wound viability by decreasing wound edema, improving graft-recipient site tissue apposition, stimulating granulation tissue, and decreasing bacterial colonization [23].

This technique involves harvesting a STSG from the inner thighs or buttocks to a desired thickness of 13–19/1000 of an inch. The STSG is meshed and trimmed. Thrombin is diluted with isotonic saline to a concentration of 5 IU/ml and applied to the graft. Diluted and aerosolized fibrin tissue adhesive, Tisseel®, was applied to the recipient site followed by application of the graft. Direct pressure was then applied for 3 min to allow adhesion. The wound VAC was set to a

pressure of 100 mm Hg at an intermittent setting and removed at postoperative day 3 or 4. Practicality issues that may arise include ability to achieve a good occlusive dressing while maintaining the ability for urination and defecation. This method resulted in great outcomes with 80% take noted on the vulva, vagina, and perianal area. No surgical site infections were noted [23]. A 2014 study also reported on the use of the wound VAC in place of conventional bolsters for the STSG in the burn population (3) [49]. In their retrospective review, they reported use of 125-mmHg suction for 5 days. Sixty-seven patients were included in this analysis. Zero returns to the operating room for repeat STSG were reported. Return to the operating rates for re-grafting with conventional bolstering is reported to be up to 19% [49].

Clinical outcomes of the wound VAC versus conventional therapy in regard to STSG viability were evaluated in a 2010 retrospective study of 142 patients (4) [50]. Conventional therapy comprised a cotton bolster, sterile compressive, or stainless steel gauze dressing used for at least 5 days. Results demonstrated significantly fewer repeated STSGs required in the wound VAC group in addition to fewer complications such as seroma, hematoma, and infection. Another recent report demonstrated the benefit of a suction drain to assist in the take of the STSG (5) [51]. An antimicrobial-impregnated dressing combined with a wound VAC has been reported to increase STSG engraftment as well (3) [52]. In a recent case-control study, one group used conventional bolsters to secure the skin graft, while the second group received an antimicrobial-impregnated dressing in combination with a wound VAC for 5 days, changed as frequently as required by the amount of exudates. All skin grafts used in conjunction with the antimicrobial-impregnated dressing achieved 100% take. No hematoma or seroma formation was observed. In the conventional therapy group, success rate was 85%. Three patients had partial loss of the skin graft, one of which was from infection [52]. These studies support the wound VAC as a viable option for increasing graft viability.

The STSG is also indicated for large defects on the extremities in the context of degloving injuries, burn injuries, and defects status post skin cancer extirpation. A recent case series in the journal *Burns* reports on the treatment of degloving injury of the finger with a pedicled split-thickness skin graft (4) [32]. The pedicled STSG benefits from two blood supplies, the pedicle and the wound bed. As a result, the survival rates of these grafts are extremely high such that they can be used in the context of bone or tendon exposure, which is a common scenario in degloving injuries. Additional advantages include the thickness of the graft relative to that of the fingers and that the time to severing the pedicle and immobilization are short. Immobilization, however, is extremely important. In this case series, the authors sutured the normal skin of a finger to the abdominal skin to avoid avulsion as the blood pressure in the tiny blood vessels is lower and small extravascular pressure may lead to skin-graft death. As always, the color of the graft should be monitored to evaluate its survival or death [32].

For burns, there is no clear consensus on whether the STSG is superior to the FTSG. A 2015 study placed the STSG against the FTSG for resurfacing the volar aspect of pediatric-burned hands. The six studies reviewed reported lower contracture rates in the hands of patients in the FTSG group when compared to those in the STSG group. These results, however, should be interpreted in the context of several key differences between the groups that include more severe (i.e., larger and deeper) burns being evaluated in one STSG study. Nonetheless, the use of the FTSG is usually preferred due to belief of lower contracture rates and thus decreased need for secondary reconstructions. The FTSG, however, has drawbacks that limit its use such as limited donor sources and its inability to cover large surface areas such as those usually typical of burns. The FTSG also has a lower take rate when compared to the STSG. Thus, there is no agreement on which the reconstructive method is superior and the decision should be case-specific.

Another study evaluated the use of spray keratinocytes and autologous meshed STSG in the treatment of acute burn injuries (4) [46]. In

this study, the authors prospectively compared the use of an autologous cell-harvesting (ACH) device with a meshed split-thickness skin graft to treat partial thickness burns in patients with two 320 cm^2 areas. The authors compared these patients on the basis of graft take, pigmentation, color match, scarring, and pain. Outcomes were similar for both methods at 52 weeks although for the ACH methods, patients benefited from smaller donor sites with comparable outcomes [46].

Thus, it becomes evident that the STSG has wide-reaching applications and can be used in a variety of anatomical locations. Once the decision has been made to utilize a STSG, however, other considerations arise. These include methods to improve graft take/survival and also, care of the donor site.

Graft survival is determined by a number of factors. The initial "take" or incorporation occurs by diffusion of nutrition from the recipient site. This process is termed "plasmatic inhibition" during which a thin fibrin network anchors the graft to the recipient site. Revascularization generally occurs within 48–72 h, and full vascularization is restored in approximately 4–7 days. Revascularization can occur via several mechanisms that include reconnection of blood vessels in the graft to recipient site vessels and growth of vessels from the recipient site into the graft [50]. Because graft survival is so largely dependent on its vascular supply, grafts generally do not take on poorly vascularized beds such as bare tendons, cortical bone without periosteum, heavily irradiated areas, or infected wounds. Any hematomas or seromas also interfere with revascularization and thus graft survival. Consequentially, graft survival is also contingent upon graft immobilization to prevent shearing, which may cause seroma or hematoma formation beneath the graft. The impact of hematoma formation was elucidated in a recent study that reported late failure of a STSG in the setting of the homozygous factor V Leiden mutation (5) [53]. Furthermore, graft survival is dependent on the presence of uniform pressure over the entire grafted area provided by a non-adherent, semi-occlusive, absorbent dressing [50].

Various methods have been utilized to address graft survival and graft "take." Argon beam coagulation has been reported to be a fast, precise, and minimally destructive manner in which to decrease bleeding between the recipient bed and the STSG (5) [54]. Platelet-rich plasma (PRP) has also been reported to be effective in this regard by improving hemostasis in addition to possessing adhesive and healing properties (1) [55]. In a 2015 randomized controlled trial, 200 patients were divided into an autologous PRP group and a conventional therapy or control group which comprised staple and suture use. Incidentally, surgical tape has also been used as a means of adhering the graft to the recipient bed (5) [56]. In the PRP group, blood was drawn into two 10 ml syringes and transferred into vacutainers containing citrate phosphate dextrose-adenine (CPD-A). Six ml of blood was transferred into each vacutainer by pouring gently along its walls to avoid damage to cells. Blood was then centrifuged at 1000 revolutions/min for 5 min. It was separated into supernatant PRP and buffy coat with approximately 5 ml of PRP used for a wound area of 100 cm^2. Graft adherence to the wound bed was found to be statistically improved in the PRP group. Another split-wound study of 20 patients demonstrated 100% graft uptake in the PRP area at 6 weeks. In the control area, there was complete graft loss in four cases, partial loss in seven cases, and complete uptake in nine cases (2) [57]. In this study, the PRP was collected via apheresis and frozen at −80 °C and then thawed at room temperature prior to its use [57].

There have also been reports of use of synthetic adhesives such as cyanoacrylate and fibrin glue. Medical honey has also been utilized as a natural alternative to enhance the attachment of the STSG to the recipient bed (4) [58]. Honey exerts its adhesive properties via its antibacterial activity, therefore addressing infection risk, which is the second-most common cause of graft failure. Wounds that contain more than 105 organisms per gram of tissues will not support a skin graft. In addition to its antimicrobial effect, honey also possesses inherent adhesive properties. One consideration is that the sterility and medical grade honey that has been previously

sterilized should be used. Low-level laser therapy (LLLT) has also been reported to improve the survival of the STSG (5) [59]. This has been reported to be particularly useful in patients with high rates of expected graft failure such as those with vascular disease. Low-level laser therapy (LLLT) has been reported to improve tissue perfusion and fibroblast proliferation, increase collagen synthesis, and accelerate wound healing in vitro studies. In the current series of cases, this method was performed using a 650-nm red laser light, 2 J/Cm for the recipient bed, and 810-nm infrared laser light, 6 J/Cm^2 for the margins, along with the intravenous laser therapy with 660-nm red light, before and after STSG. Therapy included three clinic visits a week for a total of 10–15 sessions. Results demonstrated complete healing of diabetic ulcers in all patients for at least 2 months. Healing time for the STSG in non-diabetic patients is noted to be approximately 2–4 weeks. Graft failure in this study was 2.8%. Thus, LLLT using both visible and infrared light are appropriate treatments for diabetic rats, although visible light is reported to work better (in animals) [59]. An animal model was also used to demonstrate the potential of a newly developed collagen scaffold under the FTSG as a way to improve graft quality (5) [60, 61]. A rat-based intervention demonstrated that when used with a collagen scaffold underlayment, wounds demonstrated a thicker epidermis and significantly higher epidermal cell count when compared to wounds treated exclusively with STSG [62].

For complicated wounds, cadaveric skin has been reported to be useful as a means to predict success of a STSG (4) [63]. Complicated wounds in the case of this method are reported to be infected as indicated by a positive culture swab. Whereas this usually necessitates prolonged antibiotic therapy, authors recommend cadaveric donor skin be applied, and if the donor skin has good take, antibiotic therapy is not necessary and a normal STSG can be performed with acceptable results. In their case series, 25 of 35 patients had full take of the cadaveric donor skin. In 22 of these 25 patients, a STSG was performed, which led to 91% complete graft take. These patients were not generally treated with antibiotics; however, if they were, surgery was not postponed [63].

Optimal management of the donor sites for the STSG has also become a high-yield topic in the skin graft literature. Techniques to minimize pain include ice, tumescent injection of the donor site, and PRP [16, 64, 65]. Optimal dressing materials have been evaluated in a number of studies. A recent 2010 study evaluated Aquacel®, AG, Bactigras ® with Melonin ®, Cmfeel® plus transparent, Opsite® Flexigrid, and Adaptic® (2) [66]. It reported earliest complete epithelialization with Aquacel ® AG and the latest for Bactigras ® with Melolin®. Comfeel® Plus Transparent was the most painless dressing and Bactigras ® with Melonin was the most painful. Incidence of infection was highest with Bactigras ® with Melonin ®. Opsite ® Flexigrid was the most economical and Aquacel ® AG was most expensive [66]. A subsequent randomized controlled trial evaluated the use of Helicoll with Scarlet Red and Opsite (1) [67]. Results demonstrated shorter healing time of the donor site in the Helicoll group when compared to the Scarlet Red group, however comparable to the OpSite group [67]. A "graft-back" procedure has also been suggested in which an additional graft is taken adjacent to the initial donor site and meshed 4:1 to cover both donor sites at once (4) [68]. Furthermore, honey has also been reported as an adjunct in the healing process of the skin graft donor site (2, 4, 2) [69, 70, 71]. PRP was also reported to aid in epithelialization and angiogenesis of graft donor sites as well (2) [72].

Composite Grafts

Composite skin grafts were first described by F. Konig in 1902 with subsequent modification by ensuing authors and physicians [73]. They are those comprising two types of tissues that may include cartilage, subcutaneous fat, and overlying skin; however, the most common combination is the skin and cartilage. Because these partially comprise avascular cartilage and exclusively rely on the bridging phenomenon, they are

limited in size due to risk of necrosis. In the literature, success rates for composite grafts are reported to range between 50% and 89% [73]. Their size should generally not exceed 2 cm as graft loss has been reported to rise when it exceeds 1.5 cm. The graft should never be over 1 cm from a vascular source. This requirement in turn informs the anatomic locations in which these grafts are most beneficial, which is generally the head and neck region with particular emphasis on the nose. They are often used to repair small full-thickness defects of the nasal ala and are also used for repair of the ear's helical rim. Composite grafts can also be used in defects that extend too deep for a FTSG to heal without leaving a concave defect. Donor sites for composite grafts are typically the helical crus, helical rim, and conchal bowl [7].

The general technique for harvesting a composite graft generally involves oversizing the cartilaginous portion relative to the overlying skin so as to supply cartilaginous pegs for insertion into the recipient site. The graft is then sutured although the cartilaginous portion does not need suturing, as it will heal on its own. A bolster or pressure dressing should be used. If the graft is being used to repair an alar defect, an intranasal antibiotic-impregnated gauze should be used to stabilize the graft. This is used due to the elevated baseline risk of composite graft failure in addition to the high bacterial colonization of the nares. Oral antibiotics may also be utilized [7].

For nasal defects, FTSGs are a viable option however because they must be defatted and thinned; these grafts often result in sunken areas that do not match the contour of the surrounding skin. For an aesthetically pleasing result, it has been reported that up to 3–4 mm of subcutaneous fat is needed at the base of grafts. This has also been reported to be most ideal as a component of a dermal fat graft as opposed to a free fat graft (4) [74]. Authors report two cases demonstrating the use of composite full-thickness grafts combined with fat grafts as a reliable technique for nasal reconstruction. Graft take is reported to be similar to that of skin-only grafts, however, with improved contour and match [74].

Through-and-through defects of the nose may particularly benefit from the use of composite skin grafts due to the depth of the defect and the complex structure of the nose. On the exterior surface, the nasal ala is usually plane or slightly convex, whereas the inside is more concave. This structural complexity usually requires the use of three-layer composite grafts [73]. Additional options for through-and-through defects of the nasal tip include skin grafts obtained from the earlobe, helical rim, root of the helix, local or distant flaps, and microvascular transplants (5) [75]. These options, however, have donor-site morbidity and may require several stages. A recent study reports on the use of auricular composite grafts for repair of nasal defects (4) [76]. Authors report that the composite graft of the auricle is an ideal choice due to similar anatomic structure, two skin layers, and one cartilage layer. The revascularization of the free auricular composite graft limits the distance from point of vascular contact to 5 mm. In a series of patients, the authors successfully reconstructed larger tip defects using the composite auricular skin graft by removing the skin between the columellar and composite graft and suturing the two surfaces together to increase the contact area between the composite graft and recipient tissue. After the operation, patients also had hyperbaric oxygen therapy for 7 days to improve graft oxygenation. Outcomes were positive. All grafts obtained revascularization successfully. Two patients had epidermal necrosis, although both were smokers who quit 2 weeks prior to the procedure. Thus, longer courses of hyperbaric oxygen may be required in patients with vascular pathology. This method, however, should not be used if the graft must exceed 2.5 cm, as there is a significant risk of necrosis in these cases [76].

Another study reinforced the utility of the composite graft for three-layer defects of the nostril margin (5) [73]. In this case, authors transferred a composite graft from the helix of the ear to cover a three-layer defect of the nasal ala. The helix is an ideal donor site due to the color and texture match in addition to the graft's decreased propensity for shrinkage. There is also minimal morbidity associated with a helix donor site. The

authors excised the nasal alar tumor, created a template of the defect, and used that template to excise the graft on the helix of the ear. The graft was placed in the recipient bed and fixed with simple sutures. The composite graft was also punctured with a scalpel blade to prevent venous congestion. The wound was then dressed with gauze moistened with heparin. Dressing was replaced every 12 h. At postoperative days 1–2, when the graft becomes blue as an indication of venous congestion, additional puncturing can be completed at this time. Patients should be advised that bleeding from the edge of the wound is normal due to the heparin dressings [73].

Reconstruction of full-thickness alar rim defects is reported to be particularly challenging when multiple cosmetic subunits are involved, especially the soft ones (5) [77, 78]. Common pitfalls in this area include collapse of the nasal valve and notching or thickening of the alar rim. To address these, one manuscript describes the use of a cheek interpolation flap and composite skin graft. The flap was used in conjunction with the graft to improve blood supply and thus graft survival. Composite grafts predominantly draw their nutritional supply from the wound edges, and thus large alar rim defects such as those with high metabolic requirements would likely eventuate in graft failure if used alone. Other options include nasalis-based subcutaneous island pedicle flap, a turndown nasal hinge flap (to recreate mucosal lining), a FTSG, as well as combination repairs that utilize mucosal advancement flaps plus batten cartilage graft and overlying interpolation flaps. Paramedian forehead and cheek interpolation flaps with distal flap folding to provide nasal lining are also useful although they would result in excessive tissue bulk. For this combined flap and graft procedure, the cartilage was harvested with the skin en bloc with underlying cartilage being approximately 5 mm oversized. Two subcutaneous pockets were created on the alar rim to allow insertion and anchoring of cartilage. The interpolation flap was inserted into the de-epithelialized outer surface of the graft. The inner concave surface of the graft became the internal lining of the nasal vestibule. The partial de-epithelialization enhanced graft viability by allowing imbibition of nutrients through the anterior surface of the graft in addition to wound edges. The interpolation flap was designed along the cheek such that it would reach the nasal tip without tension. The flap was undermined between the dermis and subcutaneous fat along the distal third and in the mid-fat for the middle third and deeply dissected at the proximal third to ensure fibers of the levator labi remained attached to the flap base. Additional flap thinning was performed at 2 weeks. At 3 months, the reconstruction demonstrated excellent contour and color match with no notching. Nasal aperture was patent [77]. Another application of the composite graft includes nasal perforation (2) [79].

Another study evaluated the use of the auricular composite graft in the context of secondary cleft lip nasal deformities (3) [80]. The procedure begins with marking of the auricular tissue and injection of anesthetic without epinephrine around the designed graft. Care is taken to avoid hydrodissection. The graft should be excised with the cartilage component being a few millimeters bigger than the skin component. The affected alar nose is then incised and the scar tissue is removed. The graft is carefully positioned and aligned with the edges of the defect. Measurements of nostril size were taken before and after the procedure on the right and left side. The study found statistically significant differences between the cleft and noncleft nostril at 1 year postoperatively, suggesting this technique may be a good alternative to address such nose deformities with rhinoplasty for the benefit of gaining additional alar length [80].

Columella lengthening also provides an appropriate clinical context for composite graft use and many techniques have been utilized in this regard. McIndo and Reese describe techniques that include the V-Y advancement flaps of prolabial scars. This method is efficacious; however, it creates significant scars and an abnormally wide columella. Forked flaps have also been described; however, these are also limited by an abnormally widened and scarred columella. Composite grafts are a viable option. In this case, a technique was used using conchal composite graft in the case of scar contracture of the upper

lip. Complications included necrosis in 3 cases (2%) and partial necrosis in 12 cases (8.7%). No infection and hematoma were reported (5) [81]. Additional uses of the composite graft include digital reconstructions and eyelid and eyebrow reconstructions.

Free Cartilage Graft

The free cartilage graft is comprised exclusively of cartilage and its overlying perichondrium. It is used to address both functional and aesthetic concerns. They are particularly useful in deep defects that require additional structural support to maintain function and aesthetically pleasing contours. They are therefore often used on the nose, particularly the distal nasal tip or ala and deep sidewall defects that involve loss of the lower lateral cartilage. They are also used on the eyes, lips, and ears. Donor cartilage is usually taken from the antihelix or conchal bowl but can also be taken from the nasal septum and costal joints [7].

Free cartilage grafts harvested from the conchal bowl may be taken from either the anterior or posterior aspects. In either approach, an incision of the skin is made after which a strip-, disk-, or oblong-shaped piece of cartilage is harvested. The antihelical donor site is typically harvested anteriorly. The method for securing the graft is case dependent. For narrow strips, the recipient bed tissue is undermined medially and laterally to allow insertion of either end of the graft. Sutures are used to further secure the graft.

A 2016 case series reports on the use of the scapha cartilage graft with small skin on a vascularized propeller flap, the latter of which have been reported to be increasing in popularity. One of their most important advantages is that they are easy to manipulate and may be harvested from less invasive sites on relaxed skin tension lines (4) [82]. For the lips, a recent study reports on the correction of the lower lip with cartilage graft and lip resection in patients with muscular dystrophy (4) [83]. For the first time, these authors report use of an auricular cartilage graft for this repair which boasts of several advantages that include the less invasive nature of the procedure and the longevity of its effects [83]. In regard to the ears, Friedman and Coblens report on the use of a conchal cartilage butterfly graft for repair of nasal valve collapse, which has been reported to be superior to other options such as spreader grafts in regard to cosmetics of the nasal tip and supratip (4) [84]. On the ears, reconstruction of moderately constricted ears has been reported by combining a V-Y advancement of helical root, conchal cartilage graft, and mastoid hitch (5) [85]. For the nose, recent reported indications include nasal septum perforation and full-thickness alar defects when used in combination with a reverse nasolabial flap (5) [86, 87]. The free cartilage graft has also been reportedly utilized without being paired with a flap but, rather, with second-intention healing (5) [88]. In this case, a 42-year-old male presented with a 1-cm full-thickness right-alar surgical wound after removal of a basal cell carcinoma by Mohs surgery. The anterior auricular skin was incised and elevated, and cartilage graft was excised in full thickness, removed, and placed in saline-soaked gauze, after which the skin was reapproximated and closed primarily. The graft was then secured into the recipient site using 5–0 Monocryl. Petrolatum was then placed liberally on both the skin and nasal vestibule mucosal surfaces and covered with Telfa. The patient was instructed to remove the dressing after 48 h and gently cleanse the wound twice daily followed by liberal reapplication of petrolatum to skin and mucosal surfaces followed by coverage with a Band-Aid. Once the adhesive strips on the ear began to fall off, the patient was instructed to cover the wound with petrolatum and a Band-Aid for 1 week. After 6 weeks, the full-thickness alar defect completely healed and did not require revision. There were no functional or cosmetic complaints [88].

Conclusion

Since their first use approximately 3000 years ago, skin grafts have undergone an evolution that has secured their position in the reconstructive ladder. They have become increasingly versatile

and can be utilized in a variety of patient-specific scenarios. The widest breadth of uses exists for the STSG due to their size and decreased metabolic demands, although the FTSG and free cartilage grafts are also utilized in an increasing assortment of clinical settings.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In the context of skin cancer, the FTSG should not be utilized if there is increased risk for recurrence, as view of the site and chances of visualizing will be obstructed	D
Grafts should be considered in patients without sufficient surrounding tissue reservoirs to allow local flap reconstruction	D
Recently reported options for deep nasal defects include a flap (muscle[B], dermal[B], mucosal[C]) with overlying FTSG or cartilage graft	B,B,C
While nasal defects are often repaired with tissue from preauricular, post-auricular, supraclavicular, clavicular, conchal bowl, melolabial fold, and upper eyelid skin, forehead grafts may be thicker and a more appropriate match for deeper nasal defects than traditional graft sources	C
Cosmesis for the STSG may be improved by softening the cut angle from 90° to 45°. This allows for the graft edges to drape over and better adapt to the edges of the wound	C
The wound VAC has been reported in various studies to improve take and viability of grafts by decreasing wound edema, improving graft-recipient site tissue apposition, stimulating granulation tissue, and decreasing bacterial colonization	B
Techniques reported for optimal management of the STSG donor site include ice, tumescent anesthesia, and PRP	B

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Self-Assessment Questions

1. Relative to the STSG, the FTSG should be used for _____ repairs.
   (a) Larger.
   (b) Smaller.
   (c) Size of the defect need not be considered when choosing a type of graft for repair.
2. Which type of skin graft results in better cosmesis?
   (a) FTSG.
   (b) STSG.
3. T/F: It is important to cut the graft such that it almost exactly matches the size of the defect.
   (a) True.
   (b) False.
4. What anatomic location should be harvested to allow for the greatest amount of shrinkage?
   (a) Anti-helix.
   (b) Free edge of nasal ala.
   (c) Lower eyelid.
   (d) Lip.
5. What surgical techniques are important considerations for primary closure on the scalp?
   (a) Galeal undermining.
   (b) Ensuring the defect is under 3 cm.
   (c) Avoid primary closure in the periocular region due to contraction.
   (d) All of the above.

Correct Answers

1. b: Smaller. The FTSG has higher metabolic need due to the presence of adnexal structures, and therefore the risk of necrosis increases with size of the graft.
2. a: FTSG.
3. b: False. To accommodate for graft shrinkage, a graft 3–5% larger than the template is usually harvested.
4. c: Lower eyelid. Graft should be harvested to allow for a greater amount of shrinkage to allow for contraction and avoid ectropion. Other locations have increased risk for poor cosmetic outcomes given that they are free margins; however, ectropion has the capacity to lead to functional impairment as well.
5. d: All of the above.

Linear Repairs

12

Reason Wilken, Farzam Gorouhi, Samantha Ellis, and Daniel B. Eisen

Abstract

For surgeons, there are multiple factors informing the decision of which techniques and epidermal closure materials should be used when closing specific defects in the skin. Major factors include the functionality and appearance of the scar, as well as the incidence of complications (e.g., infection, wound dehiscence, suture abscesses) among different surgical techniques. Other important considerations include the time taken to perform the closure, the cost of materials, and patient-specific factors, such as differences in postoperative care regimens and the need to return for removal of non-absorbable sutures.

Keywords

Epidermal closure · Adhesive strips · Polyglactin 910 · Tissue adhesive · Cuticular closure · Group · Patients · Sutures

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Introduction

For surgeons, there are multiple factors informing the decision of which techniques and epidermal closure materials should be used when closing specific defects in the skin. Major factors include the functionality and appearance of the scar, as well as the incidence of complications (e.g., infection, wound dehiscence, suture abscesses) among different surgical techniques. Other important considerations include the time taken to perform the closure, the cost of materials, and patient-specific factors, such as differences in postoperative care regimens and the need to return for removal of non-absorbable sutures.

In this chapter, we will review the level of evidence supporting various primary closure techniques. These techniques pertain to repairing simple cutaneous defects resulting from traumatic lacerations, extirpation of cutaneous malignancies, and excision of benign neoplasms. This includes comparisons of deep dermal suture materials and associated suturing techniques as well as comparison of techniques for epidermal closure with sutures versus adhesive strips, tissue adhesives, or staples.

In conducting this review, a total of 35 articles comparing various methods of linear closure were assessed to determine eligibility for inclusion. These articles consisted of randomized controlled trials (RCTs) comparing two or

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more techniques for linear repair of cutaneous defects on the scalp, face, and body resulting from traumatic lacerations, Mohs micrographic surgery, excision of malignant cutaneous tumors, or excision of benign neoplasms. The demographics and comparability of the study subgroups, characteristics of the defects (size and anatomic site), methods of randomization, outcome measures, and methods of statistical analysis were evaluated in all studies. Six studies were excluded based on lack of true randomization (two studies), defects not resulting from cutaneous surgery or laceration repair (one study), comparison of outcomes resulting from different excision methods rather than closure methods (two studies), and evaluation of a homemade suture material that is not commercially available in the United States (one study). Thus, a total of 29 randomized controlled trials were included in this chapter.

Comparison of Single-Layer Closure (Transcutaneous Suture Traversing Both the Epidermis and Dermis) Versus Bilayer Closure (Single-Layer Closure with the Addition of a Buried Subcuticular Suture Layer)

Four studies were reviewed that compare single-layer closures to bilayer closures for linear repair of cutaneous defects (Table 12.1).

Indications for Procedure

Both single- and bilayer closures are considered when two important criteria are met: the patient, or caregiver, desires the wound to be closed and there is enough skin laxity to accomplish this type of wound closure. It was previously thought that bilayer closures result in less epidermal wound tension and thus generate more aesthetically pleasing scars. Consequently, if the treating surgeon had the training to perform a bilayer closure, this technique would be preferred by those who prioritize cosmetic results.

Effectiveness of Procedure

Singer et al. examined the cosmetic outcomes in 65 patients following facial laceration repairs with single-layer closures (32 patients) and bilayer closures (33 patients) [1]. All patients completed the study follow-up. The primary outcome measure was cosmetic appearance at 3 months as judged on a 100 mm visual analog scale (VAS) by both patients and blinded physician evaluators. There was no significant difference in the patient (95% confidence interval (CI) of 68.9, for single-layer versus 68.5 for bilayer closure, $p = 0.88$) or physician-reported (76.8 versus 75.8, $p = 0.73$) VAS scores at 3 months. In addition, there was no significant difference in scar width at 3 months (mean width of 1.2 mm for single-layer versus 1.4 mm for bilayer closure, $p = 0.11$) noted between the two groups. However, it was noted that the average time of closure for single layers was significantly shorter (14.7 min) as compared to bilayer closures (21.6 min, $p = 0.007$). For facial lacerations, single-layer closures are significantly faster and result in similar cosmesis as bilayer closures (*Level of evidence: 1b*).

Sadick et al. compared the outcomes of conventional bilayer closure compared to single-layer closure with a modified vertical mattress suture (VMS) technique on cutaneous defects in a high-tension area of the body (the upper back) resulting from excision of benign or atypical nevi [2]. One hundred patients were enrolled in the trial (50 patients per group), with the primary outcome measures being patient satisfaction and complication rate (infection, hypertrophic scarring, suture reaction, and scar spread >3 mm). All patients completed follow-up, and no significant differences were noted regarding patient satisfaction, infection, wound dehiscence, or suture reaction between the two groups. Patients in the modified vertical mattress suture group had significantly decreased incidence of hypertrophic scarring (2% compared to 16% in the bilayer group, $P = 0.031$) and scar spread (6% versus 24% in the bilayer group, $P = 0.02$). However, this study did not specify the follow-up duration (*Level of evidence: 2b*).

Table 12.1 Suture versus suture

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Singer 2005 [1]	Parallel-group RCT comparing single-layer and bilayer closures of facial lacerations	65 (32 single layer, 33 bilayer) enrolled. 65 completed follow-up (100%)	Cosmetic appearance on 100 mm VAS rated by patients and blinded physician observers	3 months	No significant difference in patient-reported (68.9 versus 68.5, $P = 0.88$) or physician-reported (76.8 versus 75.8, $P = 0.11$) VAS scores for single- and bilayer closure	1B
Sadick 1994 [2]	Parallel-group RCT comparing single-layer with modified vertical mattress (VMS) to bilayer closure	100 (50 single layer, 50 bilayer) enrolled. All completed follow-up (100%)	% of patients satisfied Complication rate (infection, wound dehiscence, hypertrophic scarring, suture reaction, and scar spread >3 mm)	Not specified	No significant difference in patient satisfaction between single-layer closure and modified VMS No significant difference in infection, wound dehiscence, or suture reaction Significantly less hypertrophic scarring (2% versus 16%, $P = 0.02$) and scar spread (6% versus 24%) in single-layer modified VMS group	2B
Ling 2015 [3]	Randomized split-scar study comparing single-layer (1LT) versus modified bilayer (M2LT) versus standard bilayer (S2LT)	Total of 214 excisions (in 161 patients) enrolled: 116 excisions in the 1LT:S2LT group and 98 excisions in the S2LT:M2LT group 83 of 1LT:S2LT (72%) and 79 of the S2LT:M2LT (81%) excisions completed 6-month follow-up	Cosmetic appearance on 100 mm VAS, the Observer's Scale (OS), Patient Scar Scale (PS), and Stony Brook Scar Evaluation Scale (SB) rated by patients and blinded physician observers at 6 months	Suture removal at 2 weeks 6 months	S2LT slightly superior to 1LT on all four rating scales, but not statistically significant M2LT superior to S2LT on the VAS (85.9 versus 83.3, $P = 0.04$) and SB Scale (4.4 versus 3.3, $P = 0.0001$) Due to split-scar design, could not compare rates of wound complications between groups	2B

(continued)

Table 12.1 (continued)

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Kannan 2016 [4]	Parallel-group RCT in scalp lacerations comparing bilayer closure to single-layer closure with pulley sutures	21 patients enrolled (11 to bilayer, 10 to pulley suture). All patients completed 6-month follow-up (100%)	Scar assessment with Patient and Observer Scar Assessment Scale (POSAS) at all follow-up visits Single blinded assessor rating on 10 mm VAS of photographs from 6-month follow-up visits Mean repair time	Suture removal at 2 weeks Long-term at 2 months and 6 months	POSAS score for pulley suture deemed superior to bilayer closure at the 2-month (3.1 ± 1.5 versus 6.6 ± 2.3, $P < 0.001$) and 6-month visits (11.9 ± 3.2 versus 19.0 ± 7.7, $P = 0.015$) No significant difference in VAS scores of photographs (4.8 ± 2.6 in pulley versus 4.2 ± 1.9 in bilayer) Pulley suture group with significantly shorter mean time of repair (4.6 ± 1.5 min versus 10.0 ± 1.5 min, $P = 0.001$) No infections on either group. One hematoma and one wound dehiscence in pulley group (not significant)	1B
Wang 2015 [5]	Randomized split-scar study comparing subcuticular set-back sutures to buried vertical mattress sutures (BVMS) followed by adhesive tape for epidermal closure	46 patients enrolled, 42 completed 3-month follow-up (91%)	Cosmetic scar outcome on 7-point Likert Physician Global Scar Assessment scale and POSAS	3 months	Set-back sutures provided statistically significant wound eversion Set-back sutures deemed overall superior to BVMS (median score of 1 on Likert scale) Superior outcomes for set-back side in the POSAS score (13 ± 8.7 set-back versus 16.2 ± 12.0, $P = 0.039$) Near-significant decrease in spitting sutures on set-back versus BVMS sides (3 versus 11, $P = 0.058$) No significant difference in dehiscence (one wound, both sides) and infection (no patients)	1B

Table 12.1 (continued)

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Regan 2013 [6]	Parallel-group RCT comparing poliglecaprone 25 and polyglactin 910 for subcuticular closure	155 patients enrolled, 140 patients completed follow-up (90%)	Cosmetic appearance on 10 mm VAS Rates of suture extrusion and degree of scar lumpiness	1-week suture removal 1 month 2 months 3 months	No significant difference in VAS scores (1.8 poliglecaprone 25 versus 2.1 polyglactin 910) at 3 months Significant decrease in suture extrusion in poliglecaprone 25 group (3.1% versus 11.4%, $P < 0.01$) No significant difference in degree of scar lumpiness (both groups rated 22%) No reported infections or dehiscence	2B
Kia 2013 [7]	Randomized split-scar study comparing subcuticular closure with Poly-4 hydroxybutyrate (P4HB) versus polyglactin 910 suture	22 patients enrolled, 20 patients (23 defects) completed follow-up (91%)	Cosmetic outcome rated with 100 mm VAS and Hollander Wound Evaluation (HWE) scales Quantitative measurement of scar spread	Suture removal (time not specified) 3 months 2 months	Significantly decreased scar spread in P4HB group at 3 months (0.7 ± 0.7 mm versus 1.7 ± 2.5 mm, $P = 0.008$) and 12 months (0.9 ± 1.5 mm versus 3.2 ± 4.3 mm, $P = 0.001$) No clinically significant differences noted in the VAS scores at 3 months (69 ± 16 versus 62 ± 17, $P = 0.03$) or 12 months (72 ± 13 versus 62 ± 19, $P = 0.001$), though some components reached statistical significance No clinically significant differences in HWE scores at 3 months (4.2 ± 1.1 versus 3.8 ± 1.3, $P = 0.07$) or 12 months (4.0 ± 1.2 versus 3.7 ± 1.4, $P = 0.02$) Significantly more local suture reaction on P4HB halves compared to polyglactin 910 (35% versus 9%, P not specified)	1B

(continued)

Table 12.1 (continued)

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Kappel 2015 [8]	Randomized split-scar study comparing everted and planar closures	50 patients enrolled, 43 completed follow-up (86%)	Cosmetic appearance of scar on POSAS Scar height and width	3 months 6 months	No significant difference in total POSAS scores for everted and planar closures at 3 months (13.73 ± 5.41 versus 13.33 ± 6.06, $P = 0.62$) or 6 months (12.42 ± 4.73 versus 13.05 ± 5.60, $P = 0.10$)	1B
Rosenzweig 2010 [9]	Randomized split-scar study comparing epidermal closure with poliglecaprone 25 versus non-Prolene	52 patients enrolled, 44 patients (48 defects) completed follow-up (85%)	Global cosmetic appearance of wound halves relative to each other	1-week suture removal 4 months	85% of patients did not demonstrate any difference between two halves at 4 months. 10% had superior outcomes with non-absorbable Prolene®, and 4% had superior outcomes with poliglecaprone 25. None of the above were deemed significant ($P = 0.63$)	1B
Moody 2015 [10]	Randomized split-scar study comparing epidermal closure with running horizontal mattress (RHM) and simple running suture	55 patients enrolled, 47 completed study follow-up (86%)	Global cosmetic appearance of wound halves relative to each other	1-week suture removal 6 weeks 6 months	At 6-month follow-up, RHM was deemed superior in 53% of patients, equivalent in 36% of patients, and inferior in 11% ($P < 0.05$)	1B
Alam 2006 [11]	Parallel-group RCT comparing four types of epidermal closure: simple running Prolene® removed after 14 days, subcuticular Prolene® removed after 14 days, subcuticular Prolene® left in place, and subcuticular polyglactin 910 left in place	Enrolled 36 patients (each with 2 excisions for total of 72 wounds). All completed follow-up (100%)	Cosmetic appearance measured on 5-point ordinal scar scale and scar width (primary) Cosmetic appearance based on Vancouver Scar Scale (VSS) and Hollander Wound Evaluation (HWE) scores	2-week suture removal, where applicable 3 months 9 months	Statistically significant differences were detected in overall scar appearance between groups at 3 and 9 months ($P < 0.001$), vascularity ($P = 0.001$ at 3 months, $P < 0.001$ at 9 months), scar distortion ($P = 0.04$ at 3 months, $P < 0.001$ at 9 months), contour irregularity ($P < 0.001$ at 3 months), and wound edge eversion ($P = 0.01$ at 3 months) Subcuticular running polyglactin 910 left in place produced the best cosmetic outcome, followed by subcuticular Prolene® left in place.	1B

Ling et al. performed a randomized split-scar study following elliptical excision of benign and malignant cutaneous lesions on the head and neck, trunk, and extremities with three different interventions. One hundred and sixty-one patients (214 excisions) were enrolled comparing single-layer wound closure (1LT, consisting of simple interrupted monofilament nylon), modified two-layer closure (M2LT, consisting of interrupted deep dermal monofilament polyglyconate suture followed by cuticular closure with adhesive tape), and standard two-layer closure (S2LT, interrupted deep dermal monofilament polyglyconate suture followed by cuticular closure with simple interrupted monofilament nylon suture) [3]. Half of each wound was randomized to receive the standard two-layer closure and the other half would either receive the single-layer or modified two-layer closure. A total of 116 excisions compared 1LT:S2LT and 98 excisions compared S2LT:M2LT. A total of 83 of the 1LT:S2LT (72%) and 79 of the S2LT:M2LT (81%) of excisions completed 6-month follow-up, and outcomes assessed included cosmetic appearance of the scar as interpreted by the patient and blinded observers (measured with multiple validated instruments including a 100-point VAS, the Observer's Scar Scale (OS), Patient Scar Scale (PS), and Stony Brook Scar Evaluation Scale (SB)). At the 6-month follow-up, the standard two-layer closure was slightly superior to single-layer closure in the above outcome measures, but this was not statistically significant. Comparing the standard two-layer and modified two-layer closures (using adhesive tape for cuticular layer), the modified two-layer closure was shown to be statistically superior in terms of patient VAS score (85.9 versus 83.3, $P = 0.04$), Observer's Scar Scale ($p = 0.04$), and Stony Brook Scar Evaluation Scale (4.4 versus 3.3, $P = 0.0001$). This was attributed to the lack of cross-hatching when adhesive tape was used for the cuticular closure (*Level of evidence: 2b*).

Kannan et al. evaluated the closure of post-surgical scalp defects in 21 patients, comparing the use of a standard bilayer closure with 4-0 polyglactin 910 (Vicryl®) buried vertical mattress sutures (BVMS) to 3-0 nylon monofilament pulley sutures (11 randomized to the bilayer and 10 to the pulley suture group) [4]. The duration of the repair procedure was recorded, and follow-up assessments with the Patient and Observer Scar Assessment Scale (POSAS) were completed at three points in time (2 weeks, 2 months, and 6 months). All patients completed study follow-up. There was lack of consistency in the observer scores which the authors attribute to having different blinded observers perform the follow-up evaluations, and this was remedied by having a single blinded physician observer rate before and after photographs of the scars at the initial 2-week and 6-month follow-up visits according to a visual analog scale (VAS). The time for repair was found to be significantly shorter with the pulley suture technique as compared to bilayer closure (4.6 ± 1.5 min versus 10 ± 1.5 min, $p = 0.001$). The pulley suture technique was deemed superior to bilayer closure in terms of the blinded observer score at the 2-week and 6-month follow-up points (3.1 ± 1.5 and 11.9 ± 3.2 in pulley group compared to 6.6 ± 2.3 and 19.0 ± 7.7 for bilayer closure, $p < 0.001$ and $p = 0.015$, respectively). The VAS scores of before and after photographs failed to show any statistically significant difference between the bilayer and pulley groups (4.8 ± 2.6 and 4.2 ± 1.9). No infections were observed in either group, and two patients in the pulley group had wound-healing complications (one hematoma and one wound dehiscence). The conclusion of the study was that for scalp reconstruction, single-layer pulley sutures resulted in time and cost reduction compared to standard bilayer closure and there was no significant difference in scar appearance (*Level of evidence: 1b*).

Preoperative Evaluation

Determination of the most appropriate method of reconstruction (secondary intention healing, primary closure, or repair with a tissue flap or skin/cartilage graft) is primarily based on clinical evaluation by the treating surgeon. Variables such as the location and position of the defect relative to anatomic free margins, defect size, laxity of the surrounding tissue, and patient health (including comorbidities such as smoking and diabetes,

which may impact the success rate of reconstruction with a tissue flap or graft) will all factor into the surgeon's clinical decision-making process when selecting a mode of reconstruction. Evaluation of the thickness of the patient's dermis will determine if they are eligible for deep dermal sutures. Patients who are of advanced age or on long-term glucocorticoids may have extremely atrophic dermal tissue that will not hold deep dermal sutures. In general, single-layer and bilayer closures may be considered in cutaneous defects eligible for primary closure based on the surgeon's clinical determination of the above factors.

Best Techniques and Performance

In the study by Singer et al. [1], single-layer closure consisted of interrupted 6-0 polypropylene (Prolene®, Ethicon Inc.) cuticular sutures. Bilayer closure was performed with inverted deep dermal 5-0 polyglactin 910 (Vicryl®, Ethicon Inc.) sutures and interrupted 6-0 polypropylene (Prolene®) cuticular sutures.

Sadick et al. [2] performed bilayer closure with interrupted buried deep dermal 4-0 or 5-0 polyglactin 910 (Vicryl®) or polydioxanone (PDS®, Ethicon Inc.) suture followed by cuticular sutures. Single-layer closure was performed with a modified vertical mattress suture technique using 4-0 or 5-0 Vicryl® or PDS® suture. The modified vertical mattress suture was performed by inserting the needle in the near side of the wound through the deep reticular dermis at a depth of 5–8 mm, bringing the suture out to the skin surface 4–6 mm from the wound edge, and reinserting the needle through the same puncture site while angulating the suture to be placed more superficially in the dermis. The needle was then inserted into the far side of the wound at the equivalent superficial sub-epidermal level and brought out through the epidermis. Finally, the suture was reinserted through the same puncture site and angulated to exit at the equivalent level of the reticular dermis at a depth of 5–8 mm and finished with a buried surgeon's knot.

Single-layer wound closure in the study by Ling et al. [3] was performed with simple interrupted monofilament nylon. Modified two-layer closure was performed with interrupted deep dermal monofilament polyglyconate (Maxon™, Covidien) sutures followed by cuticular closure with adhesive tape. Standard two-layer closure was performed with interrupted deep dermal monofilament polyglyconate suture followed by cuticular closure with simple interrupted monofilament nylon suture.

In the study by Kannan et al. [4] bilayer closure was performed with 4-0 polyglactin 910 (Vicryl®) buried vertical mattress sutures followed with running 5-0 fast-absorbing plain gut suture (Fastgut®, Ethicon Inc.) for epidermal closure. Pulley sutures were performed by placing interrupted pulley sutures using 3-0 nylon monofilament suture (Ethilon®, Ethicon Inc.) in the center of the wound to reduce tension and subsequent placement of horizontal mattress sutures on the wound ends with the same 3-0 nylon suture.

Safety

In the study by Singer et al. [1], there were no incidences of wound infection or dehiscence reported in either the single-layer closure group (32 patients) or the bilayer repair group (33 patients) during the 3-month follow-up period.

Sadick et al. [2] compared the rates of infection, hypertrophic scarring, wound dehiscence, suture reaction, and wound spread (defined as scar diameter >3 mm) between the bilayer closure (50 patients) and modified vertical mattress (50 patients) groups. It was noted that the rate of wound infection was not significantly different in the bilayer closure (4%) and modified vertical mattress suture (6%, P = not statistically relevant) groups. In addition, the rates of wound dehiscence (2% versus 6%) and suture reaction (4% versus 6%) were not significantly different between the two groups. However, it was noted that the incidence of hypertrophic scarring was significantly higher in the bilayer closure group

(16% versus 2%, $P < 0.031$), as was development of a spread scar (24% versus 6%, $P < 0.02$).

Due to the split-scar design of the study by Ling et al. [3], it was not possible to directly compare the rates of complications (including wound infection, dehiscence, and hematoma) between the single-layer closure, standard bilayer closure, and modified bilayer closure groups. The study had an overall infection rate of 3%, with two of the six wound infections occurring in the defects closed with single-layer/standard bilayer closure (95 wounds) and four occurring in the modified bilayer/standard bilayer closure group (83 wounds). The overall rate of suture spitting was 1.5% and occurred in a total of three wounds (two in the single-layer/standard bilayer group and one in the modified bilayer/standard bilayer cohort). Wound dehiscence occurred in total of three patients (1.5%), and all occurred in the modified bilayer/standard bilayer group.

In the study of scalp wounds by Kannan et al. [4], the incidence of wound infection, dehiscence, and bleeding complications was compared between the bilayer closure (11 patients) and pulley suture groups (10 patients). No wound infections were reported in any of the study patients. One case of wound dehiscence occurred in the pulley suture group, as did one hematoma.

Postoperative Care and Follow-Up

If non-absorbable cuticular sutures are used in the repair, follow-up in 5–14 days (depending on anatomic site) is required for suture removal. If the epidermis is closed with absorbable sutures (either in a standard or subcuticular fashion) or adhesive tape is used, no return visit for suture removal is required.

Alternative Procedures and Modifications

Alternatives to linear repair with single or bilayer closure include healing via secondary intention, placement of a tissue (skin and/or cartilage) graft, and reconstruction with a cutaneous flap.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
For closure of uncomplicated facial lacerations, repair with a single-layer closure may yield nearly equivalent cosmetic and functional outcomes to standard bilayer closure (which was found to be slightly superior, but not significantly so, in terms of scar appearance), with the advantage of saving a significant amount of time [1].	B
Single-layer closure using a modified vertical mattress technique may provide equivalent functional outcomes to standard bilayer closures, with the potential benefits of improved scar appearance (decreased hypertrophic scarring and development of a spread scar) [2].	C
Comparison of a standard two-layer closure (with absorbable deep dermal and interrupted non-absorbable cuticular sutures) was slightly superior to single-layer closure with non-absorbable cuticular sutures in terms of scar appearance (but not statistically significant). Scar appearance following modified two-layer closure (using adhesive tape for the cuticular layer) was statistically superior to standard two-layer closure in terms of scar appearance assessed through multiple validated assessment tools. The modified two-layer closure was also significantly faster to perform [3]. The study was limited by a high dropout rate (28% of the excisions comparing single-layer and standard two-layer and 19% of the excisions comparing the standard and modified two-layer closures), and by the split-scar study design, it was not possible to compare rates of dehiscence, postoperative symptoms, or wound infection between the three groups.	C
For closure of scalp defects, single-layer repair using a pulley suture technique was shown to be non-inferior to standard bilayer repair in terms of cosmetic outcome and complication rates. The pulley suture technique also decreased procedure duration and material cost compared to bilayer closure [4]. However, conclusions regarding the efficacy and safety of this technique are limited by the small number of enrolled subjects in this study.	C

Comparison of Types and Techniques for Placement of Deep Dermal Sutures

A total of four studies were reviewed comparing various techniques and materials for placement of deep buried subcuticular sutures in determining the functional and aesthetic scar outcomes (Table 12.1).

Indications for Procedure

Indications for the placement of deep dermal sutures are similar to single- or bilayered wound closure.

Effectiveness of Procedure

Wang et al. [5] conducted a split-wound study in 42 patients evaluating the scar appearance and wound eversion achieved with subcuticular set-back sutures compared to buried vertical mattress sutures for deep dermal closure. The cosmetic outcomes were evaluated by two blinded observers at the 3-month follow-up visit using the Likert physician global scar assessment scale. Additionally, observers and patients completed the total Patient and Observer Scar Assessment Scale (POSAS), where lower scores are given to scars that appear most similar to normal skin. The set-back suture provided statistically significant wound eversion, and the set-back suture side was rated 1 point better than the buried vertical mattress side. Moreover, the patient and observer total POSAS scores were significantly lower for the set-back suture side (mean score of 13 ± 8.7 compared to 16.2 ± 12.0, $P = 0.039$) (*Level of evidence: 1b*).

Regan and Lawrence [6] performed a parallel-group study in 140 patients comparing poliglecaprone-25 (Monocryl®, Ethicon Inc.) and polyglactin 910 (Vicryl®) deep dermal sutures for closure of Mohs defects. The method of epidermal closure was via placement of cuticular sutures, but the type and technique varied among the participants in the trial. The rates of suture extrusion, degree of scar lumpiness, and cosmetic appearance of scars at 3-month follow-up (on a 10-point visual analog scale) were compared between the two groups. A significant decrease in the rate of suture extrusion was observed in the poliglecaprone-25 group as compared to polyglactin 910 (3.1% versus 11.4%, $P < 0.01$). There was no significant difference in scar lumpiness between the two groups (both 22%) or scar appearance at 3 months (10-point VAS scores of 1.8 and 2.1, respectively) (*Level of evidence: 2b*).

In a split-scar study of 23 wounds in 20 patients, Kia et al. [7] examined the use of long-acting absorbable suture composed of poly-4-hydroxybutyrate (P4HB, MonoMax®, B. Braun Melsungen AG) to standard polyglactin 910 (Vicryl®) for closure of high-tension defects resulting from cutaneous malignancy excisions on the trunk. Outcome measures included quantitative scar spread as well as qualitative assessment with a 100-point visual analog scale (VAS) and Hollander Wound Evaluation Scale (HWE) at 3- and 12-month follow-up points. Significantly lower average scar spread was noted in the P4HB wound halves at 3 and 12 months (0.7 mm ± 0.7 mm and 0.9 mm ± 1.5 mm, respectively) as compared to polyglactin 910 (1.7 mm ± 2.5 mm and 3.2 mm ± 4.3 mm, respectively). Investigators did not note any clinically significant differences in the VAS (PH4B scores of 69 ± 16 and 72 ± 13 versus 62 ± 17 and 62 ± 19 in polyglactin group, $P = 0.03$ and $P = 0.001$) or HWE scores (4.2 ± 1.1 and 4.0 ± 1.2, in PH4B halves versus 3.8 ± 1.3 and 3.7 ± 1.4 for polyglactin 910, $P = 0.07$ and $P = 0.02$) at 3 and 12 months, respectively. Though some of the components reached statistical significance, the difference did not reach a predetermined level of clinical significance (*Level of evidence: 1b*).

Kappel et al. [8] performed a randomized, split-scar study in 43 patients comparing cosmetic outcomes of everted (accomplished via dermal set-back or inverted vertical mattress sutures) versus planar closure (with simple buried cuticular suture) following treatment for cutaneous malignancy with either a Mohs surgical

procedure or elliptical excision. The main outcome measure was scar appearance as judged by two blinded observers on the POSAS scale at the 3- and 6-month follow-up visits. In addition, scar height and width were measured at each follow-up visit. No significant difference in total POSAS scores was seen for everted and planar closures at 3 months (13.73 ± 5.41 versus 13.33 ± 6.06, $P = 0.62$) and 6 months (12.42 ± 4.73 versus 13.05 ± 5.60, $P = 0.10$). In addition, no statistically significant differences in scar height and width were observed between the everted and planar closure halves at the 3- and 6-month follow-up times (everted heights 2.17 ± 1.07 mm and 2.0 ± 0.96 mm compared to planar heights 1.90 ± 0.98 mm and 2.03 ± 1.10 mm, respectively, $P = 0.20$ and $P = 0.77$; everted width 2.40 ± 1.17 mm and 1.93 ± 0.97 mm compared to planar width 2.18 ± 1.2 mm and 2.08 ± 1.16 mm, respectively, $P = 0.29$ and $P = 0.27$) (*Level of evidence: 1b*).

Preoperative Evaluation

Preoperative evaluation for the placement of deep dermal sutures is similar to single- or bilayered wound closure.

Best Techniques and Performance

In the split-scar study by Wang et al. [5] comparing subcuticular set-back sutures to buried vertical mattress sutures (BVMS), polyglactin 910 (Vicryl®) suture was used for all subcuticular closures except for one in which a protocol violation occurred and polydioxanone (PDS®) was used. The size of the subcuticular suture varied according to wound location and surgeon preference but was kept consistent between both sides of each wound. The set-back sutures were placed on the underside of the dermis at the dermal-subcutaneous junction to produce wound eversion upon securing the buried knot. The first throw of the set-back suture enters and exits the undermined surface of the dermis. The BVMS were placed in standard fashion, with the first throw entering the undermined surface of the dermis on the near side of the wound and exiting through the vertical edge of the dermis, before entering the dermis at the equivalent level on the far side and exiting on the undermined dermal surface where the final knot was buried. The protocol dictated cuticular closure with adhesive strips to minimize any confounding factors such as track marks from epidermal placement of sutures. Adhesive strips were used to close all but six wounds in which protocol violations occurred and cuticular closure was accomplished with rapid absorbing gut or polyglactin 910 sutures (however, these were still included in the analysis because the treatment was consistent on both sides of the wound).

In the parallel-group study by Regan et al. [6], subcuticular closure was accomplished via placement of interrupted deep dermal sutures with either poliglecaprone-25 (Monocryl®) or polyglactin 910 (Vicryl®). The authors did not specify the suture sizes used in the study. Epidermal closure was accomplished via placement of cuticular sutures, which was variable according to surgeon preference and not specified in the study.

In the split-scar study by Kia et al. [7], wound halves were randomized to subcuticular closure with 3-0 intradermal P4HB (MonoMax®) or 3-0 intradermal polyglactin 910 (Vicryl®). Cuticular closure was accomplished with polypropylene suture (size and cuticular suture method not specified by the authors).

In the split-scar study by Kappel et al. [8], the deep dermis on the everted wound halves was closed with either dermal set-back sutures (described previously in the study by Wang et al. [5]) or inverted vertical mattress sutures using 3-0, 4-0, or 5-0 polyglactin 910 (Vicryl®) sutures depending on the surgeon's judgment. The wound halves in the planar closure group received subcuticular closure with a simple buried cuticular suture. For all wounds, cuticular closure was accomplished with adhesive strips (Steri-Strips™, 3 M™).

Safety

In the study by Wang et al. [5] of 42 patients, no wound infections occurred. One wound located on the nuchal neck dehisced (on both sides). There was noted to be a decrease in the incidence of spitting sutures on the wound halves closed with set-back sutures (three patients) as opposed to the BVMS wound halves; this approached but did not reach significance (11 patients, $P = 0.058$).

Regan et al. [6] did not report any cases of wound infection or dehiscence in the 140 patients studied. The only postoperative complication reported was the rate of suture extrusion, which was found to be lower in the poliglecaprone-25 group as compared to the polyglactin 910 group ($P = 0.058$).

In their comparison of P4HB and polyglactin 910 sutures, Kia et al. [7] reported significantly more local suture reactions on the PH4B wound halves. In total, 8 out of 23 (35%) of PH4B wound halves developed erythema consistent with local suture reaction compared to 2 out of 23 (9%) of the polyglactin 910 halves. The authors theorized that the extended duration of the PH4B suture was the major factor contributing to the increase in local suture reactions observed. One patient developed a postoperative hematoma complicated by secondary dehiscence that was isolated to the polyglactin 910 side of the wound.

No postoperative complications (including wound infection, hematoma, and wound dehiscence) were reported by the authors in the split-scar study of wound eversion versus planar closure by Kappel et al. [8]

Postoperative Care and Follow-Up

As the deep dermal sutures are composed of absorbable material such as polyglactin 910 (Vicryl®), poliglecaprone (Maxon®), and poly 4-hydroxybutyric acid (P4HB, MonoMax®), a postoperative visit for suture removal is only indicated if non-absorbable cuticular sutures were placed. Placement of absorbable subcuticular sutures may however result in suture "spitting" if the suture material extrudes through the skin during the healing process, necessitating removal of the extruded suture as well as drainage of any purulent material that may have accumulated. In addition, postoperative antibiotics may be required in the event of suture abscess development at the discretion of the treating surgeon.

Alternative Procedures and Modifications

Alternatives to bilayer wound closure include healing via secondary intention as well as single-layer closure.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Use of dermal set-back sutures for subcuticular closure as described by Wang et al. [5] was associated with superior wound appearance as well as a significant decrease in the incidence of spitting sutures when compared to buried vertical mattress sutures (BVMS). Surgeons should consider their use. However, future studies would help better define both the benefits and harms of the set-back and buried vertical mattress suture technique.	B
Comparison of poliglecaprone 25 (Monocryl®) and polyglactin 910 (Vicryl®) subcuticular sutures as described by Regen et al. [6] demonstrated equivalent scar appearance and lumpiness at 3-month follow-up; however, use of poliglecaprone 25 was associated with a significant decrease in the incidence of spitting sutures as compared to polyglactin 910, indicating poliglecaprone 25 may be a superior choice. Future studies collaborating the results of Regen et al. would help improve the confidence of their conclusions.	C

Findings	GRADE score: quality of evidence
Comparison of long-acting absorbable suture poly-4-hydroxybutyrate (P4HB, MonoMax®) versus polyglactin 910 (Vicryl®) by Kia et al. [7] demonstrated equivalent scar appearance at 3 and 12 months as measured on a visual analog scale. Though the P4HB suture was associated with decreased scar width, it also demonstrated a significantly increased incidence of local suture reactions. Given equivalent cosmetic outcomes and higher complication rates with P4HB, surgeons may consider polyglactin 910 to be preferable, until further studies can be conducted.	B
Split-scar comparison of everted versus planar closure by Kappel et al. [8] failed to demonstrate a significant difference in scar appearance, scar height, and scar width at 3 and 6 months. Since many of the closures were performed off the head and neck area, more study is needed before final conclusions can be drawn on the efficacy of wound edge eversion in those locations.	B

Comparison of Types and Techniques for Placement of Cuticular Sutures

A total of three studies comparing the scar outcomes achieved with various suture types (absorbable versus non-absorbable) and techniques for cuticular closure were reviewed (Table 12.1).

Indications for Procedure

Re-approximation of the epidermis is thought to be important for ensuring optimal cosmetic outcome of the resultant scar and quick wound healing. It is indicated where cosmetic outcomes are valued or where there is a gap between the wound edges after placement of buried deep dermal sutures.

Effectiveness of Procedure

Observing that there is often enough absorbable suture remaining to utilize for cuticular closure following placement of the subcuticular sutures, Rosenzweig et al. [9] conducted a split-scar study that examined the cosmetic results of facial Mohs defects following superficial closure with 5-0 poliglecaprone-25 absorbable suture (Monocryl®) compared to 6-0 polypropylene (Prolene®) placed in a simple running fashion. A total of 52 patients with 52 Mohs defects were enrolled, and 44 patients (48 Mohs defects) completed the study. The outcome measure was the global cosmetic appearance of each wound half relative to the other at the 1-week (following suture removal) and 4-month mark, by a blinded physician evaluator. At the 4-month follow-up, 85% of patients did not demonstrate any difference between the 5-0 poliglecaprone and 6-0 polypropylene sides of the wounds. A total of 10% of patients had cosmetically superior outcomes with 6-0 polypropylene, and 4% demonstrated better cosmetic appearance with 5-0 poliglecaprone. Neither of these differences in cosmetic outcome were statistically significant between the two suture types ($P = 0.63$). The authors advocated for consideration of using remaining absorbable suture to complete cuticular closure to reduce waste and promote cost savings (estimated $6.00 per package of 6-0 polypropylene per patient), but did not directly compare mean cost of repair in this study (*Level of evidence: 1b*).

In a split-wound study, Moody et al. [10] compared the cosmetic outcomes of a running horizontal mattress (RHM) suture and simple running suture for epidermal closure of facial Mohs defects in 55 patients, 47 of which completed the study. All defects had the same method of deep dermal closure with interrupted 4-0 or 5-0 poliglecaprone (Monocryl®), and wounds were randomized to have either the superior or inferior half closed with the RHM suture technique. The outcome was global cosmetic appearance of the wound halves at 1-week, 6-week, and 6-month follow-up points, and the wounds were assessed by a blinded observer to determine the cosmetically superior half. At the 6-month follow-up, the RHM half was deemed superior in 53% of patients, cosmetically equivalent in 36%, and worse in 11% of patients ($P < 0.05$). The authors postulated that the primary reason for the observed cosmetic superiority of RHM over simple running in this study was the

increased wound eversion afforded by the RHM suture (*Level of evidence: 1b*).

In a parallel-group randomized controlled study, Alam et al. [11] compared the cosmetic and functional outcomes of four types of epidermal closures following elliptical excision of atypical nevi on the trunk or extremities in 36 patients (who each had 2 atypical nevi that were excised for a total of 72 wounds): simple running polypropylene suture (Prolene®) removed after 14 days (control arm, 18 wounds); subcuticular running polypropylene suture removed after 14 days (18 wounds); subcuticular running polypropylene suture left in place (18 wounds); and subcuticular running polyglactin 910 sutures (Vicryl®) left in place (18 wounds). All patients completed the 9-month follow-up. The primary outcome measures were scar width and blinded observer ordinal scale assessment of overall scar appearance at 3- and 9-month follow-up points. Secondary endpoints included scores on the Vancouver Scar Scale and Hollander Scar Scale. No difference in scar width was noted between groups at 3 and 9 months. Statistically significant differences were detected in overall scar appearance ($P < 0.001$ at 3 and 9 months), vascularity ($P = 0.001$, $P = <0.001$ at 3 and 9 months, respectively), scar distortion ($P = 0.04$, $P < 0.001$), contour irregularity ($P < 0.001$ at 3 months), and wound edge eversion ($P = 0.01$ at 3 months). Subcuticular running polyglactin 910 left in place produced the best overall scar appearance followed by subcuticular running polypropylene left in place. The authors also performed a secondary analysis matching high-tension sites (back and lower leg) to high- and moderate-tension sites (chest and shoulders), which was consistent with the main analysis (*Level of evidence: 1b*).

Preoperative Evaluation

Consultation with the patient regarding their expectations regarding cosmetic outcomes, willingness to return for suture removal, and tolerance for extended procedure time will help the surgeon determine which cuticular suture technique, if any, would best meet the patient's needs.

Best Techniques and Performance

In the split-wound study by Rosenzweig et al. [9], the deep dermal layer of all wounds was closed with interrupted 5-0 poliglecaprone (Monocryl®) suture, and wound halves were randomized to receive epidermal closure with either the remaining 5-0 poliglecaprone suture or 6-0 polypropylene (Prolene®) suture placed in a simple running fashion.

In the split-scar study by Moody et al. [10], comparing the running horizontal mattress (RHM) technique to simple running epidermal closure, all wounds received the same deep dermal closure with buried vertical mattress 4-0 or 5-0 poliglecaprone (Monocryl®) sutures. The superficial layer was closed using 6-0 polypropylene (Prolene®) in all defects, with half of each wound randomized to receive RHM closure and the other half to receive simple running closure. The RHM suture was performed starting with a traditional interrupted suture at the wound apex, and then the needle was reinserted on the near side of the wound 2–4 mm along the long axis and 1–2 mm from the wound edge, exiting at an equivalent point on the opposite (far) wound edge. The needle position was then reversed in the needle holder and reinserted near the skin edge of the far side of the wound, exiting at an equidistant point on the near side. The process was repeated until the midpoint of the wound was reached at which point the suture was tied off. The remaining half of the wound was closed with a simple running suture.

In the study by Alam et al. [11], all wounds received comparable deep dermal closure with vertical deep 3-0 (for sites on the back) and 4-0 (for all other trunk and extremity sites) polyglactin sutures. All four cuticular closure subgroups were performed with 5-0 caliber suture: simple running polypropylene (Prolene®) removed in 14 days, subcuticular running polypropylene (Prolene®) removed in 14 days, subcuticular running polypropylene (Prolene®) left in place, and subcuticular running polyglactin 910 (Vicryl®) left in place.

Safety

In the study by Rosenzweig et al. [9], no wound complications (infection, hematoma, wound dehiscence) occurred in any of the 44 patients (48 defects) who completed the 4-month study follow-up.

In the study of running horizontal mattress (RHM) suture compared to simple running suture for epidermal wound closure, no instances of wound infection or dehiscence were reported in the 47 patients who completed the 6-month follow-up.

In the parallel-group comparison of four methods of cuticular closure by Alam et al. [11], the only adverse events reported out of a total of 72 wounds (18 per subgroup) were partial wound dehiscence and erosion in the center of wounds closed with running subcuticular polypropylene suture left in place that were noted at the 3-month follow-up visit.

Postoperative Care and Follow-Up

When non-absorbable cuticular sutures are placed, removal is required at a separate follow-up visit, ranging from post-op day 5 (defects on the face) to post-op day 14 (defects on the trunk and extremities).

Alternative Procedures and Modifications

Alternatives to placement of cuticular sutures for epidermal closure in wounds that are closed primarily include no epidermal intervention, the use of tissue adhesives (such as Dermabond®), adhesive strips (Steri-Strips™), or staples.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
As described in the study by Rosenzweig et al. [9], cuticular closure with absorbable suture produced an equivalent cosmetic outcome to epidermal closure with non-absorbable suture in 85% of patients, 4 months postoperatively. This study supports the equivalence of absorbable suture (5-0 poliglecaprone) to non-absorbable suture (6-0 polypropylene) for epidermal closure of facial Mohs defects. Thus, surgeons need not incur the added expense of polypropylene sutures when already using poliglecaprone for subcuticular suturing.	B
In the comparison of a running horizontal mattress (RHM) suture versus simple running non-absorbable suture for epidermal closure of facial Mohs defects, Moody et al. [10] demonstrated cosmetically superior outcomes at 6 months with the RHM suture in 53% of patients and equivalence to simple running suture in 36% of patients. Though more studies are preferred before drawing final conclusions, RHM suturing appears to be superior to simple running cuticular suturing in terms of cosmetic results.	B
Looking at four different methods of cuticular closure (simple running polypropylene removed in 14 days, subcuticular running polypropylene to be removed in 14 days, subcuticular running polypropylene to be left in place, and subcuticular running polyglactin 910 to be left in place), Alam et al. [11] demonstrated the best cosmetic outcome with subcuticular running polyglactin 910 left in place, followed by subcuticular running polypropylene left in place. The authors observed that the absorbable polyglactin 910 suture produced less contour irregularity than the non-absorbable polypropylene when placed in a subcuticular fashion. Overall cosmetic outcomes for the polypropylene subcuticular sutures were improved when they were left in place instead of being removed on day 14. Given only one study has compared these three running subcuticular suturing interventions with traditional running cuticular suturing, more studies are again needed before final judgment can be determined regarding their comparative efficacies. However, it is reasonable to recommend that running subcuticular suturing with polyglactin 910 left in place be the preferred method of this type of suturing in patients with high cosmetic standards, until more studies are conducted.	B

Comparison of Sutures Versus Staples for Closure of Lacerations

A total of two studies were reviewed that compared the outcomes, time, and cost of laceration repair using either a disposable staple gun or a single layer of non-absorbable sutures (Table 12.2).

Indications for Procedure

Uncomplicated lacerations that are limited to the dermis and subcutaneous tissue without involvement of underlying structures (fascia, muscle, tendons, major vessels, and nerves) may be amenable to repair using staples or single-layer suture closure. More complex lacerations requiring a deep layer of sutures due to involvement of one of the abovementioned structures, as well as lacerations in cosmetically sensitive patients, may not be well-suited for closure with staples or a single layer of sutures.

Effectiveness of Procedure

Kanegaye et al. [12] compared the total costs and physician time requirements for repair of scalp lacerations with a disposable staple gun

Table 12.2 Sutures versus staples

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Kanegaye 1997 [12]	Parallel-group RCT comparing cost and repair time for laceration repair with staples versus single-layer suture	88 patients enrolled, 80 completed follow-up (91%)	Wound closure time and total cost of repair (materials and physician time) Patient-reported postoperative discomfort, provider-reported issues with removal	1 week for suture or staple removal	Stapling resulted in significantly shorter wound closure time (mean 65 s for staples versus 397 s for sutures, $P < 0.0001$) and lower cost of repair materials ($12.55 versus $17.59) and physician time ($23.55 versus $38.51, $P < 0.0001$) No significant difference in patient-reported postoperative pain ($P = 0.925$) Staples were more associated with increased difficulty of removal (9.8% of patients compared to 2.8% in suture group), not significant ($P = 0.24$)	1B
Orlinsky 1995 [13]	Parallel-group RCT comparing cost and repair time for laceration repair with staples versus single-layer suture	141 patients enrolled, 128 patients (161 lacerations) analyzed (91%)	Wound closure time (calculated as seconds per centimeter) Total cost of repair (materials and physician time)	No follow-up visit	Stapling resulted in significantly shorter wound closure time (8.3 s/cm versus 63.2 s/cm, $P = 0.0001$) and lower total cost of repair ($17.69 for stapling with suture kit, $7.84 without suture kit versus $21.58 for sutures) Repair time per centimeter decreased with increasing wound length	2B

compared to closure with a single layer of simple interrupted non-absorbable suture in 88 pediatric patients (aged 13 months to 16 years, 45 randomized to receive staples and 43 to suture closure) in an emergency department setting. A postoperative evaluation of the wounds was performed at 7 days in 80 patients (91% follow-up) at the time of suture or staple removal, and wounds were assessed for evidence of infection or dehiscence. In addition, parents were queried regarding the presence of postoperative symptoms (persistent pain), and the provider noted any difficulty with removal of the staples or sutures. No cosmetic or infectious complications were noted in either group, and no significant difference was noted in postoperative pain or complaints between the two groups ($P = 0.925$). There was a difference in the percentage of patients for whom the providers reported difficulties with removal (9.8% of patients in the staple group versus 2.8% in the suture group), but this was not statistically significant ($P = 0.24$). The authors found that stapling resulted in significantly shorter wound closure time (mean closure time of 65 s versus 397 s for sutures, $P < 0.0001$). In addition, the cost of staple repair was significantly less both in terms of equipment ($12.55 versus $17.59, $P < 0.0001$) and physician time ($23.55 versus $38.51, $P < 0.0001$), assuming an average compensation of $100/h for emergency department physicians (*Level of evidence: 1b*).

Orlinsky et al. [13] compared the cost and closure time for laceration repair using staples or single-layer closure with interrupted nylon sutures for wounds on the scalp, trunk, and extremities in 141 adult patients in an emergency department setting, and after excluding patients for which there was incomplete recording, a total of 161 lacerations in 128 patients were analyzed. The wound lengths, skin closure times, and number of sutures/staples used in each repair were recorded, and the cost for materials (subdividing the staple group into those in which a suture kit containing forceps, a needle driver, and scissors was used to assist with staple repair versus not used) as well as physician time (based on an hourly average of $74 for an emergency department physician) was calculated. The authors found that stapling was significantly faster than suturing (8.3 s/cm versus 63.2 s/cm, $P = 0.0001$) and that the time per centimeter decreased with increasing length of the laceration as plotted on a regression line, with the speed increasing at a more rapid rate in the staple group than the suture group ($P = 0.0001$). The average total cost for materials and labor per case was significantly lower in the staple group ($17.69 with suture kit and $7.84 without compared to $21.58 for suture repair). Notably, there was no follow-up visit or assessment of scar appearance, wound complications, or patient-subjective complaints discussed in this study. The authors stated that there was no difference in the cosmetic appearance or incidence of wound complications (infection, dehiscence) between the suture and staple groups; however, they did not report their data since some data was based on telephone reports and not direct observation (*Level of evidence: 2b*).

Preoperative Evaluation

In deciding the optimal method for laceration repair, the evaluating physician must do a thorough evaluation of both the patient and the wound to ensure that no foreign bodies are present (especially if the wound was sustained because of trauma) and there is no involvement of deeper structures such as fascia, muscle, tendons, major blood vessels, and nerves that require repair prior to closure of the skin. In addition, the location of the laceration should be considered, as wounds located in cosmetically sensitive areas such as the face may be better suited for bilayer closure. It is common practice for lacerations obtained from human or animal bite to remain open and heal by secondary intention.

Best Techniques and Performance

In the study by Kanegaye et al. [12], staples were placed using an automatic disposable sta-

pler (Precise DS-5 and DS-15, 3 M™, St. Paul, Minnesota). Wounds in the suture group were closed with a single layer of simple interrupted non-absorbable monofilament nylon or polypropylene sutures (size and manufacturer not specified).

Orlinsky et al. [13] utilized a disposable staple gun (Cricket 35 W, US Surgical Corporation, Norwalk CT) for the stapled closures and 4-0 nylon (Ethilon®) suture placed in an interrupted fashion (both simple interrupted and interrupted mattress) for cuticular closure.

Safety

Kanegaye et al. did not report any wound complications (infection or dehiscence) in either the staple or suture groups in the 80 patients (91%) that returned for 7-day follow-up and removal of staples/sutures.

Orlinsky et al. [13] did not report follow-up data (duration of follow-up, incidence of complications) but stated that there was no significant difference in the incidence of wound complications (infection, dehiscence) between the suture and staple groups. Because the actual data was not reported, it is not possible to assess the validity of this claim.

Postoperative Care and Follow-Up

If staples or non-absorbable sutures are used for the cuticular closure, the patient will need to return for a follow-up visit for removal, usually in 5–14 days, depending on the location of the laceration. If absorbable sutures were used, then the patient would not be required to return for removal.

Alternative Procedures and Modifications

Alternatives to single-layer closure with staples or sutures include bilayer repair with a deep subcuticular layer of absorbable sutures to reduce wound tension and re-approximate the dermis, as well as single-layer closure with tissue adhesive (such as Dermabond®), adhesive strips (Steri-Strips™) if it is determined that the patient is an appropriate candidate for a single-layer repair, or healing by second intention.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
For closure of pediatric scalp lacerations in the emergency department setting, Kanegaye et al. [12] reported significant savings in wound repair time as well as equipment and physician time cost in the staple group as compared to single-layer suture closure, and there was no significant difference in the rate of wound complications (none in both groups), patient-reported postoperative pain, or provider-reported difficulty of removal. However, this study did not objectively evaluate the cosmetic outcome of staple versus single-layer suture closure and this may be a significant factor in deciding the optimal method of repair in certain patients.	C
Orlinsky et al. [13] reported significant decreases in the cost and time of laceration repair with staple closure as compared to interrupted single-layer closure in the emergency department setting. However, this study had several major limitations including lack of defined patient follow-up as well as absence of data evaluating the cosmetic appearance and incidence of wound complications in the two groups. Therefore, beyond the observations that stapling is significantly faster than suturing and is associated with significantly lower material and physician time costs, it is not possible to draw any conclusion related to wound outcomes for stapled closures versus single-layer suture repairs from this study.	C

Comparison of Tissue Adhesives Versus Sutures for Closure of Lacerations or Excisions

A total of five studies were identified that compared cutaneous defects repaired with various tissue adhesives, all containing a cyanoacrylate base, versus various suture types (Table 12.3).

Indications for Procedure

N-butyl-2-cyanoacrylate (n-BCA) and 2-octyl-cyanoacrylate (OCA) adhesives are indicated for closure of clean surgical incisions and uncontaminated or thoroughly cleaned lacerations that are limited to the dermis and superficial subcutaneous tissue [14]. Generally, defect size (less than 5 cm for lacerations), skin properties including

Table 12.3 Sutures versus tissue adhesives

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Göktas 2002 [15]	Parallel-group assessor-blind, single-center, randomized trial comparing N-BCA with 5-0 or 6-0 polypropylene cuticular suture	Unknown number enrolled, 52 patients completed the study (?%)	Patient and physician 10-point VAS overall assessment, satisfaction rate, cost	3 months	Comparable VAS score for patient satisfaction: 8.12 ± 1.32 versus 7.46 ± 1.20, $p > 0.05$ Higher satisfied patients in general in the adhesives group, 23 patients (95.8%) versus 18 (43.9%, $p = 0.007$) Higher assessor satisfaction for adhesives (24 [63.2%] versus 14 [36.8%], $p < 0.001$) Lower cost for adhesive: 15 of 24 in adhesive group had costs less than $10, versus none in suture group ($p < 0.0001$) No complications in either group reported	2B

(continued)

Table 12.3 (continued)

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Quinn 1993 [16]	Parallel-group assessor-blind, single-center, randomized trial comparing N-BCA with non-absorbable monofilament sutures	41 versus 40 enrolled in adhesive versus suture group; 37 versus 38 patients completed the study in their respective groups (90% and 95%)	Mean closure time Patient VAS overall assessment VAS pain score	Day 5 for suture removal 3 months	Lower mean closure time for adhesives (7.9 min versus 15.6 min, $P < 0.001$) No significant difference for100-point VAS patient global assessment (60.6 versus 57.2, $P = 0.45$) Lower VAS pain score for adhesive (24.7 versus 43.7; $P < 0.01$) Comparable complications: Wound infection (1/37 [2.7%] versus 1/38 [2.6%], $p > 0.05$) Wound dehiscence (3/37 [8.1%] versus 2/38 [5.3%], $p > 0.05$)	2B
Kim 2015 [17]	Within-patient assessor-blind, single-center, randomized trial comparing n-butyl and 2-octyl-cyanoacrylate, with fast-absorbing gut cuticular running suture	14 versus 14 half defects were enrolled in this study; all finished the trial (100%)	10-point VAS for overall cosmesis	3 months	No significant difference in 10-point VAS scores for cosmesis (7.47 ± 0.81 versus 7.97 ± 1.25, $p > 0.05$) No complications reported in either group	2B

Table 12.3 (continued)

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Tierney 2009 [18]	Within-patient assessor-blind, single-center, randomized trial comparing 2-octylethylcyanoacrylate with rapid absorbing gut cuticular suture	8 versus 8 half defects were enrolled in this study; all finished the trial (100%)	4-point physician overall assessment 4-point pigmentation and thickness	10 days 3 months	Comparable 4-point physician overall assessment (3.19 versus 3.56, $p > 0.05$. More pigmentation with adhesives, (2.75 versus 3.5, $p < 0.05$) and comparable thickness (3.75 versus 3.88, $p > 0.05$). No complications in either group	2B
Toriumi 1998 [19]	Parallel-group assessor-blind, single-center, randomized trial comparing 2-octyl-cyanoacrylate with vertical mattress nylon cuticular suture	54 versus 57 patients enrolled in adhesive versus suture group; unknown number completed the trial (?%)	Average closure time 100-point VAS overall cosmesis Mean modified Hollander scale	Suture removal at 5–7 days 3 months 12 months	Lower average closure time in adhesives (55 s versus 237 s, $p < 0.0001$) Better 100-point VAS overall cosmesis favoring adhesive group (21.7 ± 16.3 versus 29.2 ± 17.7, $p = 0.03$) Comparable mean modified Hollander scale (0.306 versus 0.235, $p = 0.51$) No wound infections or dehiscence in either group. One acute peri-wound erythema in suture group; more erythematous suture reactions in the suture group (but was not documented)	2B

tensile properties (ultimate tensile strength, strain energy, failure stretch rate, elastic modulus rate-avoiding high-tension areas), and degree of bacterial colonization (avoiding intertriginous and hair-bearing areas) are determining factors for a dermatologic surgeon to decide whether to use tissue adhesives for epidermal closure. It has been reported to be a less effective method of closure if the deeper structures, such as deep adipose tissue or fascia, are involved.

N-butyl and 2-octyl-cyanoacrylate solution is currently approved to treat minor cuts, scrapes, burns, and minor skin irritation. As described below, some surgeons use it for superficial repair of cutaneous defects following Mohs surgery or excision. When used for this indication, it is applied after buried subcuticular sutures have been placed.

Effectiveness of Procedure

Göktas et al. [15] performed a parallel-group assessor-blind trial to compare N-BCA (Histoacryl® Blue; Braun Melsungen AG, Melsungen, Germany) to 5-0 or 6-0 polypropylene cuticular suture in a Turkish cohort population with traumatic lacerations anywhere on the body measuring less than 5 cm. Patient overall satisfaction using a 1–10 VAS score showed no significant difference between two groups at the 3-month follow-up (8.12 ± 1.32 versus 7.46 ± 1.20, $p > 0.05$ for adhesive versus suture groups, respectively). Additionally, 23 patients (95.8%) in the adhesives group, as opposed to 18 patients in suture group (43.9%), were satisfied with the results at 3-month follow-up, and this difference was statistically significant ($p = 0.007$). A similar trend was observed when the assessors were asked about the overall satisfaction regarding the outcome (24 [63.2%] versus 14 [36.8%] for adhesive versus suture groups, respectively, $p < 0.001$). Furthermore, 15 out of 24 procedures that used adhesives had costs less than 10 dollars, whereas none of the patients in suture groups ended up having less than 10-dollar costs ($p < 0.0001$). This study lacks clear descriptions of the anatomical sites of the lacerations and when and how they used 5-0 versus 6-0 sutures, and more importantly, the study has a very high dropout rate (43.4%), which decreases the generalizability of the results (*Level of evidence: 2b*).

Quinn et al. [16] in another randomized assessor-blind controlled trial compared the efficacy and safety of N-BCA with 5-0 or 6-0 nonabsorbable monofilament sutures. The study included pediatric patients with clean facial lacerations that were less than 4 cm in length and 0.5 cm in width that did not need deep subcuticular closure. The mean laceration length for both groups was about 1.5 cm (0.5–3.5). The wounds involved the hair-bearing areas, and the ones that crossed the mucocutaneous juncture were excluded in this study. Interestingly, the study only included the patients who presented between 12 p.m. and 10 p.m. All wounds were covered with an unknown subtype of Elastoplast® bandage. Mean closure time differed significantly in favor of the adhesive group (7.9 min versus 15.6 min for adhesives, the suture group, respectively, $P < 0.001$). The patient global assessment using a 1–100 VAS showed comparable results (60.6 versus 57.2, $P = 0.45$). When the patients were asked their opinion of the result 3 months after the procedure, 59% found it acceptable and 30% found it excellent in the adhesive group versus 71% and 16%, respectively, in the suture group ($P = 0.76$). Adhesive was perceived as a significantly less painful procedure using a 1–100 VAS score (24.7 versus 43.7; $P < 0.01$) (*Level of evidence: 2b*).

Kim and colleagues [17] in a randomized within-patient study included a total of 14 patients who underwent Mohs micrographic surgery for non-melanoma skin cancer (NMSC) of the forehead, temple, or cheek. They compared n-butyl and 2-octyl-cyanoacrylate (both adhesives are present within the same solution) with fast-absorbing gut cuticular running suture. The patients additionally received 5-0 polyglactin 910 (Vicryl®) buried intradermal absorbing suture as well as Steri-Strips™ for both treatments. All patients returned for the final 3-month follow-up visit. All photographs were taken in the same clinic and under the same lighting conditions. Mean closure length was 4.2 cm. These photographs were rated by six blinded individuals (one general dermatologist, one Mohs surgeon, two

nurses, and two lay persons) using a 1–10 VAS for overall cosmesis. This assessment demonstrated no significant difference between treatments in terms of 10-point VAS scores (7.47 ± 0.81 versus 7.97 ± 1.25, for adhesive versus suture group, respectively, $p > 0.05$). Most patients indicated no preference for epidermal closure technique (64%, $n = 9$), but four patients favored cyanoacrylate and only one patient favored fast-absorbing gut suture (*Level of evidence: 2b*).

In a within-patient study, Tierney and colleagues [18] evaluated the efficacy and safety of 2-octylethylcyanoacrylate cuticular closure in comparison to rapid absorbing gut closure in eight patients with Mohs defects on the chest and upper extremities. The defects were all closed with 4-0 polyglactin 910 (Vicryl®) subcuticular suture. The lesion sizes were between 3.5 and 6.7 cm. A 4-point physician overall assessment score showed comparable results (3.19 versus 3.56, for adhesive versus suture treatments, respectively, $p > 0.05$). The four-point scale for pigmentation (2.75 versus 3.5, $p < 0.05$) and thickness (3.75 versus 3.88, $p > 0.05$) showed more pigmentation and thickness post-procedure in the adhesive group than the suture group, but only the pigmentation comparison reached statistical significance at the 3-month follow-up. A similar insignificant trend was observed when the assessors evaluated wound approximation (3.63 versus 3.75, $p > 0.05$). The observations at day 10 were not blind to the assessors (*Level of evidence: 2b*).

Toriumi and coworkers [19] studied utilization of OCA in 54 patients versus vertical mattress nylon sutures for epidermal closure in 57 patients with or without subcuticular closure for linear repair of excisions or scar revisions on the face and neck in a parallel-group project. Thirty-two out of 54 patients in the adhesive group (59%) and 34 out of 57 patients in the suture group (59%) received subcuticular sutures. The mean closure volume was 112 mm^3 (range: 1–1350 mm^3). The average closure time was significantly lower in the adhesives group (55 s versus 237 s, $p < 0.0001$). Using a 1–100 VAS for overall cosmetic outcome assessed by investigators showed significantly better results in the 2-OCA group as opposed to the suture group at 1-year follow-up (21.7 ± 16.3 versus 29.2 ± 17.7, $p = 0.03$). Mean wound evaluation scores measured by the modified Hollander scale were 0.235 for the suture group and 0.306 for the 2-octyl-cyanoacrylate group ($p = 0.51$) at 3-month follow-up (*Level of evidence: 2b*).

Preoperative Evaluation

In traumatic, uncomplicated, uninfected simple lacerations, the evaluating physician must irrigate and explore the wound and ensure there is no foreign body within the defect. Also, one must determine the depth of the involvement in deciding which method should be chosen for the closure. However, in complicated wounds such as those resulting from animal and human bites, the timing and method of closure are debatable. Some experts prefer to let these defects remain open and heal by secondary intention. Moreover, it is deemed more appropriate to use adhesives and adhesive tapes in the pediatric population, as this will provide the pediatric patient and the parents with a timelier and better-tolerated experience during the laceration repair and post-procedure follow-up.

In excision or Mohs defects, closure with adhesives is best avoided in the areas including skin over the joints, intertriginous, and hair-bearing areas. However, some surgeons choose to use adhesives or adhesive tapes as adjunct support methods.

It is also important to confirm that the patient does not have a history of a contact allergy to cyanoacrylates.

Best Techniques and Performance

Göktas and coworkers [15] used N-BCA (Histoacryl® Blue) as the tissue adhesive. Patients were advised not to moisten the area for at least 2 days. They used 5-0 or 6-0 polypropylene cuticular sutures as the comparator. No further information was provided regarding the manufacturing company for the sutures or the method of suturing.

Quinn et al. [16] utilized N-BCA (Histoacryl® Blue) as the adhesive of choice. The areas were sterilized with chlorhexidine, held with gauze and man-

ual pressure to achieve hemostasis, and then the adhesive was applied with the wound edges being apposed manually. This was then held in place for 30 s to complete the application. In the comparator group, lacerations were cleaned with chlorhexidine and anesthetized with 1% lidocaine and were closed with 5-0 or 6-0 monofilament sutures. The patients were asked to return to the emergency department later to have the sutures removed.

In the Kim 2015 study [17], n-butyl and 2-octyl-cyanoacrylate (GluSeal® Tissue Adhesive, Skinstitch Corporation) cuticular closure was used as the first treatment method and was compared with 5-0 or 6-0 fast-absorbing gut simple running suture (Fast Absorbing Plain Gut, Ethicon Inc.). Both halves of the linear wound were closed with buried intradermal absorbing suture, 5-0 polyglactin 910 (Polysorb®, Covidien), and Steri-Strips™. The patients were asked to return in 7 days to have the adhesive strips removed.

Tierney et al. [18] used a bilayered closure method where the buried interrupted subcuticular absorbing sutures (4-0, polyglactin 910) were placed, and then the wound was divided into two sides. The epidermal closure was achieved by rapid absorbing gut suture in one half and with 2-octylethylcyanoacrylate tissue adhesive on the other half.

In the study performed by Toriumi and colleagues [19], patients in the first group underwent skin closure using octyl-2-cyanoacrylate. Forceps were used to maintain eversion of the skin edges during application of the adhesive when no subcutaneous suture was placed. The second group underwent vertical mattress skin closure with 5-0 or 6-0 nylon suture. An everting subcutaneous suture was used to decrease the tension of the wound edges after full-thickness skin excisions. Partial-thickness skin incisions did not require subcuticular closure.

Safety

Göktas and coworkers did not report any complications in their study (including infection or dehiscence) in either group.

Quinn et al. found an insignificant increase in peri-wound erythema in the suture group (1 of 37 [2.7%] versus 4 of 38 [11.5%], $p > 0.05$). Wound infections occurred in one patient in each group, and there was no significant difference in the rate of wound dehiscence (3 of 37 [8.1%] versus 2 of 38 [5.3%], $p > 0.05$).

Kim et al. [17] reported no incidence of wound infection, wound dehiscence, nor hematoma, seroma, or spitting sutures in any treatment groups.

Tierney and colleagues [18] also reported no side effects including infection, allergic reaction, wound inflammation, or dehiscence.

Toriumi et al. [19] reported no evidence of infection, dehiscence, or hematoma in either group. Only one patient in the adhesive group showed a significant inflammatory reaction 2 days after the procedure. Many closures with sutures showed increased redness around the wound at the 5–7-day follow-up visit, whereas the incision sites treated with octyl-2-cyanoacrylate demonstrated a lower reaction rate (data not presented in the paper). Wound approximation was achieved in both groups satisfactorily.

Postoperative Care and Follow-Up

Optionally, the patients can follow up 5–7 days after the surgery to ensure there are no complications such as wound dehiscence or wound infection. Otherwise, the patient does not require a follow-up visit for operative site evaluation.

Alternative Procedures and Modifications

Alternatives to adhesive closures include simple running or interrupted sutures, as compared above. Adhesives can also be used as a supplement to strengthen the closure in high-tensile areas. Specifically, adhesive tissue glue can be used in conjunction with adhesive tapes (Kim et al. [17]) or epidermal sutures.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In uncomplicated lacerations, less than 5 cm, N-BCA (Göktas et al. [15], and Quinn et al. [16]) or 2-octyl-cyanoacrylate can be used in areas with low tension. Deeper lacerations can be adjunctly treated with subcuticular sutures. N-BCA application is a quicker epidermal closure method than suturing. Based on the inclusion criteria of randomized trials, the use of adhesives is not advisable in lacerations with florid contamination or in hair-bearing or intertriginous areas. The rate of wound dehiscence or infection is not higher in this specific patient population. Some experts prefer manual approximation of the wound edges for at least 30 s to ensure that the fast-acting adhesives can achieve full strength before the defect returns to its previous level of tension.	B
Mohs defects closed on the forehead using n-butyl and 2-octyl-cyanoacrylate were evaluated ($M = 6.33$, SD = 0.24) as being significantly worse ($p < 0.05$) than those closed on the cheeks or temple. There was also a marginal, insignificant tendency of worse outcomes with cyanoacrylate treatment as the length of the repair increases. Based on these findings some suggest restricting the use these adhesives to smaller wounds and to those not on the forehead [17]. However, subgroup analyses of small trials are typically discouraged due to the high risk of spurious findings [20].	C
2-Octylethylcyanoacrylate was found to be comparable in most outcomes (except post-procedure pigmentation) with fast-absorbing gut cuticular sutures in the presence of additional subcuticular closure for Mohs defects on the chest and upper extremities. The relatively lower performance of 2-octylethylcyanoacrylate in terms of pigmentation was likely due to higher tension in the chest or upper extremities as opposed to the face, which is the more common site for Mohs surgery. Tierney et al. [18] support the use of cyanoacrylate adhesives for epidermal closure of Mohs defects, though their study had only a very small number of enrolled patients. No adverse events were reported in this trial.	C
Octyl-2-cyanoacrylate application is less time-consuming than vertical mattress nylon cuticular sutures in linear closures of face and neck excisions. Additionally, although octyl-2-cyanoacrylate was comparable to suturing in 3-month follow-ups, it was cosmetically superior at 1-year mark. Octyl-2-cyanoacrylate has some advantages over other cyanoacrylate derivatives including less tissue toxicity, increased 3D strength, easier application, and higher pliability. The octyl-2-cyanoacrylate's plasticizer decreases the possibility of cracking and early peeling that are more commonly seen in short-term cyanoacrylates [19].	C

Comparison of Sutures Versus Adhesive Tapes for Epidermal Closure

A total of two studies were reviewed that examined the aesthetic outcomes of wound repair using adhesive tapes in comparison to sutures for epidermal closure (Tables 12.4 and 12.5).

Indications for Procedure

The criteria determining whether wounds may be eligible for closure with adhesive strips are similar to those for the use of tissue adhesives discussed in the previous section. In addition, adhesive tapes may be appealing for eligible defects in pediatric patients as they may eliminate the need for injection of local anesthesia.

Effectiveness of Procedure

In a split-scar study, Plotner et al. [21] compared the cosmetic outcomes of post-Mohs defects on the cheek when epidermal closure was accomplished with 6–0 nylon suture versus adhesive strips. A total of 50 patients were enrolled in the study and 38 completed all follow-up endpoints.

Table 12.4 Sutures versus adhesive tape

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Plotner 2011 [21]	Randomized split-scar study comparing epidermal closure with 6-0 Ethilon® suture versus adhesive strips	50 patients enrolled, 38 completed follow-up (76%)	Cosmetic outcome assessed with 100 mm VAS	Average 3.75 months (variable between 2 and 6 months)	No significant differences in the overall VAS scores (90.1 ± 7.8 for suture, 89.1 ± 10.3 for adhesive strips, $P = 0.884$) No postoperative wound complications (infection, dehiscence) reported	2B

Table 12.5 Adhesive strips versus no cuticular closure

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Custis 2015 [22]	Split-scar, assessor-blind, single-center trial comparing adhesive strips plus subcuticular sutures to subcuticular sutures alone	48 patients enrolled, 45 patients completed the study	Scar assessment with Patient and Observer Scar Assessment Scale (POSAS) at all follow-up visits Patient and physician global assessment scale	3 months	No significant difference between groups for POSAS scores: physician (12.3 [4.8] versus 12.9 [6.3] 0.32) and patient (14.0 [7.6] versus 14.7 [7.6], $p = 0.39$) Overall assessments: Physician (2.6 [1.3] versus 2.8 [1.7] $p = 0.31$) and patient (3.4 [2.5] versus 3.4 [2.4], $p = 0.86$) No wound infections, hematomas, or seromas in either group. Wound dehiscence: 1 versus 2, $p = 0.31$. Suture abscess: 3 versus 6 ($p = 0.18$)	1B

All wounds received equivalent deep dermal closures with buried vertical mattress polyglactin 910 sutures. Outcome measures were cosmetic appearance of the wound halves on a 100-point VAS at a postoperative follow-up visit occurring after suture removal. The average follow-up time was 3.75 months. No significant differences were observed in the VAS scores between the two wound halves, including overall cosmesis (90.1 ± 7.8 for suture, 89.1 ± 10.3 for adhesive strip, $P = 0.884$), erythema (93.1 ± 8.0 for suture, 91.9 ± 10.3 for adhesive strips, $P = 0.840$), and wound contour (88.1 ± 10.5 for suture, 86.9 ± 12.3 for adhesive tape, $P = 0.811$). The authors noted that the planned study follow-up was 2 months after the procedure, but many patients followed up at different intervals due to scheduling conflicts, and this may limit the validity of the observed VAS scores as they were obtained at different postoperative points in time (*Level of evidence: 2b*).

In another split-scar study, Custis et al. [22] compared Mastisol® liquid adhesive-coated adhesive strips plus subcuticular buried vertical mattress sutures to subcuticular buried vertical mattress sutures alone. By default, side A of the defect was either superior or to the left, from the surgeon's perspective, in all treated wounds. Forty-eight split wounds were enrolled in this study, and only three wounds were lost to follow-up. This study included Mohs and excision defects in a wide range of anatomical locations. The mean length of lesions was 5.3 (SD: 2.3). Patients were advised to use petroleum to both sides of the repair defect twice daily for 7 days with a sterile cotton-tipped applicator. Physician (2.6 [1.3] versus 2.8 [1.7] $p = 0.31$) and patient (3.4 [2.5] versus 3.4 [2.4], $p = 0.86$) global assessment failed to show any difference between two groups. Scar assessment with Patient and Observer Scar Assessment scale (POSAS) did not demonstrate any significant difference between two groups based on physician (12.3 [4.8] versus 12.9 [6.3] $p = 0.32$) and patient scoring (14.0 [7.6] versus 14.7 [7.6], $p = 0.39$). This insignificant difference also includes all sub-scores (*Level of evidence: 1b*).

Preoperative Evaluation

Evaluation of subjects for the use of deep dermal sutures only or deep dermal sutures and adhesive strips is similar to that of single transcutaneous suturing and bilayered suturing.

Best Techniques and Performance

In the study by Plotner et al. [21], all wounds received equivalent deep dermal closure with buried vertical mattress (BVMS) polyglactin 910 sutures. The wound halves were then randomized to receive superficial 6-0 nylon sutures to one half and adhesive strips (brand and manufacturer not specified) to the other half.

Custis et al. [22] used interrupted subcuticular buried vertical mattress sutures for both sides of the defects. In the half assigned to adhesive strips a supplemental adhesive (Mastisol®, Eloquest Healthcare Laboratories, Ferndale Pharma Group, Inc.) was first applied and allowed to dry. Then the adhesive strips (Steri-Strips™) were applied to this half of the defect, while the wound edges were everted using Adson forceps. All dressings were applied by nurses with at least 5 years of experience and who had recently undergone one refresher course prior to the commencement of the trial. The other half of the excisions were closed with subcuticular sutures only.

Safety

No postoperative wound complications were reported in any of the 38 patients that completed the split-scar study by Plotner et al. [21].

Custis and coworkers [22] noted no wound infections, hematomas, or seromas in any study patient. They did report one patient in the adhesive strip group (2.2%) and two in the suture-only group (4.4%, $p = 0.31$) with wound dehiscence. Suture abscesses occurred in three patients in the adhesive strip plus suture group, versus six in the suture-only group ($p = 0.18$). Only one patient in the suture-only group had a spitting suture.

Postoperative Care and Follow-Up

If the epidermis is closed using tissue adhesive or adhesive strips, no return visit is required for removal, and the first postoperative visit will be determined at the discretion of the surgeon, typically occurring 2–3 months following the procedure unless specific postoperative complications arise.

Alternative Procedures and Modifications

Alternatives to the use of tissue adhesives or adhesive strips for epidermal closure include conventional cuticular closure with absorbable or non-absorbable suture or no cuticular closure after placement of deep dermal sutures.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In a split-scar comparison of the cosmetic outcomes of cuticular closure with non-absorbable 6-0 sutures versus adhesive strips, Plotner et al. [21] did not demonstrate any significant differences in overall cosmesis, erythema, or wound contour on a 100-point VAS. However, as mentioned by the authors, the validity of this result may be significantly limited by the variability in patient follow-up duration (planned follow-up was at the 2-month time point, but average follow-up duration was 3.75 months, potentially limiting comparability of the VAS scores). In addition, all the patients in the study were Caucasian and studied at a single center, limiting generalizability of the study result to patients from varying ethnic backgrounds.	C
In the Custis et al. study [22], addition of Steri-Strips™ with Mastisol® did not provide any benefit in efficacy or safety based on the overall assessments by the patient and assessor nor in any of the different variables present in POSAS scoring system including patient-related factors (pain, itching, color, stiffness, thickness, irregularity) or physician-assessed factors (vascularity, pigmentation, thickness, relief, pliability, surface area). This study did not show any increase in wound dehiscence or infection in patients with only buried vertical mattress suture. Though confirmatory studies should be performed, the use of adhesive strips as an adjunct closure method to subcuticular buried vertical mattress sutures does not appear to be necessary to achieve good cosmetic results.	D

Comparison of Tissue Adhesive to Standard Wound Closure Methods (Sutures, Staples, and Adhesive Tapes)

A total of three studies were reviewed that compared the outcomes of wound repair using either OCA tissue adhesive or standard methods of epidermal closure (sutures, staples, or adhesive tapes) (Table 12.6).

Indications for Procedure

Please refer to the Indications section for *Comparison of Sutures Versus Adhesive Tapes for Cuticular Closure* section, as discussed previously.

Effectiveness of Procedure

Sniezek et al. [23] performed a split-scar study in 14 patients comparing the aesthetic outcomes of

Table 12.6 Tissue adhesives versus standard methods of closure

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Sniezek 2007 [23]	Randomized split-scar study comparing epidermal closure with 5-0 Prolene® suture versus tissue adhesive (Dermabond®)	14 patients enrolled and all completed study follow-up (100%)	Cosmetic outcome assessed with 10 mm VAS Patient preference	1 week for suture removal 3 months	No significant difference in mean overall VAS scores (6.77 ± 1.88 for suture versus 6.64 ± 1.55 for OCA adhesive, $P = 0.35$) All patients preferred closure with OCA adhesive based on ease of postoperative care No wound complications (infection or dehiscence) reported	1B
Singer 1998 [24]	Parallel-group RCT comparing tissue adhesive to standard methods of closure (sutures, staples, and adhesive tapes)	124 patients enrolled, 112 completed follow-up endpoints (90%)	Cosmetic outcome assessed on a 100 mm VAS HWE scale	1 week for suture removal 3 months	No significant difference in VAS scores for the OCA tissue adhesive (83.8 ± 19.4) and standard closure methods (82.5 ± 17.6, $P = 0.72$) No significant difference in the percentage of wounds receiving optimal HWE score of 6 (77% of tissue adhesive, 80% of standard closure, $P = 0.67$)	2B
Singer 2002 [25]	Parallel-group RCT comparing tissue adhesive to standard methods of closure (sutures, staples, and adhesive tapes) to determine factors associated with suboptimal wound outcomes	814 patients enrolled, 769 patients completed follow-up (94%)	Cosmetic outcome assessed by score on HWE scale	3 months	Closure with OCA adhesive not a significant determinant of cosmetic outcome (OR 1.1, 95% CI 0.8–1.4) Most important variables associated with suboptimal cosmetic outcome: location on an extremity (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2–3.7), wide wounds (OR 1.08, 95% CI 1.01–1.14), incompletely apposed wounds (OR 2.9, 95% CI 1.7–5.0), associated tissue trauma (OR 3.9, 95% CI 1.4–10.7), use of electrocautery (OR 3.4, 95% CI 1.8–6.5), and infection (OR 3.2, 95% CI 1.8–5.6)	2B

epidermal closure with high-viscosity OCA (HVCOA) tissue adhesive to sutured closure of linearly repaired facial Mohs defects. Follow-up was at 7 days for suture removal and assessment of postoperative complications and at 3 months for evaluation of the cosmetic scar outcome as judged on a 10-point VAS by five blinded dermatologist observers who evaluated standardized postoperative photographs taken at the 3-month time point. The authors did not find a significant difference in the mean VAS ratings for the HVCOA wound halves (6.64 ± 1.55) compared to the sutured halves (6.77 ± 1.88, $P = 0.35$). In addition, paired comparisons of rater preferences showed no significant cosmetic differences between the HVCOA and sutured sides. All 14

patients preferred the HVCOA over sutured closures due to increased ease of postoperative care (*Level of evidence: 1b*).

Singer et al. [24] conducted a randomized controlled trial in 124 patients with traumatic lacerations comparing the cosmetic outcome and complication rates of epidermal closure with OCA to other standard cuticular closure methods (including sutures, staples, and adhesive strips). The outcome measures included the complication rate seen at the 5- to 10-day follow-up visit, as well as cosmetic appearance of the scar as determined by scores on a 100-point VAS and the Hollander Wound Evaluation (HWE) scale at the 3-month visit. A total of 112 patients (57 in the OCA arm, 55 in the standard closure arm) completed the long-term follow-up visit. There was no significant difference in cosmetic appearance between the wounds closed with OCA (83.8 ± 19.4 mm) and those closed with one of the standard methods (82.5 ± 17.6 mm, $P = 0.72$) at the 3-month mark. The percentage of wounds receiving the optimal HWE score of 6 at the 3-month visit was calculated for both the OCA and standard closure defects and failed to demonstrate a statistically significant difference (77% of the OCA group and 80% of the standard closure wounds, $P = 0.67$) (*Level of evidence: 2b*).

Singer et al. [25] conducted a large (814 patients, 924 wounds), multicenter follow-up study to compare the cosmetic appearance of wounds closed with OCA adhesive (455 wounds) to that of defects closed with one of the standard wound closure methods (469 wounds closed with sutures, staples, or adhesive tapes) with the aim of identifying specific wound characteristics that were associated with poor cosmetic outcomes. The patient group in this study was more heterogeneous and included not only traumatic lacerations but also surgical incisions resulting from minimally invasive abdominal surgery and excisions of benign and malignant cutaneous neoplasms. Multiple wound characteristics were recorded including size, shape, location, mechanism (traumatic versus iatrogenic), degree of contamination, and method of wound closure. The outcome was the score on the 6-point Hollander Wound Evaluation (HWE) scale at the 3-month follow-up (all wounds receiving a score of less than 6 were considered suboptimal), which was completed in 769 patients (94%). The authors found that closure with OCA (OR 1.1, 95% CI 0.8 to 1.4) and the use of subcuticular sutures were (OR 0.8, 95% CI 0.6 to 1) not significantly associated with the cosmetic outcome. The most important variables, in terms of cosmetic outcome, were location on an extremity (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2–3.7), wide wounds (OR 1.08, 95% CI 1.01–1.14), incompletely apposed wounds (OR 2.9, 95% CI 1.7–5.0), associated tissue trauma (OR 3.9, 95% CI 1.4–10.7), use of electrocautery (OR 3.4, 95% CI 1.8–6.5), and infection (OR 3.2, 95% CI 1.8–5.6) (*Level of evidence: 2b*).

Preoperative Evaluation

Please refer to the Preoperative Evaluation discussion under the *Comparison of Sutures Versus Adhesive Tapes for Cuticular Closure* section, as described previously.

Best Techniques and Performance

In the split-scar study by Sniezek et al. [24], all defects were closed in a linear fashion with buried polyglactin 910 sutures. Half of the wound was randomized to receive epidermal closure with HVCOA (Dermabond®, Ethicon Inc., Summerville NJ) applied in two layers extending 2 mm on each side of the wound. The other wound half was assigned to epidermal closure with interrupted 5-0 polypropylene suture.

In the study by Singer et al. [24], patients with eligible wounds (defined as being appropriate for closure with 5-0 cutaneous suture, which the authors equated to the approximate tensile strength of the OCA adhesive) were randomized to receive wound closure with either topical OCA or via one of the standard methods (sutures, staples, or adhesive tape). Deep sutures were placed prior to epidermal closure in a total of nine patients (six in the OCA group and three in the standard closure group).

In the follow-up study by Singer et al. [25], 814 patients with 924 wounds of multiple etiologies

(traumatic lacerations, dermatologic surgical procedures, abdominal incisions from laparoscopic surgery, and excisions of benign or malignant cutaneous neoplasms) were enrolled, and approximately half (406 patients) were randomized to receive closure with OCA and the remainder (408 patients) received one of the standard methods for epidermal closure (sutures, staples, or adhesive tapes). A total of 769 patients (871 wounds) completed the 3-month study follow-up. Deep sutures were placed in a total of 492 patients, but the number of patients receiving deep sutures in the OCA and standard groups was not specified.

Safety

No cases of postoperative bleeding, infection, or wound dehiscence were reported in the study by Sniezek et al. [23] at either the 7-day or 3-month follow-up visits.

In the study comparing OCA to standard methods (sutures, staples, adhesive strips) of cuticular closure, Singer et al. [24] reported a wound infection in one patient (1.8%) in the OCA group and no infections in the standard closure group. In addition, two patients in the OCA group (3.6%) developed wound dehiscence noted at the early follow-up visit, necessitating a second wound closure. Notably, these two patients had not received subcutaneous sutures. No cases of dehiscence were noted in the standard closure group.

In the multicenter study by Singer et al. [25], a total of 12 infections (1.5%) were reported, with 9 occurring in the OCA cohort and 3 in the standard closure group. Wound dehiscence was reported in a total of 10 patients, but the proportion occurring in the OCA versus standard closure groups was not specified.

Postoperative Care and Follow-Up

In instances where non-absorbable sutures or staples are used for wound closure, removal is required. In the above studies, the initial visit for suture or staple removal took place between 5 and 10 days after the procedure.

Alternative Procedures and Modifications

Alternatives to the use of tissue adhesives for epidermal closure include adhesive strips, staples, as well as placement of cuticular sutures.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In the split-scar study of linear facial Mohs defects, Sniezek et al. [23] demonstrated no significant difference in cosmetic appearance or postoperative complication rate following epidermal closure with either HVCOA tissue adhesive or 5-0 polypropylene suture. The study utilized five blinded dermatologists performing the scar assessments using standardized photographs taken at the three-month follow-up visit, and had a 100% patient follow-up rate. However, the study is limited by its small and demographically homogenous sample size, which may limit generalizability of the results, and the use of photographs instead of in-person evaluations.	C
When the use of OCA tissue adhesive was compared to other standard methods of wound closure (sutures, staples, adhesive tape), Singer et al. [24] failed to show a statistically significant difference in the rate of wound complications or cosmetic appearance of the scar at 3 months, as quantified by scores on a 100-point VAS and the HWE scale. However, as the study combined several standard closure methods (sutures, staples, and tissue adhesives) into a single group and did not separate out the components during data analysis, the validity of the data may be limited by the heterogeneity of the standard wound closure group, as multiple variables were not controlled for prior to comparison with OCA.	C

Findings	GRADE score: quality of evidence
In the large (769 patient) multicenter study by Singer et al. [25] examining factors that were significantly associated with suboptimal wound outcomes, wound closure with OCA versus a standard technique (sutures, staples, or adhesive tapes) was not shown to be a significant predictor of suboptimal wound outcome. Rather, the most significant predictors of suboptimal wound outcome included location on an extremity (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.2 to 3.7), wide wounds (OR 1.08, 95% CI 1.01 to 1.14), incompletely apposed wounds (OR 2.9, 95% CI 1.7 to 5.0), associated tissue trauma (OR 3.9, 95% CI 1.4 to 10.7), use of electrocautery (OR 3.4, 95% CI1.8 to 6.5), and infection (OR 3.2, 95% CI 1.8 to 5.6). However, the heterogeneity of the study population (containing wounds from multiple etiologies including trauma and elective surgical procedures) introduces the possibility of significant confounding factors that could be contributing to wound outcomes. In addition, as with the previous Singer et al. study [24], the individual methods of standard closure (suture, staples, and adhesive tapes) are not compared directly with OCA, which may also induce multiple confounding factors and limit the applicability and validity of the results.	C

Comparison of Tissue Adhesives Versus Adhesive Tapes or Tissue Adhesives for Epidermal Closure of Lacerations

Two studies were reviewed comparing the cosmetic outcomes of epidermal closure with standard-viscosity OCA tissue adhesive to that achieved with adhesive tapes (Steri-Strips™), as well as results using two different forms of tissue adhesive (high- and low-viscosity OCA) (Table 12.7).

Indications for Procedure

Please refer to the Indications discussion under the *Comparison of Sutures Versus Adhesive Tapes for Cuticular Closure* section, as described previously.

Effectiveness of Procedure

Mattick et al. [26] compared the cosmetic outcomes achieved with single-layer closure of lacerations in 60 children aged 1–14 years using either OCA tissue adhesive (Dermabond®) or tissue adhesive strips (Steri-Strips™) in pediatric patients who presented to the emergency department. Wounds were photographed preoperatively, and following repair all parents were asked to quantify the level of distress their child experienced during the procedure on a 100-point VAS, with 0 defined as "very distressing" and 100 as "perfect, no distress." Providers also rated the ease of application of either the tissue adhesive or adhesive strips on the VAS. The first postoperative review was between days 5 and 7, at which time parents were contacted to inquire about any wound complications. Long-term follow-up was completed in 44 children between months 3 and 12, at which time a photograph of the scar was obtained and evaluated by both the parents and a blinded plastic surgeon physician observer and rated on the 100-point VAS. The study failed to show any significant differences between the two techniques in the parents' opinions of the treatment (median 95 [range 70–100] for tissue adhesive, 96 [34–100] for adhesive strips, $P = 0.96$), parents' opinions of the scar (median 84 [range 70–100] for tissue adhesive, 80 [43–100] for adhesive strips, $P = 0.62$), or the blinded physician observer's opinion of the scar (median 87 [range 65–93] for tissue adhesive, 87 [62–96] for adhesive strips, $P = 0.81$). However, the adhesive strips were rated as easier to apply by the providers, a difference that was significant to the 95%

Table 12.7 Comparison of tissue adhesives and adhesive strips

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Mattick 2002 [26]	Parallel-group RCT comparing tissue adhesive (Dermabond®) to adhesive strips for epidermal closure	60 patients enrolled, 44 completed follow-up (73%)	Parent-reported patient distress on 100 mm VAS Cosmetic outcome evaluated on a 100 mm VAS	1 week 3–12 months	No significant differences between OCA adhesive and adhesive strips in parents' opinion of treatment (median 95 [70–100] for tissue adhesive, 96 [34–100] for adhesive strips, $P = 0.96$) No significant difference in surgeon's opinion of scar (median 87 [65–93] for tissue adhesive, 87 [62–96] for adhesive strips, $P = 0.81$)	2B
Singer 2003 [27]	Parallel-group RCT comparing two types of tissue adhesive (high- and low-viscosity OCA (Dermabond®)) for epidermal closure	84 patients enrolled, 78 completed study follow-up (93%)	Evaluation of adhesive migration >1 cm from wound Assessment of patient-subjective complaints at time of application	2 weeks	High-viscosity OCA significantly less likely to migrate than low-viscosity adhesive (21% versus 78%, $P = 0.0001$) High-viscosity OCA was associated with an increase in patient sensation of heat during application (44% versus 26%, $P = 0.11$) One dehiscence observed in the high-viscosity OCA group (2.8%), no infections	2B

confidence interval (CI) (median 91 [range 50–100] for tissue adhesive, 95 [10–100] for adhesive strips, $P = 0.07$) (*Level of evidence: 2b*).

Singer et al. [27] compared two types of tissue adhesives, high-viscosity (Dermabond® HV Topical Skin Adhesive, Ethicon Inc., Somerville NJ) and low-viscosity (Dermabond® Topical Skin Adhesive, Ethicon Inc.) OCA for epidermal closure of uncomplicated traumatic lacerations in a total of 84 patients (42 patients in each arm of the study) in an emergency department setting. Four patients (three in the high-viscosity OCA and one in the low-viscosity OCA groups) required placement of deep sutures prior to cuticular closure with the adhesives. The main outcome measure was evaluation of the tendency of the adhesive to migrate on the skin (defined as migration >1 cm from the wound) following application to the wound edges. Secondary outcomes included assessment of patients' subjective complaints (warmth, burning) at time of application and incidence of complications (infection, dehiscence) assessed 14 days following the procedure. A total of 78 patients (36 in the high-viscosity OCA group and all 42 in the low-viscosity OCA group) completed the 2-week follow-up. The authors found that the high-viscosity OCA was significantly less likely to migrate than the low-viscosity adhesive (21% versus 78%, $P = 0.0001$). However, it was also noted that the high-viscosity OCA was associated with an increase in patient sensation of heat during application (44% versus 26%, $P = 0.11$), but all patients who experienced this adverse sensation reported that they would receive treatment with OCA adhesives again (*Level of evidence: 2b*).

Preoperative Evaluation

Please refer to the Preoperative Evaluation discussion under the *Adhesive Tapes Versus Sutures for Cuticular Closure* section as described previously.

Best Techniques and Performance

In the study by Mattick et al. [26], eligible wounds were cleansed and randomized to receive either closure with OCA (Dermabond®) or adhesive tissue strips (Steri-Strips™). No subcuticular sutures were used for wound closure.

In the study by Singer et al. [27], wounds were selected based on eligibility for closure with topical skin adhesive, and the following were used as exclusion criteria: bite wounds, punctures, decubitus ulcers, stellate lacerations, crush injuries, evidence of active local or systemic infection, and location involving hair-bearing skin, mucous membranes, or the vermillion border of the lip. Eligible lacerations were then randomized to receive application of either high-viscosity OCA or low-viscosity OCA for re-approximation of the epidermis. Prior to application of the adhesive, wounds were evaluated to determine need for subcuticular sutures, which were placed in three patients in the high-viscosity OCA and one in the low-viscosity OCA group.

Safety

No wound complications (infection, bleeding, or wound dehiscence) were reported in the study by Mattick et al. [26] in the 44 children for which long-term (3–12-month) follow-up was obtained.

At the 14-day follow-up in the study by Singer et al. [27], there were no wound infections observed in either group. One patient in the high-viscosity OCA group (2.8%) developed wound dehiscence (of note, the authors did not specify if the patient had received subcuticular sutures during wound closure).

Postoperative Care and Follow-Up

As no sutures are placed that require removal, patients may return postoperatively on an as-needed basis following closure with tissue adhesive or adhesive strips.

Alternative Procedures and Modifications

Single-layer repair with cuticular suture, bilayered closure, staples, or healing by second intent

are alternatives to repair with tissue adhesives or adhesive strips in superficial lacerations.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Mattick et al. [26] failed to show any significant difference between OCA tissue adhesive and adhesive strips for closure of superficial lacerations in a pediatric population in terms of parental ratings of distress caused by the procedure or final scar outcomes (as judged by both parents and a blinded physician observer at 3–12 months). The only significant difference noted between the two techniques in this study was that the adhesive strips were regarded as easier to apply by the providers. However, this study was limited by the variable time of follow-up (ranging from 3 to 12 months), which limited comparability between participants who returned at different intervals for scar evaluation. No recommendations can be made based upon the results of this study.	C
The study by Singer et al. [27]. comparing high- and low-viscosity tissue adhesives demonstrated a significant decrease in reported adhesive migration with the high-viscosity product at the time of application (21% versus 78%, $P = 0.0001$) and there was no significant difference in the incidence of wound infection or dehiscence. It was noted that the high-viscosity adhesive was associated with a higher incidence of patient-reported sensation of warmth at time of application (44% versus 26%, $P = 0.11$), but affected patients reported this would not be a barrier to future use. However, the study had a relatively small sample size of 84 patients and thus may be underpowered to detect significant differences in the incidence of wound complications between the two groups. Also, it is unclear how important the issue of adhesive migration is to patient-centered outcomes such as cosmetic outcome or wound care. Thus, recommendations regarding the use of high versus low-viscosity adhesives cannot be made based upon the findings of this study.	C

Comparison of Sutures Versus Closure Devices

Two studies were reviewed that compared the aesthetic outcomes of wound repair using either closure devices or sutures for epidermal closure. The ClozeX™ (ClozeX™ Medical LLC, Wellesley, MA) is a wound closure adhesive film consisting of two independent parts that have an adhesive underside and multiple interlocking filaments attached to pulling ends to facilitate wound edge approximation. The Zipline® 3 system (Zipline® Medical Inc., Campbell, CA) is a noninvasive surgical skin closure device consisting of a sterile single-use adhesive sheet coupled to a releasable ratcheting device, which is used to approximate wound edges and dissipate tension at the incision site for optimal healing. Both devices are designed for closure of the epidermis following placement of deep dermal sutures, if indicated, and are left in place for 7–14 days and then removed (Table 12.8).

Indications for Procedure

The ClozeX™ and Zipline® 3 systems are sterile single-use adhesive devices designed to facilitate wound closure while also minimizing tension on the wound edges while the device is in place. The indications are similar to those for epidermal closure with either tissue adhesives or adhesive strips and are best suited to clean, uncomplicated linear lacerations that are not located in hair-bearing areas or involving mucosal surfaces.

Effectiveness of Procedure

In a split-scar study, Kuo et al. [28] compared the aesthetic outcome of bilayered suture closure to that achieved with placement of the ClozeX™ device for epidermal closure (in combination with deep dermal sutures) in patients who underwent excision of benign and malignant cutaneous neoplasms on the trunk and extremities. A total of 15 patients were enrolled and completed the scheduled follow-up visits at 2 weeks and at 4–6 weeks. The main outcome of the study was

Table 12.8 Sutures versus closure devices

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Kuo 2006 [28]	Randomized split-scar study comparing epidermal closure with 4-0 Prolene® and ClozeX™ device	15 patients enrolled and completed all follow-up (100%)	Cosmetic appearance evaluated on a global 4-point scale Wound closure time	2 weeks for suture/device removal 4–6 weeks	Significantly more ClozeX™-treated halves received a score of 2 or 3 corresponding to "extremely satisfied" and "satisfied" (66% versus 36%, $P = 0.007$) Closure time with ClozeX™ significantly shorter ($P = 0.007$) than suture placement Wound complications: two suture halves developed track marks, one suture half developed allergy to bacitracin; no infections or dehiscence	2B
Mitwalli 2016 [29]	Parallel-group RCT comparing bilayered closure with nylon cuticular sutures to the Zipline® 3 system with and without subcuticular sutures	20 patients enrolled, 17 completed follow-up (85%)	Closure time with sutures versus Zipline® 3 system Cosmetic outcomes assessed on a 10 mm VAS	2 weeks for suture/device removal 3 months	Closure time significantly shorter with Zipline® 3 device placement (1.83 ± 1.05 min versus 3.88 ± 1.3 min for suturing, $P = 0.001$) No significant difference in cosmetic outcome (mean VAS 8.5 ± 1.02 for suture versus 8.5 ± 1.14 for Zipline® 3, $P = 1$) Zipline® 3 only arm ($N = 1$) complicated by dehiscence in first patient; trial arm abandoned	2B

cosmetic appearance of the wound halves at the 4–6-week visit as judged by both blinded observers and patients on a 4-point satisfaction scale, with a score of 0 indicating "not satisfied" and score of 3 corresponding to "extremely satisfied." Secondary outcomes included comparison of the skin closure time and complication rate for each method. The percentage of wound halves receiving blinded physician assessment scores of 2 or 3 (corresponding to "satisfied" and "extremely satisfied") was 66% for the ClozeX™ halves and 36% for the sutured halves ($P = 0.007$), indicative of higher satisfaction with the appearance of the ClozeX™-treated wounds. Patient satisfaction was determined via administration of a questionnaire at the 4–6-week visit, which was completed by 13 patients and showed a preference for the ClozeX™ wound halves (69% of patients rated the ClozeX™ side higher than the suture side, with a median score difference of 1, $P = 0.02$). Finally, the median closure time with ClozeX™ was sig-

nificantly shorter (127 s, $P = 0.007$) than that of cuticular suture placement.

Mitwalli et al. [29] evaluated the cosmetic outcomes and complication rates using the Zipline® 3 system for epidermal closure in a total of 20 patients following excision of non-melanoma skin cancer (NMSC) or dysplastic nevi on the trunk or extremities. Patients were randomized to three groups: a bilayered control group that received deep dermal sutures followed by interrupted nylon cuticular sutures and two treatment arms in which the Zipline® 3 system was utilized with and without dermal suturing (however, the second treatment arm consisting of Zipline® 3 system alone was dropped after the first patient developed wound dehiscence). A total of 17 patients completed the 3-month study follow-up (eight controls, eight in the Zipline® 3 plus dermal sutures group, and one in Zipline® 3 without dermal sutures group). The primary outcome measure of the study was assessment of cosmetic outcome at 3 months using a 10-point VAS, based on assessment by three blinded observers. Secondary outcome measures included the surgeon time required for device application versus suture placement and removal, as well as the incidence of complications (infection, wound dehiscence) in the suture versus Zipline® 3 groups. The study failed to demonstrate a significant difference in scar appearance at 3 months (mean VAS 8.5 ± 1.02 for suture ($n = 8$) versus 8.5 ± 1.14 in the Zipline® 3 study arms ($n = 9$), $P = 1$). However, the time required for Zipline® 3 device placement was significantly shorter than that required for cuticular suturing (1.83 ± 1.05 min compared to 3.88 ± 1.3 min, $P = 0.001$). Similarly, the Zipline® 3 system was associated with a faster time for removal than cuticular sutures (8.2 ± 1.16 s compared to 58.1 ± 14.9 s, $P < 0.001$).

Preoperative Evaluation

Examination of the laceration to evaluate the size, depth, location, and contamination of the wound is indicated prior to determining if the defect can be appropriately closed with an adhesive closure device. Linear, opposed to stellate, lacerations allow for better alignment of tension vectors to facilitate wound edge approximation. Because the devices are occlusive, they are best suited for clean, uncontaminated wounds.

Best Techniques and Performance

Kuo et al. [28] performed a split-wound study in which the entire defect received interrupted deep dermal polyglactin 910 sutures for subcuticular closure, followed by randomization of wound halves to closure with either 4–0 polypropylene (Prolene®) in a simple running fashion or application of the ClozeX™ adhesive device. The sutures and device were removed at the 14-day postoperative visit.

In the study by Mitwalli et al. [29], the control group ($n = 8$) received bilayered closure with buried deep dermal sutures followed by interrupted nylon cuticular sutures. The Zipline® 3 system arm received deep dermal sutures followed by device application ($n = 8$) or application of the device without a subcuticular suture layer ($n = 1$, terminated due to dehiscence in the first patient).

Safety

In the split-wound study by Kuo et al. [28], there were no reports of wound infection or dehiscence in either the sutured or ClozeX™ halves of the 15 patients who completed the study. One patient developed an allergic contact dermatitis to bacitracin on the suture half of the wound, and two sutured halves developed track marks noted at the 4–6-week follow-up visit.

Mitwalli et al. [29] reported wound dehiscence in one patient in the Zipline® 3 closure group that was randomized to closure with the device alone without the use of subcuticular sutures, resulting in elimination of that arm of the study. None of the patients randomized to bilayered suture closure or subcuticular sutures plus the Zipline® 3 system experienced dehiscence.

No patients developed a postoperative wound infection in this study.

Postoperative Care and Follow-Up

Both the ClozeX™ and Zipline® 3 systems are designed to stay in place on the wound for a period of 7–14 days and are removed at a follow-up visit in the office.

Alternative Procedures and Modifications

Standard bilayer closure with placement of cuticular sutures and modified bilayer closure using tissue adhesives or adhesive tapes for the cuticular layer are alternatives to the use of adhesive epidermal closure devices such as the ClozeX™ and Zipline® 3 systems.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In their split-scar study, Kuo et al. [28] found cuticular closure with ClozeX™ to be rated cosmetically superior to that with running non-absorbable suture by both blinded physician assessors and patients on a 4-point satisfaction scale. In addition, median skin closure time with the ClozeX™ device was significantly shorter (127 s) than closure time for the sutured halves. No reports of wound quality or dehiscence were noted in the study, although due to the small sample size (15 patients) the study was not adequately powered to detect significant differences in complication rates between the two methods. More studies with larger cohorts are required before definitive recommendations can be made regarding this device.	C
At 3-month follow-up, Mitwalli et al. [29] did not demonstrate any significant difference in the cosmetic appearance of wounds closed with standard bilayered suture closure compared to bilayered repair utilizing the Zipline® 3 system for cuticular closure. The authors did demonstrate that placement of the Zipline® 3 system required significantly less time than cuticular suturing, as did the time required for the Zipline® 3 removal. Notably, the authors deemed the Zipline® 3 system inappropriate for single-layer closure based on dehiscence in the first patient who was treated in this manner. The overall conclusion of the study was that the Zipline® 3 system plus dermal suturing is more efficient than conventional bilayered suture closure, with equivalent cosmetic outcomes at 3 months. However, due to the small size of the study, it may not adequately detect significant differences in cosmetic outcomes or complication rates between the Zipline® 3 and conventional cuticular sutures.	C

Comparison of Circular Versus Elliptical Excision Methods

One study was reviewed that compared the cosmetic outcomes achieved following circular (via a standard trephine punch) excision and elliptical excision of atypical nevi on the trunk and extremities (Table 12.9).

Indications for Procedure

Circular excision is considered in the setting where the lesion to be removed is small (able to fit within the diameter of a punch instrument) and time efficiency is valued. Elliptical excision is considered for any situation where a full-thickness removal of cutaneous tissue is warranted and time is available to complete the procedure.

Table 12.9 Circular versus elliptical excision

Study: first author and year	Study design	Number of patients who enrolled and completed study (% follow-up)	Outcome measures	Follow-up interval	Results	Level of evidence
Ek 2004 [30]	Parallel-group RCT comparing circular and elliptical excision	45 patients enrolled (56 excisions); all patients completed follow-up (100%)	Median scar area Cosmetic outcome evaluated on 100 mm VAS by patients and observers	2 weeks for suture removal 6 months 12 months	Median scar area significantly less in circular group compared to elliptical at 6 months (48.7 mm^2 versus 87.2 mm^2, $P < 0.05$) and 12 months (64.8 mm^2 versus 102.2 mm^2 $P < 0.05$) No significant difference in the patient VAS scores at 12 months (57.9 versus 73.7) Elliptical excision scars rated cosmetically superior by observers on VAS (49.0 for circular excision versus 61.0 for elliptical, $P < 0.05$)	2B

Effectiveness of Procedure

Ek et al. [30] compared the scar area and cosmetic outcome of circular versus elliptical excisions of clinically atypical nevi located on the trunk or extremities. A total of 56 procedures were performed in 45 patients. Nevi were randomized to receive circular excision with an 8-mm punch ($n = 29$) or elliptical excision ($n = 27$). Sutures were removed after 14 days, and the scar area was calculated based on measurements at the 6- and 12-month follow-up visits. Cosmetic appearance was evaluated on a 100-point VAS at 12 months by both the patients and blinded observers. In addition, the incidence of early (infection, wound rupture) and late (erythema, hyperpigmentation, hyperpigmented scarring) complications was recorded in both groups.

The authors found that the median scar area was significantly smaller in the circular excision group compared to elliptical excision at both 6 months (48.7 mm^2 versus 87.2 mm^2, $P < 0.05$) and 12 months (64.8 mm^2 versus 102.2 mm^2, $P < 0.05$). There was no significant difference in the patient VAS scores for circular and elliptical excisions at 12 months (57.9 versus 73.7); however, the observers rated the elliptical excision scars as more cosmetically pleasing and this was statistically significant (49.0 for circular excision versus 61.0 for elliptical, $P < 0.05$). The circular excision group had a higher incidence of both early and late complications (28%) than the elliptical excision group (7.4%), but this did not reach statistical significance. The authors noted that complications were associated with poorer cosmetic outcome (lower patient and observer VAS scores), and when the ten excisions that had developed complications were excluded from the study, there was no longer a significant difference in the observer's cosmetic assessment of the scars (54.7 for circular, 60.3 for elliptical). However, the exclusion of this data violates the intention to treat principle and is not in keeping with good data analysis (*Level of evidence: 2b*).

Preoperative Evaluation

Clinically atypical nevi may be excised by the clinician to ensure that no histopathologic evi-

dence of malignancy is present. As the lesions are presumed to be benign, optimizing the cosmetic outcome of the scar becomes a priority. The need for complete removal of the lesion via excision, with higher incurred risks and morbidity, needs to be justifiable compared to a simple shave biopsy or shave excision.

Best Techniques and Performance

Circular excisions were performed using an 8-mm punch biopsy instrument and closed with a single non-absorbable 4-0 polybutester (Novafil™, Covidien Ltd.). Elliptical excisions were performed in standard 3:1 length-to-width ratio and closed with subcutaneous polyglycolic acid (Dexon™, Covidien Ltd.) sutures followed by interrupted 4-0 polybutester (Novafil™) sutures.

Safety

In the circular excision group (n = 29 lesions), a total of eight complications were noted consisting of four cases of wound dehiscence, two wound infections, one keloid scar, and one hyperpigmented scar. In the elliptical excision group, two patients developed wound infections; no other complications were noted.

Postoperative Care and Follow-Up

Non-absorbable sutures require removal. For excisions on the trunk and extremities, the recommended time for suture removal is 14 days.

Alternative Procedures and Modifications

Alternatives to excision include clinical monitoring, shave biopsy, or scoop shave excision.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
In their comparison of circular and elliptical excisions of clinically atypical nevi, Ek et al. [30] observed an increased incidence of early and late wound complications in the circular excisions but this was not statistically significant. Though the circular excisions had a smaller scar area than the elliptical excisions, the elliptical excision scars were rated as being slightly cosmetically superior by blinded physician observers at the 6- and 12-month follow-up (there was no significant difference in patient VAS scores between the two groups). More studies with larger numbers of patients are necessary before recommendations can be made regarding circular excisions versus elliptical excisions.	C

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Self-Assessment Questions

1. Based on the reviewed studies comparing two methods of wound closure, staples versus single-layer closure with suture (Kanegaye et al. and Orlinsky et al.), which one of the following statements is true?
   (a) There was no significant difference noted in the laceration repair time between stapling and suturing.
   (b) The cosmetic outcomes of wounds evaluated at 3 months were superior in the patients who underwent wound closure with sutures.
   (c) The average cost of laceration repair with staples was significantly lower than with sutures.
   (d) The average laceration repair time per centimeter increased with increasing length of lacerations.
   (e) Patients reported more postoperative discomfort following staple closure as compared to suture closure.
2. Regarding the cosmetic outcomes of using the set-back suture technique (as reported in Wang et al.), which of the following statements are true?
   (a) The cosmetic outcomes of wound halves repaired with set-back sutures were superior to the use of buried vertical mattress sutures.
   (b) The incidence of spitting sutures was lower in the wound halves repaired using the buried vertical mattress sutures.
   (c) Set-back sutures enter and exit the wound only though the wound edge.
   (d) Buried vertical mattress sutures produce better wound edge eversion than set-back sutures.
   (e) There were significantly more infections in the wound halves closed with set-back sutures.
3. During preoperative evaluation of a laceration, which type of wound defect would be deemed most suitable for cuticular closure with tissue adhesive or adhesive strips?
   (a) 6 cm clean, linear laceration of the forehead extending into the hair-bearing scalp
   (b) 3 cm jagged laceration of the dorsal hand following a dog bite
   (c) 3 cm linear laceration of the upper arm
   (d) 6 cm stellate laceration of the cheek
   (e) 2 cm linear laceration over the elbow
4. In terms of tensile strength, standard-viscosity octyl-cyanoacrylate (OCA) tissue adhesive is comparable to what type of suture for epidermal closure?
   (a) 6-0 polypropylene
   (b) 5-0 nylon
   (c) 5-0 fast-absorbing gut
   (d) A and B
   (e) B and C
5. Which of the following suture materials is more commonly associated with complications of suture reactions, based on published randomized trials?
   (a) Poliglecaprone-25
   (b) Polyglactin-910
   (c) Poly-4-hydroxybutyrate
   (d) Polydioxanone
   (e) Polypropylene

6. Which statement is true regarding the comparison between octyl-2-cyanoacrylate and vertical mattress nylon cuticular sutures in the presence of subcuticular closure in head and neck surgeries based on a study performed by Toriumi et al.?
   (a) Cosmesis is superior in the adhesive group at 12-month follow-up.
   (b) Cosmesis is superior in the adhesive group at 3-month follow-up.
   (c) Wound dehiscence is higher in the adhesive group.
   (d) Time to closure was not a differential factor.
   (e) Peeling of adhesive is more commonly seen in octyl-2-cyanoacrylate than other adhesives.

Correct Answers

1. (c) As reported by both Kanegaye et al. and Orlinsky et al., repair of lacerations with staples was significantly faster and more cost-effective than suturing. Orlinsky et al. noted that the time per centimeter for laceration repair decreased with increasing length of the lacerations. In the study by Kanegaye et al., no significant difference in postoperative pain was noted between the staple and suture groups at the suture/staple removal visit.
2. (a) Cosmetic outcomes were statistically better in the wound halves closed with set-back sutures. The incidence of spitting sutures was lower in wound halves closed with set-back sutures. There was a lower incidence of spitting sutures on the set-back suture sides. Set-back sutures enter and exit the underside of the undermined wound, not the wound edges. Set-back sutures result in significantly more wound edge eversion than buried vertical mattress sutures. There was no difference in terms of infections between the two suture halves.
3. (c) Tissue adhesives and adhesive strips are best suited for clean, linear lacerations located in areas that are not hair-bearing, involving mucous membranes, under high tension, or overlying a dynamic structure (such as a mobile joint). Two studies using adhesives restricted patients to those with lacerations that were 5 cm or less.
4. (e) The tensile strength of standard OCA tissue adhesive is roughly equivalent to that of 5-0 caliber suture (absorbable or non-absorbable).
5. (c) Although scars were significantly narrower on wound halves sutured with poly-4-hydroxybutyrate, there was no difference in cosmetic outcome compared with polyglactin 910 sutures and significantly more local suture reactions.
6. (a) Cosmetic outcomes are not statistically different at 3 months between wounds closed with octyl-2-cyanoacrylate adhesive and those closed with vertical mattress nylon sutures. However, at 1-year follow-up, results significantly favored wounds closed with octyl-2-cyanoacrylate adhesive. The octyl-2-cyanoacrylate's plasticizer decreases the possibility of cracking and early peeling, which is more commonly seen in short-term cyanoacrylates.

13 Sutures, Adhesives, Staples, and Other Closure Technologies

Christina Correnti, Kaitlin Blankenship, Nicole Ufkes, and John Strasswimmer

Abstract

The history of surgery, and therefore wound closure, is that of human social evolution. Social cohesion for *Homo sapiens* (which led to our species dominating other humanoid species including *H. neanderthalensis* and *H. erectus*) depended upon caring for the infirm. Some of the earliest surgical needles, dating back to at least 20,000 BC, were made of bone, and primitive sutures were made of plant material and linen (5). Middle-Kingdom Egyptians used strips of linen coated with honey and flour as some of the first documented adhesive material for wound closure. South American cultures even used the pincers of decapitated ants as a means of wound closure. The use of gut as suture material was first mentioned in ancient Greece around the time of Galen, a material still used today.

Keywords

Sutures · Skin · Surgery · Subcuticular · Wound closure · Barbed sutures · Vertical mattress

History of Wound Closure

The history of surgery, and therefore wound closure, is that of human social evolution. Social cohesion for *Homo sapiens* (which led to our species dominating other humanoid species including *H. neanderthalensis* and *H. erectus*) depended upon caring for the infirm. Some of the earliest surgical needles, dating back to at least 20,000 BC, were made of bone, and primitive sutures were made of plant material and linen (5) [1]. Middle-Kingdom Egyptians used strips of linen coated with honey and flour as some of the first documented adhesive material for wound closure [1]. South American cultures even used the pincers of decapitated ants as a means of wound closure [1]. The use of gut as suture material was first mentioned in ancient Greece around the time of Galen, a material still used today [1].

Since then, wound closure materials and wound closure techniques have allowed for

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significant advances in the field of surgical dermatology. Over the past several decades, there has been increasing interest in seeking the evidence behind traditionally passed down surgical tenets (such as wound eversion for improved scar cosmesis). Indeed, many times no differences are found for the effects of the choice of closure material or technique on wound healing. This chapter attempts to synthesize evidence in the literature regarding closure materials and common closure techniques.

Indications for Wound Closure and Preoperative Evaluation

Surgical wounds are closed in order to increase rate of healing, to preserve function, and to optimize cosmetic outcome. Wounds may be allowed to heal by primary intention, meaning that the surgeon will place appropriate closure devices, such as sutures. Alternatively, wounds may be allowed to heal by secondary intention, which implies that no sutures or other devices are placed. The choice of whether to close a wound primarily may depend on factors related to healing such as a patient's overall health, comorbidities, nutrition, and smoking status; more practical factors such as nearby free margins that may distort, repair cost, the need for a suture removal visit, and the restriction of physical activity after primary closure; the risk of bleeding due to blood thinners; and patient preference with regard to wound care, healing time, and scar appearance. Regardless of the choice, the surgeon continues to direct and intervene as necessary to ensure complete wound healing (5) [2] (3b) [3] (5) [4].

Preoperative evaluation should include a review of vital signs, patient allergies, medications, the presence of devices that may influence the method of hemostasis (pacemaker, defibrillator, or cochlear implant), and factors influencing whether preoperative antibiotics should be given (e.g., history of recent joint replacement) (5) [5] (4) [6]. In general, prescribed anticoagulant medications should be continued if possible. Detailed justification can be found in evidence-based reviews of patient safety in dermatologic surgery [5] and in antibiotic guidelines for dermatology surgery [6].

Alternatives to Wound Closure: Second Intent Healing

Wound closure is not always necessary for satisfactory healing; patient or surgeon preference may become more important in these cases. Studies have shown no difference between the healing of punch biopsy sites when sutured versus when allowed to heal by second intent. Christenson and coauthors examined scar appearance after a punch biopsy using secondary-intention versus primary closure with 4-0 nylon sutures (1b) [7]. For smaller 4-mm size punch biopsies, there was no significant preference by participants for either method. However, for the larger 8-mm biopsies, participants preferred primary closure. No difference was noted in the rate of complications between the two closure options. Although sutures may be preferred at larger biopsy sites, eliminating use of sutures for punch biopsies can result in reduced costs and time saving for both patients and medical institutions.

A retrospective survey of 1250 patients showed no difference in patient satisfaction for Mohs defects closed primarily versus healed with secondary intention (3b) [8]. The only factor associated with decreased long-term patient satisfaction was age younger than 68 years. This age group had a slightly lower satisfaction with outcome regardless of closure method, consistent with earlier studies showing older patients are typically more satisfied with surgical outcome than younger patients.

Becker and coauthors have also completed a number of studies on second intention healing in Mohs defects. Based on this experience, they conclude that most defects heal by secondary intention within 3–6 weeks on average, wounds in areas likely to cause distortion (near free margins) are better closed surgically, and scars may be more cosmetically pleasing with second intent healing (5) [9, 10].

In a prospective study of 102 Mohs defects of the head and neck allowed to heal by second intent, scar location was the most important factor for the final cosmetic outcome [3]. Concave surfaces of the nose, eye, ear, and temple (NEET) and forehead, antihelix, and eyelids and the remainder of the nose, lips, and cheek (FAIR) areas showed equivalent rates of wound contraction (74%) and acceptable cosmesis (97%). Convex surfaces of the nose, oral lips, cheeks and chin, and the helix of the ear (NOCH) showed lower rates of wound contraction (66%) and acceptable cosmesis (78%).

Alternatives to Wound Closure: Partial Wound Closure

A third approach is partial wound closure. The most documented is the use of purse-string suture, to aid in second intent healing by decreasing the lateral dimensions of the surgical defect. The technique is most commonly deployed using nonabsorbable material in a subcuticular or cuticular approach. Alternatively, absorbable suture may be placed in a subcuticular manner.

Intradermal purse string with nonabsorbable sutures clearly decreases the surgical defect. In 51 consecutive patients (ages 26–93), Patel et al. treated large circular or oval defects of the head and neck with the purse-string suture (3b) [11]. When the wound could not be closed completely with the suture, any residual defect was closed with a skin graft ($n = 11$) or second intent healing ($n = 5$). Overall, the mean defect size reduction was 89%. The nonabsorbable sutures were left in place at least 4 weeks. Ridges were flattened after 2–3 weeks. The resultant scars were often linear and along relaxed skin tension lines (except when grafted). Alopecia occurred in one scalp lesion. Infection occurred after the loss of a full-thickness skin graft in one case. The authors suggest the best results occurred in the neck and retromandibular region due to lax skin, the worst results being on the scalp.

Intradermal purse string with absorbable suture may be employed as well. Spencer et al. assessed 54 wounds managed with running intradermal purse-string closures with 3-0 or 4-0 polyglactin for circular wounds after Mohs surgery (4) [12]. Immediate wound areas decreased by 60–100%, with most improvement, especially in the neck and arm. Long-term cosmetic results were calculated on a 4-point scale in 52 cases and were best in head and neck locations (face and neck, mostly excellent; trunk, fair to good; shin, fair to good; thigh, good; upper arm, good; forearm, good; ear, excellent; and scalp, fair) with caution in areas near a free tissue margin [12].

Cuticular purse-string closure may have the added benefit of increased hemostasis compared to subcuticular purse-string closure. In a retrospective review of 98 patients where cuticular purse-string sutures were placed, wound area decreased by a large variation (6–90%, mean 60% (3b)) [13]. Anticoagulant or antiplatelet medications were noted in over 50% of patients, suggesting that this approach may be suitable even in patients at increased risk of bleeding. The purse-string suture was usually removed after 3–4 weeks. Six patients (6%) had complications including one hypertrophic scar, one exuberant granulation tissue, two wound infections, and two cases of allergic contact dermatitis. All healed completely with round or linear scars. The authors conclude the cuticular purse-string technique is particularly useful in patients who want to maintain an active lifestyle or who are on one or more anticoagulant or antiplatelet medications.

In a discussion of purse-string approaches, Scholl et al. described that cuticular purse strings with nonabsorbable suture are preferably used on the scalp with a main benefit of hemostasis, whereas subcuticular purse-string sutures are preferable on the forehead, temples, neck, and extremities where they are indicated for defect reduction and accelerated secondary intention healing and/or completed with absorbable monofilament sutures (5) [14].

In summary, primary closure methods are most common, but partial closure and secondary intention wound management are used for specific circumstances. Considerations such as activity restrictions for sutures and the requirement and cost for a suture removal visit come into play. Physicians can consider the patient's abili-

ties, expectations, and preferences when deciding between methods [3, 7, 8].

Introduction to Sutures and Suture Materials

Sutures are the most commonly used closure material in procedural dermatology. In 2006, a prospective survey of closure techniques and suture types used by 101 members of the American Society of Dermatologic Surgeons was completed with a response rate of 60% (4) [15]. Respondents most often used simple interrupted sutures (38–50%) to close the epidermis, followed by simple running sutures (37–42%), and vertical mattress sutures (3–8%). On the trunk and extremities, subcuticular sutures were more often used (28%). Superficial sutures were mostly nylon (51%), followed by polypropylene (44%). Absorbable suture was most commonly polyglactin 910 (73%). At least 90% of the time, a bilayered closure with undermining and electrocoagulation was used. Primary closures were the most common (54%) followed by local flaps (20%), and skin grafting (10%). The remaining 15% of wounds healed by second intent (10%) or were referred for reconstruction (5%). Dermatologic surgeons repair defects themselves at least 90% of the time, even among the quartile of those practitioners who are most likely to refer reconstructive procedures to other specialists. In bilayered closures, vertical deep sutures were used 90% of the time compared to horizontal deeps (5%) or oblique deeps (1%). Interestingly, larger wounds were significantly more likely to be treated by surgeons with more years of experience, and more experienced surgeons were significantly less likely to use bilayered closures or undermine on the face.

Time to suture removal varies by surgeon experience and preference. The choice can depend on many factors such as wound tension, wound location, and anticipated patient activity level. In general, sutures on the face are removed after 5–7 days; of particular concern is for the potential to develop "train track" scars for sutures left in for longer or under high tension. Sutures in the scalp, trunk, and extremities are removed after 7–14 days and potentially longer on the hands and feet (5) [16] (5) [17].

Due to the expansive variability in suture products, it is important to understand suture properties and characteristics to be able to choose an appropriate suture for each closure scenario. Pertinent suture properties include tensile strength (dependent on suture diameter), knot security, capillarity (which can increase infection risk), elasticity, plasticity, memory, pliability, tissue reactivity, and coefficient of friction (ability to slide through tissue). Dyed sutures increase visibility and the color fades over time after embedding in tissue (5) [18].

Suture size is classified based on the US Pharmacopeia designation. Suture sizes in dermatologic surgery generally range from 2-0 to 6-0. The more zeros the suture material has, the thinner it is. Sutures have either natural (e.g., silk or gut) or synthetic (e.g., nylon) composition, with natural materials more prone to cause inflammatory tissue reactions and less even strength distribution. Natural suture materials are degraded by proteolysis, whereas hydrolysis degrades synthetic suture materials. A suture is said to be absorbable if it loses most of its tensile strength by 60 days after implantation and nonabsorbable if it retains most of its strength past 60 days [4, 18]. For tables comparing the detailed properties of absorbable versus nonabsorbable sutures, see the review authored by Regula et al. in 2015 [18].

Sutures can either be monofilament or multifilament braided or twisted. Multifilament sutures tend to handle well due to greater pliability and lower memory; they also have increased tensile strength. They have a higher coefficient of friction (creating drag) and high capillarity and inflammatory potential (which is thought to increase the risk of infection). Monofilament sutures have minimal tissue drag (low coefficient of friction), lower inflammatory potential, and theoretically lower infection risk; however, they are more difficult to handle due to high memory [4, 18]. Silver et al. demonstrated that knot security appears to depend on technique (surgeons knots > square knots > slip knots), the number

of throws, and suture material independent of suture size or whether the suture is monofilament or multifilament; for example, out of four materials, two multifilaments had the both the highest (Vicryl) and lowest (silk) knot security in comparison with chromic gut and nylon (5) [19].

Traditionally suture surfaces are smooth; however, barbed sutures are a newer wound closure technique. Barbed sutures offer three advantages over traditional sutures. First, barbed sutures eliminate the need for knot tying, potentially saving time. Second, interrupted knots are a focus of high tension with gaps of low tension in between the individual suture knots. In contrast, barbed sutures are placed in a continuous looping fashion, which distributes tension more evenly. Third, barbed sutures are used to close using the pulley principle, whereby tension vectors during the act of wound edge approximation are evenly distributed. Therefore, barbed sutures can be used to close wounds where the skin is very fragile, such as photo-damaged arms. Likewise, barbed absorbable sutures can be used to close large wounds which otherwise would not close primarily (4) [20].

Barbed sutures may be endo- or exobarbed. Endobarbed sutures are nicked monofilaments; thus their diameter is functionally decreased along with tensile strength (5) [21]. Thus upsizing endobarbed sutures may be prudent to achieve a strength comparable to the smooth suture size that is typically preferred for a given body location. Barbed 2-0 polypropylene suture has been found to have same strength as at least 3-0 non-barbed polypropylene suture and greater stiffness according to a rater in a blind controlled trial using a tensile testing device (5) [22]. In contrast, exobarbs are attached to the core suture and strength is not decreased. Barbs also come in uni- or bidirectional forms (changing direction at the midpoint). Barbed sutures distribute tension more evenly along their length, eliminating ischemic foci of suture loops, and have the potential to reduce dehiscence (3b) [23–25]. They are more expensive than traditional sutures, but will save procedure time and empower the surgeon to close challenging wounds [20, 22, 23], (2b) [26].

Introduction to Tissue Adhesives and Surgical Strips

Surgical glues (cyanoacrylate tissue adhesives) are useful wound closure tools for wounds under minimal tension (with or without deep sutures) and give comparable cosmetic outcomes. They are fast to apply and avoid a visit for suture or staple removal. They also do not require anesthesia for wound closure, making them ideal for use in children or patients with low pain tolerance. Wounds must be perfectly approximated before application. The cost can be comparable to one rapid absorbing suture if purchasing multiuse vials. Surgical glue should not be used over joints or areas that experience repetitive motion, unless the area is immobilized. Surgical glue should also not be used on contaminated wounds, mucosal junctions, hair-bearing areas, or contaminated or infected skin. Other disadvantages include drying time, glue seeping into the wound impairing healing and approximation, and peeling due to repetitive movement [4, 16–18, 27].

Surgical adhesive strips are another alternative to conventional wound closure with sutures. Like surgical glue, surgical strips should be used to close wounds that are already well approximated, with or without deep sutures, and under low tension. Surgical strips can also be used to reinforce wounds that are superficially closed with sutures; however, there is little evidence to support any added benefits (1b) [28], (3a) [29]. Disadvantages and benefits of using surgical strips are very similar to those of surgical glue mentioned above, with the additional consideration of risk of adhesive tapes causing allergic or irritant reactions [16, 17, 29]. Adhesive liquid agents, such as Mastisol, can be used to better secure surgical strips and can allow for prolonged adhesion across the wound [4, 18].

Introduction to Staples

Stainless steel staples are rapidly applied, have the highest tensile strength of closure materials, have low reactivity, and are an efficient means of closing long- or high-tension wounds such as those on the scalp [18].

Evidence-Based Review of Suture Materials: Selection, Effectiveness, and Safety

Literature Search Strategy

PubMed (1809 to present) was searched and limited by human species and English language. Articles unavailable in full text were excluded. The remaining articles were screened by title and abstract for relevance to cutaneous closure materials in terms of selection, effectiveness, and safety. Examples of excluded topics were studies focused solely on subcutaneous or deeper closure techniques, burn wounds, ptosis correction, traumatic lacerations, rejuvenation/lifting (non-closure) sutures, laparoscopic trocar wounds, and graft immobilization. Relevant articles were reviewed and references were cross-checked. Single-case reports and narrative reviews (without systematic methods or data analysis) were excluded, but references were cross-checked. Duplicative studies were excluded, such as individual studies sufficiently covered in meta-analyses. Duplicates also included older meta-analyses if all studies overlapped and the conclusions of the two meta-analyses were concordant. Numerous dermatologic expert technical pearls and modifications for unique closure challenges were beyond the scope of this review. Rather, this chapter aims to synthesize the larger body of evidence related to dermatologic closure materials and their common applications.

Sutures

The following search parameters were used: ("Sutures"[Mesh] OR "Suture Techniques"[Mesh]) AND "Dermatologic Surgical Procedures"[Mesh] AND (sutur*[Title/Abstract]. Of 764 results, 601 full text articles were screened.

Staples

The following search parameters were used: "Wound Closure Techniques"[Mesh] AND ("surgical staples"[Title/Abstract] OR "surgical staple"[Title/Abstract] OR "staple"[Title/Abstract] OR "staples"[Title/Abstract]) AND "Reconstructive Surgical Procedures"[Mesh]. Of 90 results, 66 full text articles were screened.

Adhesives and Tape

The following search parameters were used: "reconstructive surgical procedures"[Mesh] AND ("tissue adhesives"[Mesh] or "surgical tape"[Mesh]) AND "wound closure techniques"[Mesh]. Of 102 results, 77 full text articles were screened.

Other Closure Devices

The following search parameters were used: ("reconstructive surgical procedures"[MeSH Terms] AND "wound closure techniques"[MeSH Terms]) AND ("film"[Title/Abstract] OR "coaptive"[Title/Abstract] OR "sutureless"[Title/Abstract] OR "op-site"[Title/Abstract] OR "opsite"[Title/Abstract] OR "zipper"[Title/Abstract] OR "closure device"[Title/Abstract] OR "adhesive device"[Title/Abstract]). Of 50 articles, 35 full text articles were screened.

Overall

After screening, removal of duplicative studies, and cross-checking references, 129 articles were identified for inclusion.

Evidence-Based Review: Sutures

1. *Five systematic reviews and meta-analyses comparing suture techniques and/or materials were reviewed. Topics addressed included triclosan-coated sutures, barbed sutures in knee arthroplasty, barbed sutures in hip and knee arthroplasty, absorbable versus nonabsorbable sutures in surgical and laceration wounds, and continuous versus interrupted sutures in non-obstetric surgery.*

In a 2015 systematic review and meta-analysis of 6 randomized controlled trials in 2168 patients (1102 treated and 1066 controls), the analysis found no protective effect of triclosan-coated sutures on the rate of surgical site infections after elective colorectal resections. Further large randomized controlled trials are needed

before introducing this technology into clinical practice (1a) [30].

Two 2015 systematic reviews and meta-analyses studied barbed sutures versus traditional sutures in orthopedic surgery. In the first meta-analysis, four randomized trials, one prospective trial, and five retrospective trials of mostly moderate and one high quality were included. In 1729 knee arthroplasty patients, knotless barbed sutures ($n = 814$) allowed for significantly shorter wound closure times (saving 3.56 min, CI = −5.05 − 2.08, $p < 0.01$) and lower total cost (considering the costs of operating room time) compared to traditional sutures ($n = 915$). There was no significant difference in postoperative Knee Society Scores or complication rates compared to traditional sutures. Subgroup analysis appeared to show that closure of arthrotomy, subcutaneous, and subcuticular tissues with knotless barbed sutures decreased the total complication rate. If the arthrotomy itself was closed by traditional methods, there was a higher complication rate (1a) [31].

In the second 2015 meta-analysis, 588 patients in 4 randomized controlled trials of hip and knee arthroplasty were included. Barbed sutures were 6.3 min faster to place than conventional sutures ($p < 0.05$), major complication rates (deep infections) and minor complication rates (superficial infections, prominent sutures, stitch abscesses, erythema) were similar (both $p > 0.05$), and the overall cost savings (considering operating room time) was US$ 298 per case. Twelve suture breaks and 1 needle stick were reported in the barbed closure cohort versus 3 suture breaks and 5 needle sticks in the conventional cohort (1a) [32]. Cost-savings may be less immediately evident for the dermatologic surgeon who is rarely in the operating room, since barbed sutures cost more than traditional sutures.

In a 2013 systematic review and meta-analysis of 1748 patients from 19 randomized controlled trials, there was no significant difference between nonabsorbable and absorbable sutures in terms of wound infection incidence, cosmesis, scarring, dehiscence, and patient or caregiver satisfaction. Wounds were secondary to surgery (across multiple specialties) and lacerations. Subgroup analysis suggested intradermal absorbable suture may yield better cosmesis; however, insufficient follow-up may have influenced these results. Absorbable sutures could be recommended for cost and time savings; however, further research is needed to clarify whether intradermal absorbable sutures provide better cosmesis in the repair of lacerations or surgical wounds (1a) [33]. The results agree with an older meta-analysis of a subset of the above studies (1b) [34].

In 2013, a Cochrane database systematic review and meta-analysis of non-obstetric randomized controlled trials were performed to evaluate the benefits and harms of continuous compared to interrupted skin closure techniques. All randomized trials were eligible for inclusion. The final analysis included five trials for abdominal or groin operations with unclear or high risk of bias. For a total of 827 participants, outcomes were available for 730 (interrupted $n = 346$ and continuous $n = 384$). Overall, 6.5% of participants developed wound infections, with no significant difference between groups. Superficial wound dehiscence occurred in a statistically significantly lower proportion of the group closed with continuous sutures compared to the interrupted group (RR 0.08; 95% CI 0.02–0.35). Most of the dehiscence occurred in trials where absorbable subcuticular sutures were left in place and compared to nonabsorbable interrupted sutures that were removed after 7–9 days. Length of hospital stay was equivalent between the two groups. The results suggest continuous subcuticular sutures may reduce the risk of wound dehiscence; however, uncertainty exists due to the low quality of the evidence (1b) [35].

2. *Twenty-nine randomized trials were reviewed, of which 23 represented Level 1b evidence. Six trials were downgraded to Level 2b due to <80% follow-up or poorly described methods for at least one follow-up interval making the quality and conclusions of the study uncertain.*

Several Studies Comparing Outcomes Based on Varying the Suture Technique Only

In 2005, Moody et al. compared the cosmetic results of traditional simple running nonabsorb-

able sutures with running horizontal mattress sutures (1b) [36]. Forty-seven patients completed the prospective randomized split-wound trial of 55 patients with facial Mohs surgery defects over 2 cm in length. Repairs were bilayered using 4-0 or 5-0 poliglecaprone deeply and 6-0 polypropylene superficially. Sutures were removed at 1 week. Cosmesis was determined by partially blinded ratings of three discrete possibilities: superior half better (1), inferior half better (−1), or no difference (0). Cosmesis was superior in the portion of the scar repaired with the running horizontal mattress suture at all time points. At 6 months, 25 (53%) patients did better, 5 (11%) did worse, and 17 (36%) had no difference ($p < 0.05$). The scars appeared smoother, flatter, and narrower. Scores at 6 weeks correlated with those at 6 months. The authors prefer to remove running horizontal mattress sutures at 5 days since they find them more difficult to remove over time (5) [36]. They have also found that interrupted horizontal mattress sutures seem to cause superficial vascular constriction which may relate to wound edge necrosis, and the authors no longer use them for most flaps and grafts (5) [36].

In 2002, a randomized clinical trial reported the results of comparing running nylon sutures ($n = 31$) to interrupted vertical mattress sutures ($n = 27$) in 58 patients (mean age 52 years) undergoing lower midline laparotomies. Interrupted vertical mattress sutures took an average of 5.3 min longer than running sutures to perform ($p < 0.001$), caused significantly less suture markings at 2 weeks and 6 months, less pronounced color at 1 year, and had a significantly better mean scar score at all time points. The 6-month score was equivalent to the score at 1 year. The mean difference of 1.0 on their assessment scale could be the difference between minimal to marked color differences compared to adjacent skin or between minimal scar elevation and hypertrophic scar (1b) [37].

In a 2015 prospective randomized controlled trial, 34 patients (mean age 51.5 years) with upper blepharoplasty wounds had closure by starting the running intradermal suture either externally or internally. After 1 week, 12 suture abscesses (40%) were found medially in externally started suture lines and 4 abscesses (13.3%) were found in internally started intradermal suture lines ($p = 0.02$). Erythema and edema were also lower in the internally started suture lines ($p = 0.02$). All differences resolved by 6 weeks (1b) [38].

A widespread surgical tenet holds that everted closures are necessary in order to counteract scar inversion that may result from wound contraction. This may not be true. In a prospective, randomized, split-scar intervention in cutaneous surgery patients, everted versus planar repairs of defects of at least 3 cm in length were compared. There was no restriction for location, and 10% of procedures were performed on the face. Eversion was carefully achieved with dermal setback or interrupted vertical mattress sutures alone. The comparator was simple subcuticular sutures for planar closure. Both sides were covered with adhesive strips to re-approximate the epidermis and avoid the confounding of track marks. Out of 50 patients enrolled (mean age 61.8 ± 11.9 years), 47 and 43 completed the 3- and 6-month follow-ups, respectively. The 3- and 6-month patient scores and two blinded observer scores were not significantly different between groups using the Patient Observer Self-Assessment Scale. There was also no significant difference in scar height, depth, or width at follow-up (1b) [39].

A second study directly measuring eversion was a prospective split-wound randomized study of 46 elliptical dermatologic surgical wounds of at least 3 cm in length. Forty-two patients (mean age 65 ± 13.5 years) completed the trial comparing 3-month cosmetic outcomes and eversion between the setback suture and buried vertical mattress suture. Polyglactin 910 and adhesive strips were used on the surface to prevent confounding by track marks. Nineteen percent of procedures were performed on the face, and 66.7% were performed by an attending surgeon. Both eversion (height and width) and scores on the Patient and Observer Scar Assessment Scale were significantly superior on the setback suture side (patient mean 13.0 ± 8.7 vs 16.2 ± 12.0 [$P = 0.039$]; two blinded observers mean 24.5 ± 10.4 vs 27.7 ± 13.6 [$P = 0.028$], respectively). Complications included 3 spitting

sutures on the setback side and 11 on buried vertical mattress side and 1 case of dehiscence on both sides (1b) [40].

In a randomized controlled multi-center trial of 142 patients, simple interrupted sutures (n = 73) versus running subcuticular sutures (n = 69) were compared as the superficial layer for bilayered closures of the face after Mohs or excisions. Cosmetic results at 3 and 12 months and associated complications were recorded. Cosmesis was evaluated by the Patient and Observer Scar Assessment Scale with a blinded observer. The deep layer was closed with absorbable suture in all patients and the two superficial arms were closed with nonabsorbable monofilament sutures. Wounds were supported by adhesive strips, and sutures were removed at 7 days. Of 69 assigned to subcuticular closures, 8 patients received interrupted instead of subcuticular sutures due to inability to close the wounds with subcuticulars, and 2 subcuticular closures were converted to interrupted closures later due to wound dehiscence and re-excision. Overall, 13 patients were lost to follow-up by 12 months. In the interrupted suture group, 16% of the patients developed permanent suture marks. Both methods yielded equivalent rates of complications (infection in 1.3–3.3%, dehiscence in 4.4–5.5%), cosmetic scores, and rates of dysesthesia (at 12 months 4.5–12.9%, p = 0.09) by per-protocol and intention-to-treat analyses. While the authors concluded that interrupted sutures had less dysesthesia and may be preferred, those results were not significant (1b) [41].

In a prospective randomized split-wound trial, 101 patients were sutured with either continuous or interrupted nylon stitches to repair facial Mohs wounds. The cosmetic appearance was assessed with multiple scar scales at 1 week, 8 weeks, and 6 months by the principal investigator, and blinded cosmetic appearance was assessed by a plastic surgeon and general dermatologist at 1 week and 6 months. There was no statistically significant difference in scar outcome at any time point for any assessor. By tabulating the ratings of all three assessors into the overall number of times one method was better, worse, or equivalent, running sutures were equivalent or better than interrupted sutures 72% of the time (1b) [42].

In a prospective single-blinded randomized trial, 50 patients underwent layered closure to one half of the wound and buried sutures with adhesive strip closure for the other half of the wound after removal of cutaneous malignancies on the cheek. Wounds were at least 3 cm in length after Mohs or excision, and all had buried vertical mattress sutures with polyglactin 910. Superficial closure was with 6-0 nylon and adhesive strips to the opposite half. Thirty-eight patients completed the trial (mean age 47–82 years). By blinded evaluation between 1 and 24 months, contour, erythema, and overall cosmetic outcomes were equivalent between sides. Adhesive strips may be a less expensive and time-saving option for cutaneous repairs of the cheek (2b) [43].

Several Studies Comparing Outcomes Based on Varying the Suture Material Only

In a 2017 report of a blinded prospective randomized controlled trial, 520 (95%) patients completed the study comparing subcuticular 3-0 poliglecaprone 25 (n = 263) versus subcuticular 4-0 polyglactin 910 (n = 257) in the closure of Pfannenstiel incisions following cesarean delivery. Subcuticular poliglecaprone 25 was associated with a significantly lower rate of overall wound complications compared to polyglactin 10 (8.8% vs. 14.4%, relative risk 0.61, 95% confidence interval 0.37–0.99; p = 0.04). However, differences between groups were not significant for individual wound complications (surgical site infections which could be superficial, deep, organ, seroma, or separation) making up the overall wound complication outcome (1b) [44].

In a prospective trial reported in 2013, 140 patients completed a study (out of 155 randomized) of bilayered Mohs repairs comparing deep absorbable poliglecaprone 25 versus polyglactin 910 sutures. Epidermal closures (in terms of techniques and materials) were completed according to the discretion of the surgeons. There was sta-

tistically less suture extrusion with poliglecaprone 25 compared to polyglactin 910 (3.1% vs. 11.4%, $p < 0.01$). There were no differences in the percentage of lumps (both 22%) or in 1-week or 3-month overall scar ratings by two blinded dermatologic surgeons on a visual analog scale (1b) [45].

In a randomized trial, interrupted 4-0 nylon ($n = 17$), 4-0 polyglactin 910 ($n = 25$), and 4-0 stainless steel ($n = 19$) sutures were used to close the skin after carpal tunnel surgery in 61 patients (ages 30–83 years). There was no significant difference in pain as recorded on a visual analog scale at any time point. Four blinded reviewers assessed scar photographs at 6 weeks for redness, granuloma, and hypertrophy on a three-value scale (none, mild, severe). Granulomas were scored significantly more often in the Vicryl group ($p < 0.05$); there were no differences for erythema or hypertrophy between groups. Two patients in the Vicryl group developed superficial wound infections (8%) and one developed post-traumatic dystrophy. The authors conclude that absorbable Vicryl sutures should not be used, due to higher incidence of infections and suture granulomas (1b) [46].

In a multicenter prospective randomized controlled trial evaluating 241 patients, dermal closure with barbed versus non-barbed sutures was performed on opposite sides of the body. Overall, 229 patients were treated with barbed and smooth sutures (115 with slow-absorbing barbed sutures and 114 with rapid-absorbing barbed sutures). Deep dermal sutures were mostly or completely eliminated on the barbed side, making the mean dermal closure time significantly quicker for barbed sutures. Rapid-absorbing barbed suture showed no difference in complication rates compared to smooth suture; however, slow-absorbing barbed suture showed a higher incidence of minor suture extrusion (1b) [47].

In a randomized trial, 72 of 88 open-heart surgery fair-skinned patients completed a study comparing skin closure with subcuticular 3-0 chromic catgut ($n = 20$), 3-0 polyglycolic acid ($n = 28$), or 3-0 Prolene removed 8–10 days after surgery ($n = 25$). There was no significant difference in wound infections (0–3%), scar width, or hypertrophy between groups. Scar width increased significantly from top to bottom of the sternum in all groups. The lower third of the scar was significantly more likely to show hypertrophy and the middle third of the scar was significantly more likely to show marked hypertrophy (overall incidence of 37%). Marked hypertrophy occurred more often in females (males 24% vs. females 53%, Fischer's exact test significant at $p = 0.05$) (1b) [48].

In a prospective randomized study, 59 patients completed a trial (out of 62) where Dupuytren's contracture fasciectomy wounds were closed with interrupted irradiated 5-0 polyglactin 910 absorbable sutures ($n = 38$ digits) or interrupted 5-0 nonabsorbable polypropylene sutures ($n = 41$ digits). Outcomes included time spent attending to the wound at the first postoperative visit (day 1014), pain score, and complications. Absorbable sutures fell off after a mean of 3.2 weeks (range 3–5 weeks). Wound care took significantly more time for the nonabsorbable suture group, but there was no significant difference in pain scores or complications between the two groups. There was one case of delayed wound healing in the polyglactin group and one case of a swollen hand; in the polypropylene group, there was one case of wound infection, two of delayed wound healing, and two with retained suture material. Absorbable sutures are recommended to save time and resources compared to nonabsorbable polypropylene sutures (1b) [49].

In a randomized study, Pfannenstiel incisions were closed with continuous subcuticular poliglecaprone 25 ($n = 106$) or polypropylene ($n = 107$). The dropout rate was high with 30% of participants lost to follow-up by week 1 and 64% lost to follow-up by week 4. Nonabsorbable polypropylene was removed at 1 week. The primary outcome showed no difference between methods for patient satisfaction (by visual analog scale) at 1 and 4 weeks. Secondary outcomes assessed by yes or no questions showed a significant difference in wound itch at 4 weeks, favoring polypropylene (0%) over poliglecaprone (8.5%, $p = 0.04$) (2b) [50].

In a randomized trial, 70 of 100 randomized patients completed 5-month questionnaires

(visual analog scale and a 6-point validated scar assessment tool) regarding scar cosmesis. At 6 weeks, no dehiscence, hematomas, or infections were noted. At 6 weeks, no dehiscence, hematomas, or infections were noted. There was no difference in cosmesis 5 months after elective hand and wrist surgeries were repaired with absorbable 3-0 Vicryl compared to nonabsorbable 3-0 nylon interrupted sutures (2b) [51].

Comparing Various Suture Techniques and Materials in Several Studies

In 2001, a prospective randomized study compared intracutaneous 3-0 poliglecaprone ($n = 150$) versus transcutaneous 3-0 polyamid ($n = 150$) sutures in the closure of sternal wounds after cardiac surgery. The subcutis was closed with 2-0 polyglactin in both groups. There was a lower rate of total infection in the transcutaneous group (3% vs. 5%, $p = 0.007$) compared to the intracutaneous group. This was due to a lower rate of superficial infections in the transcutaneous group (2% vs. 6.7%, $p = 0.01$), with no difference in the deep infection rate between groups. The 6-week cosmetic results were equivalent on a visual analog scale as judged by the patients (1b) [52].

In a prospective randomized observer-blinded study of 21 patients (ages 40s to 80s) with post-Mohs scalp defects, pulley closure was compared to bilayered closure in terms of closure time and scar cosmesis. Bilayered closure was accomplished with buried vertical mattress 4-0 polyglactin 910 sutures with running 5-0 fast absorbable plain gut. The pulley closure was accomplished by placing interrupted pulley 3-0 monofilament nylon sutures at the center until tension was decreased, along with horizontal mattress along the ends. The Patient and Observer Scar Assessment Scale was completed at 2 weeks, 2 months, and 6 months. A blinded observer assessed before and after photographs on a visual analog scale. The pulley technique resulted in significantly shorter closure times (4.6 ± 1.5 versus 10 ± 1.5 min, $p < 0.001$). Blinded observer scores of cosmesis were similar in both groups, but overall scores were superior in the pulley group by patient scores at 2 weeks and observer scores at 6 months (1b) [53].

In a split-scar prospective randomized controlled trial, deep barbed 3-0 sutures versus deep 3-0 Maxon and subcuticular sutures (both polyglyconate monofilament synthetic absorbable sutures) were compared in 33 elective plastic surgery cases with long wounds. Patients' ages ranged from 34 to 74 years. Photographs at 2 years were assessed by 9 blinded plastic surgeons and specialist registrars using the modified Hollander cosmesis score in 24 patients. Wound closure time and number of suture packets used were significantly less with barbed sutures ($p < 0.001$). Complication rates were equivalent with both methods. Cosmesis at 2 years was superior with barbed sutures ($p = 0.0075$). Patient pain ratings on a 10-point visual analog scale were equivalent between groups. Barbed sutures distribute wound tension evenly and eliminate the need to tie knots which may decrease the risk of needle-stick injuries (1b) [54].

A prospective randomized study of 113 patients compared 4 methods of leg wound closure after coronary artery bypass grafting: (1) a continuous vertical mattress suture of 2-0 nylon ($n = 27$ patients); (2) a continuous subcuticular suture of 2-0 polyglycolic acid ($n = 29$ patients); (3) disposable metal skin staples ($n = 27$); or (4) "Op-site" transparent adhesive sutureless skin closure. Wounds were examined by two independent observers at 5, 10, and 45 days. The overall infection rate was 4.5%. Continuous subcuticular sutures led to significantly less discharge at 5 days; significantly better healing at 10 days in terms of wound overlap, inflammation, dehiscence; and final cosmesis significantly better than metal staples or vertical mattress nylon sutures but equivalent to closure with "Op-site" sutureless closure. The authors conclude continuous subcuticular polyglycolic acid is superior in all criteria except speed of insertion and cost and recommend it for standard use (1b) [55].

In a prospective randomized trial of 58 hands in 50 patients, subcuticular absorbable 4-0 polyglytone 6211 sutures were compared to interrupted nonabsorbable 5-0 polybutester sutures

for closure after endoscopic release of the carpal tunnel. Overall, 36 females and 14 males with ages ranging from 21 to 70 years entered the trial, and 54 hands of 47 patients completed the study. Pain diaries were completed by patients on a visual analog scale until a nurse visit for suture removal at days 10–14. There was a significant reduction in pain scores on days 1 and 2 in the subcuticular suture group. One patient in each group had inflammation during the first 14 days. There were no infections or suture granulomas. There was no significant difference in terms of inflammation, infection, or 3-month cosmesis assessed by the surgeon (a nonsignificant trend toward better cosmesis with subcuticular polyglytone was noted) (1b) [56].

Intracutaneous or transcutaneous sutures were compared in 100 sternal closures (50 per group) after median sternotomy for open-heart surgery. Cosmetic results were similar between groups, no deep infections occurred, and superficial infections occurred in one patient or 2% of the transcutaneous group (4-0 polypropylene) and eight patients or 16% of the intracutaneous group (4-0 polycaprolate). One patient in the transcutaneous group was diabetic, and six patients in the intracutaneous group were diabetic. Transcutaneous sutures may decrease the risk of superficial infection, particularly in diabetics (1b) [57].

In a rater-blind randomized controlled trial, superficial simple running 5-0 polypropylene sutures were compared to subcuticular running 5-0 polypropylene sutures removed after 14 days, subcuticular running 5-0 polypropylene sutures left in place, and subcuticular running 5-0 polyglactin 910 sutures left in place. Deep dermal closure was accomplished with simple interrupted polyglactin 910 sutures (size 3-0 for the back and 4-0 for all other sites) in all cases. The trial included 72 wounds in 36 adult patients (ages 19–65 years) needing concurrent elliptical excision of at least 2 clinically atypical nevi of the trunk and/or extremity with an expected suture line of at least 2 cm in length. At 3 months and 9 months, scar width, a blinded assessment of overall scar appearance on an ordinal scale, the Vancouver Scar Scale, the Hollander Scar Scale, and pruritus were recorded. Results showed that immediately after closure all methods appeared similar. At 3 months, vascularity was significantly less, and overall appearance was superior with subcuticular polyglactin 910 suture left in place compared to all other groups. By 9 months, both subcuticular polyglactin 910 suture and subcuticular polypropylene suture left in place were significantly superior in overall appearance compared to the other two groups. At both time points, subcuticular polypropylene suture left in place had a significantly better overall appearance than simple running polypropylene removed after 14 days. Subcuticular polypropylene left in place had significantly more contour irregularities at 3 months than all other groups and also significantly less inversion at 3 months compared to simple running Prolene removed after 14 days. Simple running Prolene also led to significantly greater vascularity at 3 months than in all other groups. In post hoc analysis, back wounds resulted in significantly greater width than non-back locations. At 3 months, two cases of erosion and partial dehiscence were reported with running subcuticular polypropylene left in place. No differences in pruritus were noted. Vascularity was the only parameter that differed across surgeons. In conclusion, superficial subcuticular sutures left in place appear to be superior for bilayered closures of the trunk and extremities. This could decrease closure costs by half if the same caliber sutures were used for deep and superficial sutures, and even if different caliber polyglactin 910 sutures were used, this would be less expensive than using polypropylene superficial sutures (1b) [58].

In a prospective randomized trial of 40 hand surgery defects, continuous subcuticular absorbable 3-0 polyglactin 910 sutures were compared to nonabsorbable 3-0 polypropylene sutures in the closure of open carpal tunnel release. A total of 36 hands completed the study. No significant differences between groups were found in terms of pillar pain, scar tenderness, wound inflammation, and overall surgical outcomes at 2, 6, and 12 weeks after evaluation by an independent observer (1b) [59].

Fifty consecutive saphenous vein coronary artery bypass graft patients aged 33–71 were

randomized to leg closure with subcutaneous 2-0 Dexon and 2-0 Prolene subcuticular ($n = 25$) versus a single layer of interrupted 2-0 Ethilon sutures ($n = 25$). Sensory perception was assessed at 48 h, 7 days, and 6–8 weeks in all patients. Sensory recovery was significantly better in the group closed with interrupted Ethilon sutures at 7 days and 6 weeks. No wound infections or hematomas were reported. In 37 patients, no difference was reported in cosmetic results (rated excellent, good, or average) at 14–18 months. There was a higher incidence of sensory abnormality in the subcutaneous Dexon and Prolene group at 14–18 months, but this was not assessed for significance (2b) [60].

In a randomized trial of 43 hernia repairs or cholecystectomies, closure with interrupted 3-0 nylon mattresses was compared to 3-0 polyglactin 910 for interrupted inverted subcuticular sutures. Assignment was by lot drawing; there was no mention of dropout rate. After 12 weeks, no objective or subjective differences in scar appearance or adverse events were reported. Subcuticular sutures took twice as long but saved the patient the need for a suture removal visit (2b) [61].

Twenty of 30 patients completed a prospective upper eyelid blepharoplasty trial and were treated with both 5-0 running subcuticular polypropylene and 6-0 running superficial fast absorbing catgut in a randomized fashion. Results were comparable in terms of operative time, minor complications, senior author and patient aesthetic preferences, and postoperative discomfort. Patients and the senior author rated the scar slightly superior with running catgut after 1 month (0.3–0.7 points higher on a scale of 1–10). No statistical comparisons were performed (2b) [62].

In one study, single-layer versus double-layer closure was compared. The suture materials used were not specified. In the double-blind randomized study of excisions of atypical nevi on the upper back, 50 patients were treated with conventional bilayered closures (with simple interrupted buried and surface sutures) and 50 patients were treated with buried vertical mattress sutures alone. The modified technique showed less hypertrophic scarring and keloid formation (2% vs. 16%, $p < 0.031$), less wound scar spread >3 mm (6% vs. 24%, $p < 0.02$), and no difference in infection rates, dehiscence, suture reactions, or patient satisfaction (96% vs. 88% in conventional closure, nonsignificant). The authors conclude it produces excellent cosmetic results (statistically superior in terms of hypertrophy and wound spread) for the closure of elliptical excisions in anatomic locations with thickened dermal skin under moderate to severe wound tension and obviates the need for suture removal (1b) [63].

Evaluation of Several Nonrandomized Studies Representing Mostly Level 3 Evidence

Study Comparing Suturing Techniques

In a blind, nonrandomized, prospective, longitudinal, comparative study, 90-day esthetic results were compared after excision of benign facial growths and closure with simple interrupted ($n = 47$) versus running intradermal 5-0 polypropylene sutures ($n = 46$). Most lesions were intradermal nevi (86%) with a mean size of 9 or 10 mm, and all were removed by a single surgeon. Suture removal and inspection for erythema, edema, dehiscence, and infection occurred on day 5. The surgeon assessed the scars at 30 days. Two independent dermatologist observers made blinded esthetic assessments of pictures of the wounds before and after 90 days. Of 100 procedures (on patients aged 2 months to 70 years), 93 scars were assessed in patients completing the study. Five patients were lost to follow-up and two were excluded due to wound infection within the first 10 days. Suture marks and tracks present at 30 days in 28% of scars after simple interrupted sutures had disappeared by 90 days. Hypertrophic scars occurred more frequently at 30 days ($n = 16$ overall); however, by 90 days only two scars in each group were hypertrophic. Erythema decreased in both groups from 30 days to 90 days but was more frequent in the inter-

rupted suture group at both time points. A similar proportion of 90-day esthetic results were rated by the patients and blinded observers as fair/poor, good, or excellent (45–75% excellent) with both methods. Patients were more benevolent in their ratings than the blinded observers (75% excellent). No statistical analyses were performed (2b if cohort 3b if case control) [64].

Several Studies Comparing Suture Materials

In a prospective clinical study, intradermal closures for 80 patients undergoing facial rhytidectomy were compared using 6-0 polydioxanone versus 6-0 polyglactin 910. The superficial skin was closed with 6-0 catgut in all cases. There were no statistically significant differences between intradermal suture material groups in double-blind evaluations of erythema, induration, scar spread <1 mm, infection, and hypertrophic scarring at 5 months and 1 year (3b) [65].

In a follow-up survey study, 1 year after 876 operations and histologic study of 60 scars at 20–100 days postoperatively, polydioxanone (n = 486) and polyglactin 910 (n = 399) were compared using buried, butterfly-shaped, interrupted sutures for Mohs wounds with tension. By histology, nonsignificant trends noted that polydioxanone showed less thread reaction and granulocytes; however, milder tissue reaction for polyglactin 910 could be expected when buried deeper than 1.6 mm as opposed to 0.8 mm. Polydioxanone showed slighter better overall patient-rated cosmesis, more hypertrophic scars, fewer dehiscent scars, and less inflammation, suture reaction, and suture perforation, but no statistical differences were reported. Operator experience was reported to affect cosmetic results independent of suture material used (3b) [66].

In a prospective study of 28 patients undergoing upper eyelid blepharoplasty, healing with 6-0 absorbable fast-absorbing catgut was equal to healing with nonabsorbable 6-0 nylon suture in terms of patient satisfaction 1 year or more after surgery, pain, and scarring on a visual analog scale (3b) [67].

In a nonrandomized prospective split-wound study, 44 skin cancers were removed from the head and neck area in 41 adults. Defects were repaired with rotational flaps using absorbable simple interrupted 5-0 Vicryl Rapide sutures and the other half of the wound with 5-0 Prolene sutures. Closure lengths ranged from 3.5 to 12.0 cm (average 7.5 cm) and were mostly facial in location (n = 37). The deep layer was closed with poliglecaprone 25. Prolene was removed at 7 days, and photographs were evaluated at 3 and 6 months for observer evaluation. Railroad tracking occurred in 3 cases with Prolene and in 2 cases with Vicryl Rapide, all located between the mandible and the neck. Overall, no significant difference was noted between the areas closed with Prolene and those closed with Vicryl Rapide. Wound infection did not occur (3b) [68].

A nonrandomized prospective split-wound study compared simple running sutures using absorbable 5-0 poliglecaprone 25 with nonabsorbable 6-0 Prolene in the superficial layer of primary closure of 48 facial Mohs defects. Rosenzweig et al. found no significant difference in blinded cosmetic outcomes at 1 week and 4 months postoperatively. At 4 months, there was no difference in 85% of cases; poliglecaprone 25 was better in 4%, and polypropylene was better in 10%. No complications of infection, hematoma, or dehiscence occurred (3b) [69].

It is possible that single-layer closure may be sufficient. A follow-up study of 149 excision procedures evaluated whether buried absorbable monofilament vertical mattress sutures alone could be used safely without superficial suturing. Wounds were located on the face (43%), trunk (29.5%), upper extremities (13.4%), head/neck (10.7%), anogenital area (2.7%), and lower extremities (0.7%). Patient ages ranged from 1 to 89 years. Wounds were evaluated for color, dehiscence, hypertrophy, granulomas, and keloid at 13–64 weeks. Buried interrupted vertical mattress sutures were placed with the arc coming as close to the epidermis as possible for perfect apposition of skin edges. Single superficial sutures were needed in 14.7% of cases. Wound closure tapes were applied to the wounds and removed after 5 days along with any single sutures. The over-

all outcome was excellent (< 5% dehiscence and no hypertrophy, granuloma, or keloid) to good (5–10% dehiscence and no hypertrophy, granuloma, or keloid) in 78.5% of cases, satisfactory in 19.5%, and poor in 2%. Wound dehiscence expressed as a percentage of wound length was <5% in 68.5%, 5–10% in 20.8%, 10–20% in 9.3%, and > 20% in only 1.4%. Hypertrophic scarring was present in 10.1%, keloid formation in 1.3%, and granulomas in 3.4%. No suture marks or infections were recorded. Hypertrophic scarring was significantly more frequent with polyglactin (31%) than polydioxanone (8%) ($p < 0.0001$). The mean overall score for scars in facial locations was significantly better than all non-facial locations (excellent in 78.1%, even with a mean wound length of 5.9 cm). Increased length of the wound was significantly correlated with scar dehiscence; however, the overall cosmetic result was not significantly affected by wound length. The authors conclude the technique is safe, easy to use, and prevents suture marks as long as exact skin edge apposition can be achieved with intradermal sutures alone (3b) [70].

Several Studies Comparing Combinations of Sutures and Techniques

In order to identify patient and technique factors relating to early (up to 2 weeks) complications, a nonrandomized study of 1000 consecutive outpatient primary closures of small (<3 cm) defects was designed. In multivariate analysis, older age, male sex (for bilayered wounds), and longer wound length were significant risk factors for tissue reactivity. Suture materials had little effect, with silk having the highest, though not significant, risk of tissue reactivity. In terms of dehiscence, male sex, surgeon experience (for one-layer wounds), and patient age ≤50 years (for two-layer wounds) were significant risk factors in multivariate analyses. Smaller caliber external sutures were associated with a borderline risk of dehiscence. In terms of infection, male sex and age >50 years were significant risk factors in multivariate analyses for the combination of one-layer and bilayered closures (2b or 3b) [71].

In a large prospective study of 866 sequential blepharoplasties over 5 years, 6-week complication rates and 3-month satisfaction rates were compared between repairs using different suture materials and techniques. Four techniques were compared: (1) 5-0 running subcuticular polypropylene (n = 198), (2) 5-0 running cutaneous locked polypropylene (n = 45), (3) running 6-0 plain gut suture (n = 177), and (4) running 6-0 fast-absorbing gut suture and two simple interrupted 5-0 polypropylene (n = 466). Nonabsorbable sutures were removed at 5 days. Groups 1 and 4 had significantly lower rates of milia (2.5% and 2%) and groups 2 and 3 had higher rates (17% and 6.7%). Group 4 had significantly less scarring than expected (0%) and Group 3 had significantly more scarring than expected (2.8%) (Groups 1 and 2 also had 0% scarring). Group 3 had statistically more erythema (9%) than all other groups (2%). There were no differences in standing cone deformities between groups 1 and 2. There were no differences between groups 3 and 4 in terms of suture marks. There was no difference between groups 1, 3, and 4 in terms of minor hematoma. There were no infections or cases of dehiscence. Of 568 patients surveyed at 3 months, 74% were highly satisfied, 21% were satisfied, and 5% were unsatisfied with their results (2b or 3b) [72].

Blood supply is a factor in closure site healing. In a nonrandomized study of 63 patients, cutaneous blood flow was evaluated on the first and fifth postoperative day in relation to 3 suturing techniques (n = 21 per group). Infrared laser Doppler flowmeter on either side of abdominal incisions with uninjured adjacent skin as a control showed statistically higher blood flow with subcuticular sutures compared to mattress sutures and staples (3b) [73].

In a nonrandomized split-wound study of five patients, fast absorbing gut suture placed in a running subcuticular technique was compared to simple interrupted nylon sutures for layered facial Mohs closures under minimal tension. No complications or differences in cosmetic outcome were noted at 1 week and 3 months (3b) [74].

Among a group of boys aged 14 months to 18 years, 146 orchidopexies were closed with subcuticular 4-0 polyglycolic acid and 27 were closed with interrupted 3-0 silk. Follow-ups occurred 12–37 months after surgery. Hypertrophic scars were raised above the surrounding skin and measured more than 1 mm in width. No hypertrophy was noted in 94.5% of wounds sutured with subcuticular polyglycolic acid. With interrupted black silk sutures, 18.5% of the scars developed medial hypertrophy. Hypertrophy was found to be dependent on location rather than suture material (3b) [75].

In a prospective study of 60 patients, postoperative pain assessments for the first 5 days were compared when hernia repairs or upper abdominal closures were completed with either simple full-thickness 2-0 nylon interrupted sutures or 3-0 polydioxanone subcuticular interrupted sutures. In the hernia group, the subcuticular method resulted in significantly less pain. Both groups were equivalent in terms of wound healing, sepsis, and cosmetic outcome (3b) [76].

In a retrospective nonrandomized case-control study, 186 consecutive patients with primary closure of 188 full-thickness lower eyelid defects with single or bilayered closure techniques were compared. Single-layer closures (n = 82) were with nonabsorbable polypropylene. Bilayer closures (n = 106) were with absorbable polyglactin. Single-layer closure of full-thickness eyelid defects is equally as safe and effective as bilayer closure with no differences in terms of notching, dehiscence, or other complications (3b) [77].

In a retrospective cohort study of 142 patients undergoing breast reconstruction, half were closed with standard suture material while the other half were closed with barbed sutures. The standard suture group closed Scarpa's fascia with interrupted 2-0 Vicryl, deep dermis with 3-0 Monocryl, and subcuticular closure with 4-0 Monocryl. In the barbed group, fascia was closed with 2-0 V-Loc 180 unidirectional barbed sutures, deep dermis with fewer 3-0 Monocryls, and subcuticular closure with 3-0 V-Loc 180. There was no significant difference in operation times, seroma, infection, or wound dehiscence; however, less hematomas were observed in the barbed suture group (3b) [23].

In a prospective case-control study, 117 craniotomy scalp closures with continuous 2-0 nylon sutures were compared with intradermal 2-0 Monocryl sutures. Intradermal suture was performed in 44 cases, and continuous suture was performed in 56 cases; 17 patients died and were excluded from the study. Equivalent rates of wound infection were observed with one case (2.2%) of wound infection in the intradermal group and three cases (5.3%) of wound infection in the continuous suture group (P = 0.73). There were no cases of wound dehiscence in either group (3b) [78].

Review of Studies Consisting of Level 4 Evidence

In a small case series of three patients, Wong (1993) described successful use of a running locked intradermal suture in elliptical facial excisions that accomplished the following goals: to close dermal dead space under light tension, to allow for good wound edge apposition, to make superficial sutures unnecessary (avoiding suture marks and giving good cosmesis), and to reduce the need for wound care and suture removal (4) [79].

In a case series where barbed sutures were used for wound closure on 11 ft in 8 patients undergoing hallux valgus correction or revision correction, 5 (45%) had delayed wound healing with irritation or dehiscence due to prominent barbs, and 4 (36%) required open suture excision and formal scar excision due to adverse reaction at around 4 weeks (4) [80].

A limited cost analysis by Fosko et al. calculated an average savings of US$ 3.36 per dermatologic reconstruction by using polyglactin 910 only instead of an additional package of nylon. This results in saving US$ 336 per 100 repairs (4) [81].

There is a report of two cases of allergy to poliglecaprone 25 sutures confirmed by patch testing (4) [82].

Evidence-Based Review: Tissue Adhesives and Glue

1. *Three systematic reviews and meta-analyses on the topics of tissue adhesives or surgical glue were reviewed; one was downgraded due to quality of the included studies and heterogeneity for some outcomes.*

A systematic review and meta-analysis performed by Gkegkes et al. included 12 randomized controlled trials. A total of 1317 incisions were compared using adhesive strips for wound closure versus conventional wound closure methods such as sutures. Eight of these studies showed that there was no significant difference in infection rates between closure with surgical strips and sutures (odds ratio = 0.47; 95% confidence interval = 0.12–1.85). Of nine studies that provided data regarding cosmetic outcome, only five studies provided data that was eligible for statistical synthesis by the authors, which showed no significant difference in the cosmetic outcome when using surgical strips (standardized mean difference = 0.01; 95% confidence interval = −0.19–0.20), though a variety of scoring techniques were used. The authors also showed no significant difference with regard to wound dehiscence (odds ratio = 1.22; 95% confidence interval = 0.32–4.64). More studies are needed to determine the distance between wound edges where use of surgical strips is still an effective means of wound closure to gauge how much tension can be allowed, the need for resuturing, patient satisfaction with this method of wound closure, and whether surgical strips offer any time-saving benefits (1a) [83].

A meta-analysis investigating the early cosmetic outcomes with the use of skin adhesives conducted a search through PubMed, Medline, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between January 1990 and December 2011. The limitations of the study included differing techniques for tissue adhesives between studies, only 3 months of follow-up for cosmesis leading to significantly heterogeneity, and small sample sizes of the studies. To be included, a study was required to compare skin incision closure with tissue adhesive versus traditional wound-closure methods, and a visual analogue scale (VAS) must be mentioned. A total of 9 publications were included in the meta-analysis. There was significant heterogeneity between studies regarding overall effect on the incision's cosmetic appearance 3 months postoperatively. No significant differences in overall cosmetic outcomes were found between the use of tissue adhesives and staples or when using sutures (P = 0.54, P = 0.99). There was no significant difference for facial wounds (P = 0.79), body wounds (P = 0.46), older patients (P = 0.07), or selective surgery (P = 0.78). However, the VAS results between the use of sutures and tissue adhesives were significant, and there was no heterogeneity of studies. The evidence indicated that the cosmetic results of incisions closed by tissue adhesives were worse when dermal sutures were not used (P = 0.04) or when a laceration wound was involved (P = 0.03). Study authors concluded that dermal suture is required to decrease wound tension and prevent dehiscence in laceration wounds, and therefore any tissue adhesive used must also include dermal sutures (1b) [84].

Another meta-analysis investigated the use of tissue glue for surgical incision closure. A literature search for randomized controlled trials was performed using PubMed, the Cochrane Database, Ovid, Medline, Google Scholar, Ovid, Embase, and Medline. To be included, studies had to compare surgical skin closure with tissue adhesive and another type of standard closure method. A total of 26 studies were included. There was no significant difference in wound infection rates between the two groups (I^2 = 0%, risk ratio [RR] = 1.10; 95% CI, 0.71–1.69). This included subgroup analysis between tissue glue and sutures, tissue glue and monofilament sutures, tissue glue and interrupted sutures, and tissue glue and subcuticular sutures. Similarly, no significant difference was identified in wound infection rates between tissue glue and staples (skin clips) (I^2 = 0%, RR = 1.05; 95% CI, 0.41–2.65). Of the 26 studies, 19 included data on time for wound closure. Of these 19 studies, 14 found closure to be significantly faster using

tissue glue compared with sutures, with 1 more finding tissue glue faster but included no tests for significance. One study found no significant difference in times between tissue glue and sutures. Four studies compared the use of tissue glue with staples (skin clips), and three of these found staples (skin clips) to be considerably faster for skin closure, while one study found no significant difference between the groups. A study comparing tissue glue with adhesive tape found no significant difference between groups. Twenty studies analyzed wound dehiscence after skin closure by tissue glue, and a statically significantly increased wound dehiscence rate was found when using tissue glue (I^2 = 14%, RR = 3.29; 95% CI, 1.77–6.15). Further subgroup analysis between tissue glue and skin sutures also demonstrated statistically significant increases in dehiscence for tissue glue (I^2 = 33%, RR = 3.31; 95% CI, 1.73–6.34), as well as tissue glue versus monofilament sutures (I^2 = 5%, RR = 4.61; 95% CI, 2.17–9.79), and tissue glue versus subcuticular sutures (I^2 = 34%, RR = 7.39; 95% CI, 2.49–21.94). Cosmetic results were included in 21 studies, but due to heterogeneity in scoring, these results were not included. However, of note is that 15 studies found no significant difference in cosmetic outcome in wounds closed with tissue glue versus standard wound closure, while 2 studies reported that tissue glue produced better cosmetic outcomes. With regard to patient satisfaction, eight studies stated that patients were more satisfied with the use of tissue glue, while another two studies stated that standard wound closure increased patient satisfaction. Equivalent patient satisfaction for standard wound closure and tissue glue was reported in two other studies. Finally, nine studies assessing the material cost of tissue glue in comparison with standard closure methods reported tissue glue as more expensive. However, two studies that included time savings in addition to material costs found tissue glue was less expensive. In summary, tissue adhesives/glue have the advantages of reduced closure time, reduced pain, and no follow-up for removal as compared to standard wound closure methods. These traits make tissue glue/adhesives particularly useful in pediatrics. However, there is a small increase in risk of wound dehiscence for wounds closed with tissue glue and no definitive evidence of improved cosmetic outcome (1a) [85].

2. *Review of several randomized controlled trials studying tissue glue*

In this randomized control trial, subjects undergoing total knee arthroplasty (TKA) were randomly assigned into one of four cohorts based on wound closure method with any one of n-butyl-2-cyanoacrylate tissue adhesive, 2-octyl tissue adhesive, Visistat 35W Stapler, or Monocryl suture (control). Of the 90 subjects recruited, a total of 75 subjects completed the study. Staple-based closure was deemed the fastest and least-expensive TKA wound closure technique in the operating room, but was associated with a statistically significant longer hospital stay in comparison with tissue adhesives and suturing. Of the 4 closure methods, tissue adhesives and staples were faster than sutures. The 2-ocytl and n-butyl-2 tissue adhesives required an average of 2.5 and 2.6 s/cm, whereas staples required 1.8 s/cm, and subcuticular Monocryl 4-0 suturing required an average 26 s/cm ($P < 0.0007$). However, the intraoperative efficiency of staples may be offset by lengthened hospital stay, thereby making tissue adhesives an efficient, viable alternative to TKA closure. Further study is needed to determine if the relationship between hospital stay and staple closure may be causal. The successful use of tissue adhesives for high tensile strength knee replacement in this study was believed to be due to added underlying reinforcement with 50% higher frequency (7.5 mm for adhesives vs. 10-mm staples, 8-mm suture) interrupted subcutaneous sutures. The adhesive and staple cohorts experienced an average 17% greater occurrence of peripheral edema with respect to subcuticular suturing ($P < 0.03$). However, there were no statistically significant differences in infection, dehiscence, cosmesis (patient-assessed visual analog scale), general health (SF 12v2), and functional and clinical assessments (extension, flexion, ROM, Knee Society knee score, and pain visual analog scale) (1b) [86].

In a blind randomized controlled trial, differences in operating time, wound complications, and cosmetic outcomes were assessed in wounds of 29 patients closed using either octyl-2-cyanoacrylate (2-OCA) tissue adhesive or conventional subcuticular skin sutures. A total of 15 patients (20 incisions total) received closure by 2-OCA and 14 patients (20 incisions total) received closure by subcuticular sutures. On days 5–10 postoperatively, the wound was evaluated for healing. A total of 3 months postoperatively, wounds were assessed for cosmetic outcome by a plastic surgeon (independent of the study) using a Hollander Wound Evaluation Scale (HWES) and a visual analog scale (VAS). Patient satisfaction was also evaluated using a VAS. There were no significant differences between treatments with regard to adverse outcomes. At the 3-month follow-up, there was no significant difference in the frequency of an optimal HWES score between the two closure groups ($P = 0.835$). The surgeon's VAS scores had no significant differences ($P = 0.332$) between treatment groups, as did the patients' VAS scores ($P = 0.129$). The results indicate that 2-OCA significantly reduced time required for wound closure, as compared with the time required for sutures (2-OCA at 69.50 ± 33.39 s vs. 379.00 ± 75.39 s for sutures) ($P < 0.005$). 2-OCA proved to be a verified alternative to sutures for an effective and faster method of maxillofacial incision closure. However, the authors noted that 2-OCA has a maximum tensile strength equivalent to that of 5-0 suture, and should not be used for high tension wounds that would require 3-0 or 4-0 sutures. In addition, no analysis of cost-effectiveness was included in this study, but one can deduce that tissue adhesives are more economical (1b) [87].

In this randomized controlled trial investigating optimal closure materials for upper lid blepharoplasty, 36 patients underwent a split-eyelid study to compare the efficacy of polypropylene, fast-absorbing gut, and ECA (Dermabond). Patients were randomized for treatment into 1 of 3 groups: (1) fast-absorbing gut suture versus ECA, (2) ECA versus polypropylene suture, and (3) polypropylene versus fast-absorbing gut suture. All surgeries were conducted by the same surgeon, and in all groups the lateral third of the defects were standardized for wound tension via one deep dermal suture with 5-0 Vicryl. At the 1-month follow-up, a blinded-physician evaluation scored ECA with a statistically significant better cosmetic outcome than fast-absorbing gut suture and nonsignificantly better outcome than polypropylene. Polypropylene was nonsignificantly better than fast-absorbing gut suture. At the 3-month follow-up, a statistically significant better cosmetic outcome was demonstrated for group 1, in which ECA had superior cosmetic outcomes than fast-absorbing gut ($p = 0.03$). Overall, the study concluded that the use of ECA resulted in speedier application and cosmetic results equivalent if not superior to that of sutured wounds. Tissue adhesive is recommended for closure of low-tension wounds during cosmetic surgery, especially for the eyelid. However, patients should be warned about potential for irritation and pruritus with the use of ECA (1b) [88].

In this single-blind RCT, Bartenstein et al. reported that cyanoacrylate tissue adhesives produce equivalent cosmetic outcomes to that of sutures, in addition to increased ease of use, patient satisfaction, and speed of application. After completing skin cancer removal (via Mohs or excision) and following placement of deep absorbable sutures, patients were randomized to receive wound closure by Prolene suture, LiquiBand (butyl-cyanoacrylate), or Dermabond (octyl-cyanoacrylate). Upon surgery completion and until the 2-week follow-up, patients were asked to write a daily record on the amount of time needed to care for their wound and how much the wound interfered with daily activities (VAS 0–10). At 3 months, subjects rated satisfaction with their wound and evaluated wound cosmetic outcome (VAS 0–10). A photograph was taken at the 3-month follow-up and was used by an independent, method-blinded panel of three dermatologists and three plastic surgeons. Wound closure with either tissue adhesive was found to be significantly faster than sutures (median 256.0 s, range 172.0–530.0 s; $p < 0.0001$ for LiquiBand vs. suture, $p < 0.0001$ for Dermabond vs. suture). At the 2-week follow-up, nurses required significantly more time ($p = 0.01012$) with the subjects

who had sutures than they did with subjects who had either type of tissue adhesive. At the time of wound closure, the surgeon found it significantly easier to close wounds with either tissue adhesive as compared to sutures ($p < 0.001$ for both Dermabond vs. sutures and LiquiBand vs. sutures). However, the surgeon reported more initial satisfaction with the wounds closed by sutures compared with adhesives ($p = 0.0004$ for LiquiBand vs. sutures and $p = 0.0001$ for Dermabond vs. sutures). It is worth noting that 24 subjects underwent past surgery with wound closure by traditional suturing but in this study were randomized to closure by tissue adhesive. When these patients were asked to rank their satisfaction with tissue adhesive as compared to suture, the ratings were statistically significantly for an increase in satisfaction for tissue adhesives (LiquiBand: $p = 0.0039$, Dermabond: $p = 0.002$) as compared to suture (1b) [89].

3. *Review of several randomized controlled trials studying adhesive strips*

In a prospective randomized split-wound controlled trial, researchers investigated if addition of adhesive strips to a wound closed with subcuticular sutures improved cosmetic outcomes. Study subjects were adults with postoperative defects of at least 3 cm resulting from either Mohs surgery ($n = 35$, 73%) or surgical excision ($n = 13$, 27%) located anywhere on the body. Buried vertical mattress subcuticular sutures were used to close the wound. Following closure by the surgeon, the wound was divided in half, and one side was randomly chosen to receive adhesive strips applied by a nurse (with supplemental tissue adhesive, Mastisol). At 3-month follow-up, two blind observers and the patient evaluated the scar using the Patient and Observer Scar Assessment Scale (POSAS). No significant difference in mean POSAS scores was found between the two closure techniques regarding vascularity, pigmentation, thickness, relief, pliability, surface area, and overall opinion. Additionally, there was no significant difference for scar width between the sides of the scars with or without adhesive strips. The mean width of both scar sides was 1.1 mm (SD = 0.8, $P = 0.89$). Any adverse events (suture abscess, wound dehiscence) that occurred were not statistically significant with regards to either closure group. Therefore, it was concluded that adhesive strips did not improve the appearance of scars from cutaneous surgical procedures using subcuticular sutures. Equivalent outcomes were observed on both wound sides with no changes by addition of tissue adhesive (1b) [28].

In a prospective randomized study, Steri-Strips were compared to running absorbable subcuticular sutures for skin closure following median sternotomy in 36 patients. There were no significant differences in closure times between the groups. Steri-Strips led to significantly less erythema ($p = 0.003$) and edema ($p < 0.001$) with no difference in pain or cosmesis on day 7. At 21 days, the only difference remaining was less erythema ($p = 0.01$) in the adhesive group. The suture technique used about two packets of Vicryl sutures per patient (US$ 4.36 per patient), whereas about three packets of adhesive strips were required per patient (US$ 32.91 per patient). The strips are safe and effective but not clearly superior for the average patient (1b) [90]. They may be of potential benefit for patients where it may be desirable to avoid additional inflammation from superficial sutures such as in the case of diabetics, or patients with immunosuppressive or inflammatory disorders (5) [90].

A prospective randomized study of 113 patients compared 4 methods of leg wound closure after coronary artery bypass grafting: (1) a continuous vertical mattress suture of 2-0 nylon ($n = 27$ patients), (2) a continuous subcuticular suture of 2-0 polyglycolic acid ($n = 29$ patients), (3) disposable metal skin staples ($n = 27$), or (4) "Op-site" transparent adhesive sutureless skin closure. Wounds were examined by two independent observers at 5, 10, and 45 days. The overall infection rate was 4.5%. Continuous subcuticular sutures led to significantly less discharge at 5 days; significantly better healing at 10 days in terms of wound overlap, inflammation, and dehiscence; and final cosmesis significantly better than metal staples or vertical mattress nylon sutures but equivalent to closure with "Op-site" sutureless closure. The authors conclude continu-

ous subcuticular polyglycolic acid is superior in all criteria except speed of insertion and cost and recommend it for standard use (1b) [55].

In a randomized controlled trial of 169 patients (ages 15–78 years) undergoing acute appendectomy, inguinal herniorrhaphy, or saphenofemoral ligation, traditional interrupted 2-0 Prolene sutures were compared to subcuticular 2-0 Prolene sutures and sterile porous adhesive tape (Micropore Surgical Tape). All sutures were removed at 7 days, and the micropore tape was left for 2 weeks. Scars were graded at 4 weeks by the patients, surgeon, and a blinded assessor. The combination closure resulted in significantly higher percentages of "excellent" grading by surgeons for herniorrhaphy and by all raters for appendectomies. No differences in "excellent" gradings were noted for saphenofemoral ligation. The appendectomy group had the highest number of patients, and it is possible the sample sizes for the other two groups were too small to show more significant differences. Seven cases of wound infection were reported (four in the traditional group and three in the combination group) (1b) [91].

Op-site sutureless skin closures of at least 7 cm were compared to continuous nylon sutures in a randomized controlled trial in 55 orthopedic surgery patients. Sutures were removed at 10–12 days, and Op-site was removed at 2 weeks. Op-site gave better cosmesis, comfort, and less wound inflammation but problems were identified in terms of safety, accuracy of wound edge apposition, and ease of use. The sutureless system could not close the skin due to oozing in one case, skin could not be apposed perfectly in two cases, indented scars formed in four cases, and there was dehiscence in one case (2b) [92].

A polyurethane membrane coated with firm adhesive skin closure method (Op-site) was compared to skin closure by interrupted silk sutures and subcuticular nylon. Wound closure by Op-site proved statically significant for reduced erythema ($P = 0.0457$) and tenderness ($P = 0.0464$) compared to suture closure (2b) [93].

This randomized controlled trial compared skin closure time using either subcuticular Monocryl sutures or coaptive film (Steri-strip) in eight children undergoing bilateral soft tissue releases. Cosmetic outcome was scored by a blinded plastic surgeon using a visual analog scale (1–10). Both methods resulted in similar cosmetic results with no statistically significant differences ($P = 0.44$). No complications occurred. Incisions closed with coaptive film required less time as compared with suture closure of the corresponding incision on the contralateral limb ($P < 0.0001$). Average time saved for skin closure using coaptive film was 87.68 s per incision (1b) [94].

Closures of 102 breast biopsies were randomized to either subcuticular Prolene, subcuticular Dexon, or Op-site adhesive. One subcutaneous fat stitch was used to approximate wound edges before Op-site closure. Fourteen patients were withdrawn from the study due to malignancy being diagnosed and one Dexon patient was lost to follow-up. After follow-up at 1 week, 3 months, 6 months, and 12 months or more, no difference in wound appearance (by an independent assessor) or patient preference was found for any method. One hematoma developed in the nylon group and one hypertrophic scar developed in the Dexon group (2b) [95].

One Study Using both Tissue Glue and Adhesive Strips

Ten patients undergoing excision of a single benign or malignant lesion on the back were recruited to participate in this split-scar randomized controlled trial. All patients were Caucasian with Fitzpatrick skin types I–III, all lesions were removed by elliptical excisions, and the subcutaneous layer was closed by buried vertical mattress 4-0 polyglactin 910 sutures in all wounds. The wound was divided in half as Side 1 or Side 2. Side 1 of the wound was closed with running 4-0 polypropylene sutures. Following application of liquid adhesive (Mastisol), Side 2 was closed with 1/4" Steri-Strips spaced approximately 3–5 mm apart. Wound closure was timed for each method. Scar cosmetic outcome was assessed by the Patient and Observer Scar Assessment Scale (POSAS) at a minimum of 2 weeks, 14 weeks,

and 26 weeks postoperatively. The adhesive Steri-Strips required significantly less time than the sutures ($p = 0.0002$), resulting in an average of 3 min of time savings. At 26 weeks, patient and observer POSAS scores of scar appearance were not significantly different. In summary, Steri-Strips resulted in equivalent scar cosmetic outcomes in comparison to sutures but reduced the time necessary for wound closure for surgical excisions on the back (1b) [96].

4. *Review of a number of nonrandomized studies of adhesive strips*

In a prospective nonrandomized controlled study of 300 patients undergoing elective colorectal resection, 150 patients each underwent clean-contaminated wound closure with adhesive paper tape or interrupted sutures. The paper tape group (Micropore Hypoallergenic Surgical Tape) took significantly less time for wound closure than the silk interrupted suture group (116 ± 23 versus 457 ± 64 s, $p < 0.01$). Paper tape was retained for 7–10 days, and sutures were removed at 7 days. The overall wound complication rate (infection + separation, in 3.3% per group) and infection rate were equivalent in both groups. There were three cases of wound infection and two cases of skin wound separation in the paper tape group and five cases of wound infection in the suture group. However, peeling of the paper tape due to wound secretion requiring replacement was noted in 14 cases (9.3%), blistering was noted in 1 case, and a mild allergic reaction was noted in 1 case. No differences in scar width were found at 6 months. In the paper tape group 95% of patients were satisfied with their scar compared to 92% in the suture group ($p = 0.03$) (3b) [97].

As mentioned in the suture review section, there has been a follow-up study of 149 procedures, where buried vertical mattress sutures were only covered by wound closure tapes, removed at 5 days. The technique was concluded to be safe, easy to use, and prevented suture marks as long as wound edges could be exactly opposed. Wound length was correlated with scar dehiscence and facial locations healed best (3b) [70].

In a trial of 120 patients (ages 14–63 years), sutureless skin closure with a new adhesive polyurethane membrane (op-site) was compared to standard skin closure with interrupted 2-0 silk sutures for various surgeries (e.g., appendectomies, laparotomies, thyroidectomies, herniorrhaphies). Wounds closed with sutures were also covered with the membrane to standardize the healing environment. Patients were matched for age and sex. Results after 1 month were comparable in both cases; however, the membrane group experienced higher rates of uneventful recovery, no risk of suture marks, and a higher percentage of patient satisfaction with cosmetic appearance (no statistical comparisons made) **(3b)** [98].

5. *Review of several nonrandomized studies of tissue glue*

In a retrospective analysis of 60 patients (ages 4–40 months) with unilateral ($n = 59$) or bilateral ($n = 1$) cleft lip, skin closure with 6-0 Prolene was compared to closure with medical-grade cyanoacrylate glue. Glue closure took significantly less time than closure with Prolene ($p < 0.01$). One wound infection occurred in the Prolene group. Three of five blinded observers favored cyanoacrylate in terms of cosmesis by visual analog scale ($p = 0.05$). Patients were significantly more satisfied with the healed scars in the glue group (3b) [99].

In a prospective study of 46 wound closures in patients ages 5–85 years, a less costly cyanoacrylate, 2-etil-cyanoacrylate, was investigated. Excisions (97.8%) and traumatic wounds (2.2%) were closed by this method. Complications recorded over 3 months included unsatisfactory scars (22%), infection (2.1%), dehiscence (2.1%), and allergic contact dermatitis (2.1%). Patients were satisfied with the results in over 97% of the cases (3b) [100]. Study authors concluded that the use of ECA achieved satisfactory cosmetic outcomes, while reducing cost and rates of complication. However, ECA use is contraindicated in contaminated, bleeding, or infected wounds,

wounds in tight skin or mucosa, areas subject to friction and/or moisture, or when allergy to ECA is indicated (5) [100].

The use of cyanoacrylate in skin closure was studied in 30 patients undergoing planned surgery from September to March 1984, and compared to 25 patients undergoing similar procedures whose skin was closed with 4-0 monofilament (nylon) polyamide sutures. Closure of the wound required less time when using cyanoacrylate. Infection occurred in 1 of the 28 (7.14%) cyanoacrylate patients versus 3 of the 25 (12%) suture patients. A single linear scar was observed upon use of cyanoacrylate, while a linear scar with cross-hatch marks was observed for wounds closed by suture (3b) [101].

Two cases of allergic contact dermatitis to 2-octyl cyanoacrylate (Dermabond) were confirmed by patch testing (4) [102].

In this case series, Tayebi et al. present a novel technique for primary wound closure as used in six patients with atrophic skin undergoing Mohs surgery on the upper and lower limbs (defect size 1.5–3.0 cm). Adhesive glue was used to fortify the edges of atrophic, sun-damaged skin so that the sutures held better. An additional layer of adhesive was applied along the suture line, and sterile adhesive strips were placed over epidermal sutures to further decrease wound tension. No adverse events were reported (4) [103].

Evidence-Based Review: Staples

1. *Review of four meta-analyses after removal of duplicates, with the downgrading of one based on quality*

In a 2015 meta-analysis of randomized controlled trials of cesarean skin closure by subcuticular absorbable sutures versus staples, data were gathered regarding cosmesis, pain, patient satisfaction, wound complications, and operating time. The results from 12 randomized trials including 3112 women showed that suture closures were less likely to result in overall wound complications than staple closures (risk ratio, 0.49; 95% confidence interval, 0.28–0.87). This was largely due to a 71% lower chance of wound separation in the suture group and the effect remained significant even after stratifying by obesity. The two methods performed equally with respect to pain perception, patient satisfaction, and cosmesis; however, operating time was approximately 7 min longer with suture closure (95% CI, 3.10–11.31) (1a) [104].

This meta-analysis searched PubMed, Scopus, and Cochrane Central Register of Controlled Trials for randomized controlled trials comparing sutures with staples for surgical wound closure. A total of 20 studies were included, involving a total of 2111 patients. Specifically, 1233 patients underwent suture closure, whereas 878 patients underwent staple closure. Among the 20 included studies, 5 studies referred to obstetrics and gynecological operations, 7 to general surgery, 4 to emergency care treatment (2 involving pediatric patients), 3 to head/neck operations, and 1 to vascular surgery. Studies referring to orthopedic operations were not included. The follow-up period ranged from 7 days to 11 months among the included studies. Wound infections occurred significantly less in the staples group in comparison with the sutures groups (12 studies, 1529 patients; odds ratio [OR], 2.06; 95% CI, 1.20–3.51). Regarding time needed to close the wound, staples were found to be superior to sutures in 5 studies. The mean difference observed between the sutures and staples groups was 5.56 min per wound (95% confidence intervals [CI], 0.05–11.07). The majority of the included studies reported nonsignificant differences regarding the cosmetic outcome using sutures versus staples, yet in four studies, use of sutures was significantly associated with a superior cosmetic outcome compared with staples. This meta-analysis suggests that staples are better than sutures regarding the development of wound infections in obstetrics/gynecology, abdominal, head/ neck, and vascular operations in addition to emergency care surgical procedures. However, in five of the studies, staples were associated with significantly more pain compared with sutures. With regard to patient satisfaction, the majority of the included studies reported nonsignificant differences between the sutures and staples groups.

Considering that use of staples is quicker than suturing and that the majority of the studies reported analogous results for these two methods with regard to patient's satisfaction and cosmetic result, surgeons may consider using staples for wound closure for the mentioned procedures. More trials of higher methodological quality, incorporating more objective assessments of pain perception, patient satisfaction, and cosmetic outcome, are required to better answer this question (1a) [105].

In this systematic review of systematic reviews with panoramic meta-analysis of pooled estimates, 11 systematic reviews, including 13,661 observations, were analyzed. The authors note that there was wide variation in method preference between specialties, some finding a statistically significant benefit to sutures, others to staples. In orthopedic surgery, sutures were preferred, as staples were associated with a statistically significant increase in surgical site infection (OR 4.27 95% CI 1.00, 19.08). Staples were found to increase postsurgical complications in caesarean sections. However, staples were found protective against leak in ileocolic anastomosis. For all other surgery types, there was no consistent evidence that staples or sutures outperform the other. While there was some indication that staples resulted in increased odds of postsurgical complications, the 95% confidence interval was wide, indicating considerable uncertainty (OR 2.02 95% CI 0.69, 5.86). Evidence across surgical specialties indicated that staples reduced mean wound closure time. In conclusion, despite including several thousand observations, there was no clear evidence of an advantage for either staples or sutures with respect to length of stay, postsurgical complications, or surgical site infection incidence (1a) [106].

A systematic review and meta-analysis of sutures versus staples in orthopedic surgeries were conducted using Review Manager V 5.0 and included 13 studies published between 1990 and 2015. The cumulative sample size of all studies was 563 patients within the suture group and 692 patients within the staple group. Ten studies were randomized controlled trials and three were observational studies. The primary outcome was the incidence of surgical site infection. There was no significant difference in infection comparing sutures to staples. The cumulative infection relative risk of sutures versus staples was 1.06 (0.46–2.44). In addition, there was no difference in infection comparing sutures to staples in hip and knee surgery, respectively. Secondary outcomes included closure time, inflammation, length of stay, pain, abscess formation, necrosis, discharge, wound dehiscence, allergic reaction, and health-related quality of life. This meta-analysis found no significant difference in superficial infection and secondary outcomes comparing sutures to staples. Based on qualitative analysis, there seems to be a trend that staples cause more pain on removal than sutures, and this trend is consistent with non-orthopedic surgeries. However, the results from studies reporting pain data could not be combined quantitatively. Regarding closure time, the mean difference (MD) of closure time was significant in favor of staples, with a MD of 5.84 min (4.52–7.15) comparing suture and staple groups. Two other included studies also noted faster closure times with staples, but the data could not be used in the cumulative MD assessment. It was concluded that there may be no difference in effect between the two skin closure methods, and due to the methodological limitations of the included studies, the authors should begin to consider the economic and logistic implications of using staples or sutures for skin closure. Future studies should focus on conducting high-quality randomized control trials that include detailed baseline characteristics, and in addition a detailed patient recruitment flow chart should be presented. Poor quality of evidence and significant heterogeneity was found across included studies (2a) [107].

2. *Review of several randomized controlled trials*

As mentioned in the adhesives section, in a randomized control trial, subjects undergoing TKA were randomly assigned into one of four cohorts based on wound closure method with either n-butyl-2-cyanoacrylate tissue adhesive, 2-octyl tissue adhesive, Visistat 35W Stapler, or

Monocryl suture (control). Of the 90 subjects recruited, a total of 75 subjects completed the study. Staple-based closure was deemed the fastest and least-expensive TKA wound closure technique in the operating room but was associated with a statistically significant longer hospital stay in comparison with tissue adhesives and suturing. Of the four closure methods, tissue adhesives and staples were faster than sutures. The 2-ocytl and n-butyl-2 tissue adhesives required an average of 2.5 and 2.6 s/cm, whereas staples required 1.8 s/cm, and subcuticular Monocryl 4-0 suturing required an average 26 s/cm ($P < 0.0007$). However, the intraoperative efficiency of staples may be offset by lengthened hospital stay, thereby making tissue adhesives an efficient, viable alternative to TKA closure. Further study is needed to determine if the relationship between hospital stay and staple closure may be causal. The successful use of tissue adhesives for high tensile strength knee replacement in this study was believed to be due to added underlying reinforcement with 50% higher-frequency (7.5 mm for adhesives vs. 10-mm staples, 8-mm suture) interrupted subcutaneous sutures. The adhesive and staple cohorts experienced an average 17% greater occurrence of peripheral edema with respect to subcuticular suturing ($P < 0.03$). However, there were no statistically significant differences in infection, dehiscence, cosmesis (patient-assessed visual analog scale), general health (SF 12v2), and functional and clinical assessments (extension, flexion, ROM, Knee Society knee score, and pain visual analog scale) (1b) [86].

A blinded randomized controlled trial compared skin closure using subcuticular suture, staples, and OCA (Dermabond) in patients undergoing total knee or hip replacement. The primary outcome measure was the development of complications in the wound, either as an inpatient or after discharge. The absence of blood strike-through onto the dressing was assessed at 24 h as a measure of how well the wound was sealed. OCA was proved significantly better than staples or suture for both hip and knee replacements. There were significantly more cases without strike-through indicating that more wounds were sealed completely with OCA in both the THR (Fisher's exact = 15.77; $p = 0.0004$) and TKR (Fisher's exact = 12.68; $p = 0.002$) groups. The Mann–Whitney U test indicated that wound closure with skin staples was significantly faster than with OCA (Mann–Whitney U test = 8; $p < 0.0001$) which was significantly faster than with suture (Mann–Whitney U test = 174; $p < 0.0007$). There was no significant difference in the median length of stay in hospital, the Hollander wound evaluation score and patient satisfaction for the three groups in both THR and TKR. There were no reported adverse events or side effects. For subjects undergoing total knee replacement, there was a trend toward a longer stay in hospital with OCA compared with suture ($p = 0.09$), but no significant difference compared with staples ($p = 0.50$). The studies' results suggest that there is little difference between the three techniques of closure following replacement of the hip. However, the increased tensile forces associated with total knee replacement makes OCA inappropriate as increased wound discharge occurred upon early rehabilitation. Study authors now use staples routinely for the wounds following arthroplasty of the hip and knee (1b) [108].

In a blind prospective randomized control study, patients undergoing bilateral breast reconstruction with tissue expanders received wound closure on one breast using INSORB absorbable dermal staples and on the contralateral breast using 3-0 braided polyglactin 910 suture. Each patient's left or right breast was randomly assigned a closure method, and a randomly selected surgeon completed closure on both sides for each patient. The wound was examined objectively by a blinded attending plastic surgeon at each follow-up visit. The dermal stapler was four times faster than standard suture closure, reducing closure time by 10.5 min ($p < 0.001$). No wound complications or infections were documented in any patients. Early preoperative wound assessment was initially 1.13 points higher (Vancouver Scar Scale) for wounds closed by INSORB dermal stapler due to improved skin edge eversion ($p = 0.048$). However, after 136 days postoperatively, wounds closed by dermal stapler or dermal suture became statistically equivalent, indicating

a comparable cosmetic result between the two methods. At 6 months, histological analysis of scars indicated decreased inflammatory cell division in scars closed by the INSORB dermal stapler method. Overall, cost savings with the dermal stapler was US$ 220 per case. This study supports the beneficial qualities of the dermal staple device for surgical wound closure, as the INSORB dermal staple was significantly faster than standard suture closure techniques with equivalent cosmetic outcomes and reduced cost. However, the authors note that the small size of the stapler head, reduced tensile strength of the staple in settings of edema or tension, and the learning curve required to operate the technology must be considered (1b) [109].

One study evaluated the safety, efficacy, and cosmesis of wound closure using an absorbable subcuticular stapling system (INSORB) compared to wound closure by conventional percutaneous metal staples in 16 female patients requesting aesthetic facial rejuvenation (endoscopic eyebrow-lift or rhytidectomy). The mean age was 59 years, ranging from 48 to 76. Skin incisions for both procedures were placed in bilateral temporal and postauricular hair-bearing scalp. Each patient had 50% of incisions closed by one method, with the other 50% closed by the second method, resulting in one side of the head closed with absorbable subcuticular staples and the contralateral side closed with percutaneous metal staples. Use of a particular method on right or left side of head was assigned randomly. Both staple types were placed at ~7-mm intervals. Incisions closed with subcuticular staples were oversewn with running 5-0 plain gut suture. During the early postoperative period, metal staples produced more incisional erythema and crusting. In contrast, subcuticular staples produced better tissue eversion, less erythema, and less crusting. Both systems were deemed easy to use intraoperatively; however, it was noted that the thin skin of the scalp created difficulty with accurate subcuticular staple placement. One year postoperatively, incisions closed with either stapling method showed no significant differences in cosmesis or quality of healing. However, two patients reported greater comfort and improved cosmesis with subcuticular staples. Untoward bleeding and dehiscence were absent with both techniques. The INSORB Stapler is more expensive than percutaneous metal stapler, but theoretically faster incision closure times with INSORB system would result in reduced operative room times with future device modifications (such as improved ability to properly engage dermis in thin skin) (1b) [110].

In a randomized controlled trial of closure of groin incisions after cardiac bypass surgery, 114 patients were randomly assigned 1 of 4 skin closure methods: subcuticular Maxon, interrupted nylon, continuous nylon, or clips (staples) following a 2-layer closure of subcutaneous tissue using 3-0 Maxon. No correlation was demonstrated regarding skin closure method and subsequent infection. Staples were found to be the most expensive method, followed by subcuticular Maxon or interrupted nylon, whereas continuous nylon was the least expensive. Thus since the results fail to prove superiority of one closure method in terms of infection rate, skin closure method should depend on surgeon preference or financial considerations (1b) [111].

In a randomized controlled trial involving 106 Black-skinned subjects undergoing Caesarean section, wound/scar appearance, pain, and operation time/costs were compared. Of the 106 participants, 53 were randomly allocated to receive subcuticular suture (2-0 polyglycolic acid) and 53 were allocated to receive metal skin staples (B/Braun Manipler AZ-35W). The patients, surgeons, and nurse were not blinded to the types of skin closure techniques used. Use of staples resulted in a statistically significant shorter mean operating time (40.26 min.) compared to the suture group (47.55 min.) ($P = 0.025$). The mean estimated blood loss and wound length for the participants in both groups were similar. There was no significant difference in mean pain score for participants in either group. The mean VAS by participants in suture and staple groups was similar on day 5 ($P = 1.00$); however, at 6 weeks, the score was slightly higher for participants in staple group than in suture group but was not statistically significant. Mean patient satisfaction scores for the two groups were similar ($P = 0.0452$). The

VAS by the nurse and independent observers in the staple group was better than the mean VAS for the suture group on the fifth postoperative day ($P = 0.023$). However, the mean VAS score at 6 weeks was not significant ($P = 0.566$). In conclusion, the use of staples was better than subcuticular suture in terms of scar appearance and wound closure time and resulted in no difference in pain. However, staple use was significantly more expensive ($P < 0.001$). The perceived benefit of subcuticular suture versus skin staples was not observed and participants were satisfied with both wound closure techniques **(1b)** [112].

3. *Review of several cohort or case-control level studies*

In a nonrandomized observational prospective study, 100 patients undergoing abdominal dermolipectomy or surgery for breast hypertrophy received skin closure using either INSORB absorbable subcuticular staples or sutures. Operators from seven different centers were requested not to modify usual procedure, except for replacement of absorbable thread with INSORB staples during subcutaneous closure. For each patient, length of suture, time for closure, and operator ease of use was assessed. The results for average speed of closure per site and method were statistically significant and demonstrated that the use of staples reduced skin closure time by an average of fivefold. All operators considered the stapler easy to handle (mean 4.3, range 4–5). At 1-year follow-up, healing quality was evaluated by the surgeon depending on swelling, inflammation, and hypertrophy on a scale from 0 (very poor) to 5 (excellent result), as well as by the patient (scale of 0–10). Of the 95 patients (5 lost to follow-up), overall results were not different for the 2 methods as assessed by the surgeons and patients (Wilcoxon signed rank test, $P < 0.05$). Thus, the INSORB stapler was found easy to use and saved time while ensuring healing quality equivalent to that observed for conventional sutures. However, the authors noted that in some cases staples do not appear preferable, such as when there is marked tension between the two skin edges that cannot be controlled as it could be with a slipknot or when the skin is too thin to allow proper positioning of the stapler. Overall, the study's analysis would benefit from the inclusion of a larger number of patients (2b) [113].

A retrospective review of 511 patients receiving sarcoma resections of the buttock, thigh, and femur from 2003 to 2010 assessed outcomes following wound closure by staples or sutures. Surgical protocols were standardized across the cohorts, and only two surgeons were used who preferred use of either sutures or staples. Of the 511 patients reviewed, 376 had closure with sutures and 135 had closure with staples. Wound closure by staples was an average of 5.3 min faster than by sutures, resulting in a mean savings of 2.1% of total operating time. No significant difference was found in wound complications upon closure with either sutures or staples. Study authors noted that obesity and radiation treatment appeared to affect outcome and that future investigation of wound closure specific to orthopedic oncology with respect to specific patient variables is needed. In conclusion, closure by staples may be preferred due to speed and time savings, but preoperative clinical evaluation of patients is most important in determining closure method (2b) [114].

A total of 90 patients undergoing total knee arthroplasty (TKA) were evaluated to determine the pain score, cosmetic score, and wound complication rate of a zip-type skin closing device compared to conventional staple devices for wound closure. All TKAs were performed by the same surgeon. Pain evaluation was assessed using a visual analog scale (VAS) on postoperative days 1, 3, 14, 42, and 90. Cosmetic wound evaluation was conducted using the Vancouver Scar score 90 days postoperatively. The mean VAS of the zip group was significantly lower compared to that of the staple group on postoperative days 1, 3, and 14 ($P < 0.01$). The Vancouver Scar score for cosmetic outcome on postoperative day 90 was significantly better in the zip group versus the staple group ($P < 0.05$). There was no significant wound complication rate between the two groups. In conclusion, the zip-type skin closing device showed less pain and better cosmetic outcome. However, the authors noted that

3 of the 45 zip-type closure patients experienced a mild allergic reaction to the adhesive tape area, so this should be taken into account before use in patients with sensitive skin. In addition, the zip-type closure device has a medical cost twice that of conventional staples (3b) [115].

In this study, patients received wound closure by either staples or discontinuous nylon sutures (20 per group). The closure time was recorded for each patient. Patients were assessed postoperatively and then followed up 30, 60, 90, 120, 180, and 360 days after surgery. Each return visit was conducted by the same physician who was blinded as to which group the patient belonged to. Complications were recorded and wound appearance was rated (good, moderate, or poor). There was no statistically significant difference between the two groups regarding complications according to Fisher's exact test ($P = 0.6945$). Cosmetic scar results in the two groups were statistically the same (Fisher's $P = 1.000$). The time needed for wound closure in bilateral neck dissection for the staple group (5 min) was significantly faster than nylon suture group (25 min) (Mann–Whitney U test, $P < 0.0001$). According to this study, staples are more expensive than nylon sutures; however, the time saved during wound closure was not included in the cost assessment. The authors suggest that the use of staplers for skin closures should be considered mainly for closure of large or multiple incisions when saving time is an important factor. The use of staples will not affect the final cosmetic result or increase incidence of complications (3b) [116].

Evidence-Based Review: Other Closure Devices

1. *Review of one meta-analysis and several randomized trials*

In a meta-analysis of four randomized controlled trials of moderate risk of bias including 678 patients, the surgical zipper technique ($n = 333$) was compared to traditional intracutaneous sutures ($n = 354$) in various surgical procedures (open-heart surgery, orthopedic surgery, spinal fusion surgery, and saphenous vein harvesting). The zipper technique resulted in equivalent rates of wound infection and dehiscence, significantly less time for closure (although there was significant heterogeneity for this result), and no need for suture removal. Cosmesis was reported to be better in the zipper group in two of the trials and no different in the remaining two trials. The authors report that excellent cosmesis can be expected with the exception of areas of substantial curvature, with wound secretion, when patients are obese, or when wounds are under high tension (1a) [117].

In a randomized controlled split-wound trial, a new adhesive skin closure system (Prineo Skin Closure System) was compared to standard intradermal sutures in 83 patients undergoing elective plastic surgery closures. The Prineo system consists of pressure sensitive mesh tape with octyl-2-cyanoacrylate placed overtop. Approximation of wounds was equivalent between groups, and mean wound length was about 22 cm in both groups. Closure was about 5 min faster with the Prineo system ($p < 0.0001$). Both groups had equivalent cosmesis and healing over 90 days, 6 months, and 12 months by the modified Hollander Cosmesis Scale and at 6 and 12 months by the Patient and Observer Scar Assessment Scale. There were no differences in wound infection, inflammatory response, or adverse cosmetic outcome rates between groups. Blistering was present in 2 (2.4%) of 83 patients at day 7 and days 12–25 with the new closure system. Overall, the two methods are concluded to be equivalent for closure of full-thickness surgical incisions (1b) [118].

In a prospective randomized controlled trial, the novel "zipper" device for skin closure was used in 203 of the 610 cases of abdominal surgery. The device consists of a zipper between two adhesive strips of Polyamide with an elastic band on both ends that is pulled to close the skin. There were 205 patients closed with staples and 202 patients closed with sutures. Sutures and staples were removed on days 7–11, and the zipper was removed on days 7–9. Six patients in the zipper group developed complications such

as hematoma, lymphorrhea, wound infection, and reintervention, necessitating second intention healing or an alternative to the zipper closure (2b) [119].

In a prospective randomized controlled trial of 20 patients (mean age 51.17), a novel closure device called the Zipline 3 system (Zipline Medical) was assessed by blinded evaluators. The device is a single-use, sterile adhesive with a releasable ratcheting device that tightens the wound edges, and it is applied after deep sutures. The two treatment arms ($n = 9$) included Zipline with or without dermal suturing versus a control arm of nylon interrupted sutures ($n = 8$) for closure after excisions of skin cancers or nevi on the trunk or extremities. The treatment arm without dermal sutures using the Zipline device was dropped after the first case resulted in dehiscence. After 3 months of follow-up, three patients withdrew. Mean wound length was 3.06 cm ± 0.38 cm. There was no significant difference in aesthetics based on high-resolution photographs which were assessed by averaging the scores of three blinded evaluators on a 10-point visual analog scale. Time to both place and remove the device was significantly shorter than time to place and remove sutures. It took about 2 min to place and 8 s to remove the device, versus taking about 4 min to place and 1 min to remove sutures (to place $P = 0.001$; to remove $p < 0.001$). The cost of the device was about US$ 40 (3b) [120].

2. *Review of several nonrandomized studies*

As mentioned in the staples section, a total of 90 patients undergoing TKA were evaluated to determine the pain score, cosmetic score, and wound complication rate of a zip-type skin closing device compared to conventional staple devices for wound closure. All TKAs were performed by the same surgeon. Pain evaluation was assessed using a VAS on postoperative days 1, 3, 14, 42, and 90. Cosmetic wound evaluation was conducted using the Vancouver Scar score 90 days postoperatively. The mean VAS of the zip group was significantly lower compared to that of the staple group on postoperative days 1, 3, and 14 ($P < 0.01$). The Vancouver Scar score for cosmetic outcome on postoperative day 90 was significantly better in the zip group versus the staple group ($P < 0.05$). There was no significant wound complication rate between the two groups. In conclusion, the zip-type skin closing device showed less pain and better cosmetic outcome. However, the authors noted that 3 of the 45 zip-type closure patients experienced a mild allergic reaction to the adhesive tape area, so this should be taken into account before use in patients with sensitive skin. In addition, the zip-type closure device has a medical cost twice that of conventional staples (3b) [115].

In a prospective study, MEDIZIP closure system was used for 45 immunocompromised patients (ages 12–73) undergoing median sternotomy. The device was kept in place on average 9.98 days (range, 8–13 days). The average time taken for inspection was 70.00 ± 2.48 s. No wound infections occurred. In five patients, blood obstructed the device and it had to be replaced (11%). On a 3-level scale, cosmetic results were very good in 39 patients (87%) and satisfactory in 6 (13%) after 8 months (4) [121].

In 14 cases, a novel wound closure device, the Zip Surgical Skin Closure device, was evaluated. The device consists of two strips coated with hypoallergenic adhesive with plastic locks and straps that bridge the incision. The straps are pulled to bring the skin edges closer together. The device was removed after 10 days. The investigators used a 6-point wound evaluation score accounting for wound edge step-off, contour irregularity, scar width over 2 mm, edge inversion, inflammation, and poor cosmetic result. A 100-point VAS was also rated at 2–3 months. Ease of application, patient comfort with placement, patient pain with removal, and ease of removal by the investigators were all favorable. Wound scores, cosmetic scores, and patient satisfaction with the device were also reported as favorable. One subject experienced minor dehiscence in the setting of postoperative trauma. Limitations include inability to place on hair bearing or excessively oily areas and contraindication for high-tension wounds (4) [122].

In a prospective study of 96 patients with 103 lesions <3 cm in diameter, a sutureless foil flip-over system (Opti-Close System) was evaluated. The foil keeps the excision area sterile and the flip over system provides fast and easy skin closure. Deep 3-0 or 4-0 monofilament sutures were placed under the device, which remained in place for 10–14 days. Most lesions were on the back (44%) or chest (26%). No wound infections occurred, 96% of wounds were scored excellent or good in terms of healing by the surgeon, and 92% of the patients reported comfort with device removal based on a 100-point VAS. Seven cases (7%) of allergic reactions were found; one was severe with bulla; the system should not be used in those with a history of tape or adhesive allergy. Itching or discomfort was significantly more common on the back. Patient satisfaction with the scar was significantly lower on the chest. The cost of the system is similar to one polypropylene suture (3b) [123].

In a prospective nonrandomized study, 22 wounds not suitable for primary closure were closed with a novel skin and soft-tissue stretching device, Wisebands. The device has a tension feedback control mechanism (force is limited to 1 kg/cm^2), a flat plastic band, and a metal needle that is passed through the wound edges. The device was used to gradually close defects until the edges could be approximated for primary closure in 18 patients (90%). The calf (59%) and forearm (18%) were the most common defect locations; trauma and surgery were the most common causes followed by tumors and burns. The mean defect size was 12.5 × 5.5 cm. One to four devices were applied per wound, and the treatment time ranged from 1 h to 7 days. Major wound complications necessitating removal occurred in two patients, one with infection and one with intractable pain with tightening (10%). Two minor complications (10%) occurred with one case of local pain and skin irritation and one case of temporary neurapraxia. By 1 year, acceptable scarring and aesthetics were achieved (only 3 patients or 15% with wide or hypertrophic scars) (3b) [124].

In a series of cases, the initial clinical experience with a new device called the Suture Tension Adjustment Reel is reported. With the steel device, suture loops are passed through the device, and a reel tightens the suture loop incrementally to close the wound. It effectively functions as an adjustable knot that can be loosened or tightened without removing the sutures. The device was used uneventfully for intraoperative tissue stretching without undermining for a basal cell excision site on the knee, preoperative tissue stretching of an excision site of the left arm, intraoperative stretching of an advancement flap on the left lateral forehead, and intraoperative tissue mobilization (replacing an assistant's hands) in a scalp reduction surgery. In cases 1 and 3, three to five tension cycles lasted 3–5 min with rest cycles of 1–2 min (unless blanching occurred, then tension was for <1 min) until no further stretching could be achieved. In case 2, the skin was slowly tensioned over a period of hours. A disposable version of the device may be more useful (4) [125].

In two patients who underwent wide local excision of squamous cell carcinomas on the scalp and feet, an acellular dermal regeneration template (Integra LifeSciences Corp) was successfully combined with split-thickness skin graft and negative-pressure wound therapy to promote the healing of defects when vital structures (tendon, cartilage, bone) were exposed. The template is a scaffold of bovine collagen and choindroitin-6-sulfate which promotes neovascularization and formation of a neodermis. Silicone is added as a temporary epidermis. In these two cases, the template was applied for 10–14 days before a split-thickness graft was applied. The authors cite several randomized controlled trials which have shown negative-pressure wound therapy to improve graft take and appearance compared to traditional bolsters. Negative pressure therapy is contraindicated over ischemic wounds or those with fragile skin or wounds with active malignancy. The authors also cite studies showing synergy between the Integra Template and negative pressure therapy with skin grafts (4) [126].

In a retrospective case series of eight patients (men aged 17–95 years) with resection of nine moderate to large scalp tumors, the TopClosure® device was investigated as an alternative to skin grafts, flaps, or tissue expanders. The device was used to achieve intraoperative cycles of stress relax-

ation without undermining and, in some instances, was followed by additional cycles for mechanical creep and securement of scar. Defects averaged 3.5 cm, and the device enabled primary closure of all wounds. Two wounds were closed within 1 h after stress relaxation. Seven wounds required further stretch by mechanical creep and staged primary closure was completed in the outpatient setting (the device was used to secure the skin for up to 3 weeks postoperatively). The TopClosure® device is both invasively and noninvasively attached to the skin to accomplish skin stretching. Stress relaxation cycles consisted of 2–3 min of high tension (causing blanching or shininess at wound edges) followed by 5 min of relaxation. No complications or device failures occurred (4) [127].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Sutures	
Triclosan-coated sutures do not decrease the rate of surgical site infection	A
There is evidence to suggest barbed sutures decrease operating time without increasing complications. Cost savings are less likely for the dermatologist without operating room costs	A
There is no evidence to suggest differences between the use of absorbable and nonabsorbable sutures for cutaneous closure in terms of complications, cosmesis, or satisfaction; absorbable sutures may be preferable for time and cost savings	A
Continuous subcuticular sutures may reduce risk of wound dehiscence	B
Superficial mattress sutures (horizontal or vertical) give superior scar outcomes compared to simple running sutures	B
Subcuticular poliglecaprone 25 sutures give a lower rate of complications than polyglactin 910	B
Transcutaneous sutures may have a lower risk of superficial infection than intracutaneous sutures	B
A modified vertical mattress technique can result in superior outcomes compared to traditional suturing for moderate to severe tension wounds on thickened dermal skin	B
Dermal suturing alone with wound closure tape or adhesive can be safely used and may perform significantly better on the face compared to other locations	B
Evidence is needed to determine whether eversion achieves superior cosmesis; it may be more important in certain areas (facial) and perhaps not in others (trunk, extremities)	C
Most studies find no difference in outcomes between running subcuticular sutures, interrupted sutures, and simple running sutures for closure	C
Tissue adhesives or surgical glue	
Surgical glue may increase the risk of wound dehiscence, and there is no definitive evidence of improved cosmetic outcomes	A
Adhesive strips or membranes provide no long-term benefits over buried vertical mattress sutures alone or running subcuticular closures	B
Tissue glues or adhesives may save time compared to sutures	B
Concerns with tissue glues or adhesives in place of sutures include peeling or inability to close due to wound secretion, inability to perfectly approximate wound edges, inverted scars, and irritant or allergic reactions	B
Staples	
In orthopedic surgery, sutures give a lower risk of surgical site infection compared to staples	A
In cesarean sections, sutures lower the risk postsurgical complications compared to staples	A
For other surgery types, there is no consistent evidence that either staples or sutures outperform the other	A
Other closure devices	
The surgical zipper technique gives equivalent rates of wound infection and dehiscence compared to intracutaneous suture closure	A

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Self-Assessment Questions

1. Compared to nonabsorbable sutures, absorbable sutures have been shown to:
   (a) Result in increased complications
   (b) Result in time and cost savings associated with closure and suture removal
   (c) Result in equivalent cosmetic outcomes
   (d) b and c
   (e) All of the above
2. Superficial mattress sutures have been shown to:
   (a) Result in cosmetically inferior closures compared to superficial running sutures
   (b) Result in equivalent closures compared to interrupted sutures
   (c) Result in increased complications compared to superficial running sutures
   (d) a and c
   (e) None of the above
3. With regard to wound edge eversion, evidence suggests that:
   (a) Eversion results in superior cosmetic outcomes compared to planar closure.
   (b) Eversion prevents inverted scar formation.
   (c) Roughly equal evidence exists showing improved outcomes with eversion and no difference in outcomes for eversion.
   (d) Eversion may improve outcomes in some, but not all locations of the body.
   (e) None of the above.
4. Tissue glue and adhesives have been shown:
   (a) To improve cosmetic outcomes compared to sutures
   (b) To decrease closure time compared to sutures
   (c) To be safe to use without dermal sutures
   (d) To decrease closure costs compared to sutures
   (e) To increase short-term inflammation compared to sutures
5. Meta-analysis has shown that staples:
   (a) Increase complications compared to sutures in orthopedic surgery
   (b) Increase complications compared to sutures in obstetric surgery
   (c) Decrease complications compared to sutures in surgical fields other than obstetrics and orthopedics
   (d) a & b
   (e) All of the above.

Answers

1. d: Choices b and c are correct. Meta-analysis has shown there is no evidence to suggest differences between the use of absorbable and nonabsorbable sutures for cutaneous closure in terms of complications, cosmesis, or satisfaction; absorbable sutures may be preferable for time and cost savings since they are often cheaper than nonabsorbable sutures and they have the potential to obviate the need for suture removal visits.
2. e: None of the above. Two studies have shown horizontal or vertical mattress sutures give superior scar outcomes compared to simple running sutures.
3. c: Roughly equal evidence exists showing improved outcomes with eversion and no difference in outcomes for eversion. To our knowledge, only two studies have directly investigated eversion with regard to scar outcomes and produced conflicting results. Further research is necessary to determine whether eversion may be more important in certain locations (such as facial) compared to others.
4. b: To decrease closure time compared to sutures. While tissue glues and adhesives can save time compared to sutures, most glues and adhesives require the support of dermal sutures, increase the risk of dehiscence, and have not been proven to have superior cosmetic outcomes in most studies. In the short term, less inflammation compared to sutures has been shown in a number of studies. Tissue adhesives, glues, or membranes can be more expensive to use than sutures. While sutureless adhesive membranes can be used, there can be significant rates of complications related to inability to close or approximate wound edges, inversion of scars, issues related to wound oozing, and dehiscence.
5. d: Choices a and b are correct. Staples have been shown to increase the rate of surgical site infection or postoperative complications in the fields of obstetric and orthopedic surgery, but there is no clear evidence regarding the superiority of sutures or staples in other fields of surgery.

Non-invasive Fat Reduction

14

Neil Sadick

Abstract

The field of cosmetic medicine has evolved rapidly in the recent years offering patients and their treating physicians a plethora of non-invasive options for body rejuvenation. Particularly for indications such as fat reduction, innovations in technology and scientific breakthroughs have led to non-invasive strategies validated for their safety and efficacy through several high-evidence-level peer-reviewed studies. Four main types of energy-based devices have dominated the field of fat reduction: radiofrequency, laser, ultrasound, and cryolipolysis. In addition, injectable biologics have been developed with the goal to target localized pockets of fat. In this chapter, our goal is to provide an unbiased overview of the scientific evidence regarding procedure selection, effectiveness, and safety for non-invasive fat reduction.

Keywords

Ultrasound · Radiofrequency · Low-level laser · Cryolipolysis · Injectable biologics

Introduction

Nonsurgical fat reduction is a new frontier in the realm of cosmetic procedures. According to the latest data from the American Society of Plastic Surgery, the percentage of consumers considering a cosmetic medical procedure has almost doubled since 2013, with 15.9 million surgical and minimally invasive cosmetic procedures performed in the United States in 2015, a 2% increase over 2014 [1]. Among the most popular procedures sought were those for non-invasive body reduction, whereas requests for liposuction experienced a 37% reduction from 2000. The rise in popularity for non-invasive fat reduction is indicative of the public's desire for nonsurgical alternatives in lieu of their invasive counterparts. Although procedures such as liposuction are effective at removing large amounts of excess fat, they are accompanied by a significant risk of complications and severe adverse effects, including post-procedural pain, infection, prolonged recovery, scarring, ecchymosis, or edema. Currently, the four leading strategies for non-invasive fat reduction are radiofrequency, laser, ultrasound, and cryolipolysis. Additionally, minimally invasive strategies for fat removal using injectable biologics that target localized fat pockets have been recently approved by the FDA, and several other candidate drugs that target fat are in the R&D pipeline. All of these strategies target the subcutaneous fat layer with the goal to destroy adipocytes either through necrosis or apoptosis.

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Table 14.1 Patient consultation for non-invasive fat reduction

Patient selection for non-invasive fat reduction
Medications
Allergies
BMI
Family history (heart, pulmonary, liver disease)
Psychiatric history (depression, body dysmorphic disorder)
Lifestyle (smoking, alcohol, diet)
Previous surgeries
Infections, sores
Pregnancy/nursing

Patient Selection

Success in non-invasive fat reduction relies on suitable patient selection that can be achieved through a thorough medical consultation (Table 14.1). Non-invasive fat reduction treatments are ideal for nonobese patients (body mass index (BMI) < 30) with mild/moderate skin laxity. With a BMI of more than 30, patients often have visceral fat, which increases cardiovascular and other health risks. These patients need to be referred to internists that can aid them achieve a global weight reduction with careful medical monitoring. Qualified patients are healthy individuals who have mild to moderate areas of stubborn fat that seem resistant to diet and exercise. When selecting patients, it is important to thoroughly discuss their motivations for treatment and gain an appreciation of their social and psychological well-being during the consultation. The treating physician needs to understand the patient's concerns and expectations and relay to the patient all available options, side effects, and anticipated results. The need for maintenance follow-up treatments should also be discussed as many non-invasive fat reducing approaches require multiple sessions and additional sessions to maintain the clinical results. Psychosocial assessment is important, and specific questions regarding psychiatric history and medical treatment should be posed. Signs of body dysmorphic disorder and eating disorder should warrant a full psychiatric assessment. It is reported that as much as 15% of patients requesting fat reduction procedures suffer from mental illness [2, 3]. Pregnant or breastfeeding women should defer treatment until after delivery or when they have stopped nursing. Finally, although these treatments are safe for all skin types, patients should be evaluated for any open sores, infections, or hernias in the treatment area, and treatment must be delayed until issues resolve.

Radiofrequency

Radiofrequency-based devices harness energy from the emission of focused electromagnetic waves that generate heat upon meeting tissue impedance [4, 5]. The subsequent cascade of collagen contracture and neocollagenesis stimulates fibroblast activation resulting in increased dermal thickness without affecting the epidermis, while heating of the subcutaneous layer results in adipocyte necrosis and release of triglycerides. Thus, radiofrequency (RF) devices can mitigate both skin tightening and non-invasive fat removal [6, 7]. Depending on the number of electrodes, RF devices can be classified into unipolar, bipolar, and multipolar devices; the latest generation of RF devices also commonly combines other treatment modalities such as broadband light, lasers, ultrasound, pulsed electromagnetic fields, and vacuum devices, allowing enhanced efficacy and reduced adverse effects. Treatments with RF are typically customized depending on the parameters set by the manufacturer, but for most devices an average of four to six treatments is necessary spaced out weekly or biweekly. The average treatment duration is 30–40 min, and no side effects are reported other than self-resolving erythema.

For the indication of fat reduction, there is both a time and temperature dependence for internal temperatures at the adipose layer to remain at ~45–46 °C for at least 1 min to stimulate lipolysis. Since not all RF devices meet these requirements, it is important to highlight the select RF technologies shown through peer-reviewed studies to safely and effectively result in fat reduction.

In a study using a bipolar radiofrequency, infrared, vacuum, and mechanical massage device, 19

subjects underwent 5 weekly treatments of the upper arms, and 10 subjects underwent 4 weekly treatments of the abdomen and flanks. Circumference measurements, photographs, and subject weights were performed prior to treatment and at 1- and 3-month follow-ups. Results showed that the change in arm circumference at the fifth treatment was statistically significant with a mean loss of 0.625 cm. At 1- and 3-month follow-ups, mean loss was 0.71 cm and 0.597 cm, respectively. Reduction of abdominal circumference at the third treatment was statistically significant with a 1.25-cm mean loss. At 1- and 3-month follow-ups, average loss was 1.43 cm and 1.82 cm, respectively. In conclusion, with an average of four to five treatments, statistically significant fat reduction was achieved in the arms and flanks (2b) [8].

In another study evaluating a novel suction-coupled RF device with ultrashort pulse duration, high-voltage electrical pulses for its efficacy and safety on adipose tissue reduction, 21 subjects underwent treatment of their abdominal fat once weekly for 6 weeks. Clinical outcomes including abdominal circumference, adipose tissue thickness (measured by ultrasound), adipose tissue weight, body weight, and clinical photographs were obtained at visits 1 and 3 months after the last treatment. Biopsies from the RF-treated and untreated sides were harvested and measurements of adipocyte size and shape, rate of apoptosis, collagen production, and dermal thickness were determined. Results showed significant clinical improvements for the following clinical outcomes: reduction of abdominal circumference (113.4–110.7 cm), reduction of subcutaneous adipose tissue thickness (40.5–38.5 mm), and reduction in adipose tissue weight (32.2–30.7 kg) at 3-month follow-up visits. Histologically, adipocytes were observed to have decreased size and withered shape, with increased levels of apoptosis; increased collagen synthesis, with compaction and reorganization of the dermis was also observed. Overall, the study demonstrated clinical and histological evidence of the safety and efficacy of the RF device in non-invasive fat reduction (2b) [9].

Fat reduction has also been demonstrated using a non-contact radiofrequency device in a series of clinical studies (5, 2b) [10–13]. This device features a selective RF applicator that shapes the energy field to optimize the penetration and maximize the treatment area. It automatically tunes the tissue-applicator-generator circuitry to selectively deliver the energy to tissue layers with the specific impedance such as adipose tissue layers with minimizing the risk of overheating of the skin, muscles, or internal organs. In a study of 40 subjects with a significant volume of subcutaneous fat tissue on the abdomen and waistline, four once-a-week sessions were performed, and abdominal circumference was measured at the baseline and after the last treatment. The average decrease in abdominal circumference at the end of the study was 4.93 cm, demonstrating the selective RF system designed for contactless deep tissue heating as a painless, safe, and effective treatment for nonsurgical body contouring and circumferential fat reduction.

Finally, a recent study using a high-powered monopolar radiofrequency with a real-time temperature feedback system evaluated its efficacy in 21 subjects with submental fat accumulation. Subjects were treated twice at 1-month intervals, and submental fat thickness and circumference were evaluated with ultrasonography and a tape measure, respectively, at baseline followed at 1 and 6 months after the last treatment (0, 2, and 7 months). The submental circumference and thickness showed a statistically significant reduction after treatments, and physician's assessment showed that 82.3 and 52.9% of patients demonstrated above mild improvement at 2 and 7 months (2b) [14].

Overall, multiple treatments with radiofrequency devices were shown to be safe and effective for reducing localized fat in several anatomical areas including the trunk, abdomen, arms, and chin. Although new RF devices keep entering the clinical arena, it is important to validate their efficacy toward this indication through clinical studies.

Laser

External low-level laser devices represent another category of energy-based devices employed for adipose tissue reduction [15, 16]. Although the

mechanism of action remains controversial, it is postulated that low-level laser therapy activates the cytochrome-C-mediated mitochondrial pathways that ultimately leads to the formation of pores in adipose cell membranes through which lipids are released [17]. Wavelengths for laser treatments range from 630 nm to 640 nm as these have been shown to be optimum for biomodulation. Treatment may involve six to eight sessions lasting approximately 20–30 min, and adverse effects are limited to erythema and transient pain at the site of treatment.

In a randomized, placebo-controlled trial of 67 patients, six laser treatments over a period of 2 weeks were associated with a mean reduction of 2.6 cm in waist circumference versus baseline value (1b) [16]. In a second randomized, placebo-controlled trial of 40 healthy men and women, laser therapy administered twice weekly for 4 weeks resulted in a 0.87-cm reduction in waist circumference after eight treatments compared with an increase of 0.47 cm in the placebo group, but this difference was not statistically significant (2b) [15].

Although there are no peer-reviewed published studies to date, a new laser device for body contouring was recently cleared by the FDA for non-invasive lipolysis of the flanks and abdomen. The device emits laser energy at a 1060-nm wavelength that penetrates to the level of subcutaneous fat inducing lipolysis and stimulating dermal remodeling (1b) [18]. Treatments can be performed in various anatomic areas and can last an average of 25 min; no adverse side effects have been reported so far.

Ultrasound

High-intensity focused ultrasound (HIFU) devices have also been used effectively for non-invasive body sculpting to either tighten skin by contracting collagen fibers or remove adipose tissue stores via ablation. Ultrasound is unique in that the penetration depth can be freely selected with the choice of frequency, and precise focusing can be easily achieved with a small handheld transducer. HIFU can target a specific volume within the body cavity without harming surrounding tissues via two major mechanisms: hyperthermia and cavitation. By concentrating energy, HIFU causes temperatures to exceed the upper limit of protein denaturation (43 °C), and can reach as high as 80 °C, causing instant coagulative necrosis of targeted cells without damage to surrounding areas. Moreover, at high energy levels, alternating compression and expansion of sound waves create gas cavities that implode and subsequently cause mechanical damage to the target tissues (e.g., adipose) through the release of high levels of pressure and heat in the microenvironment. Average treatment times using HIFU for fat reductions are at 45–60 min with minimal to no recovery time. The procedure typically involves two or three passes over the treatment area, with each pass taking 15–20 min, and during treatment, patients report feeling localized tingling/prickling sensations along with mild warmth and pain. Commonly reported adverse effects include discomfort, ecchymosis, paresthesias, and edema that are temporary and mild in intensity, with the vast majority resolving within 12 weeks [19, 20].

Preclinical and clinical studies of HIFU devices have shown that when treating the fat tissue, macrophages ingest the lipids contained in adipocytes ablated by HIFU in a mild local inflammatory response; thus they do not become liberated systemically, raise serum lipid levels, alter the lipid profile, or provoke prolonged or diffuse inflammation.

A pivotal study on 180 patients using a HIFU system with an internally focused transducer and a pattern generator to ensure that the HIFU waves are directed evenly and at a predetermined depth within the treatment area showed that the treatment was well tolerated and resulted in reduced waist circumference. In the study, subjects with subcutaneous abdominal fat ≥2.5 cm thick received high-intensity focused ultrasound treatment of the anterior abdomen and flanks at energy levels (a total of three passes each) of 47 J/cm (141 J/cm total), 59 J/cm (177 J/cm), or 0 J/cm (no energy applied, sham control). The primary endpoint was changed from baseline waist circumference at the iliac crest level at posttreatment week 12.

For the primary endpoint, in the intent-to-treat population, statistical significance versus sham was achieved for the 59-J/cm but not the 47-J/cm treatment group. In a per-protocol population, statistical significance versus sham was achieved for both the 59-J/cm and the 47-J/cm treatment groups. Investigator subjective measures of global aesthetic improvement and patient satisfaction also favored each active treatment versus sham, while adverse events included mild to moderate discomfort, bruising, and edema (1b) [21].

A subsequent study using the HIFU device assessed the effectiveness and tolerability of treatment using high- and low-fluence settings with either grid repeat (GR) or site repeat (SR). Subjects underwent one HIFU treatment with one of five treatment protocols (150–180 J/cm), and endpoints were changed from baseline in waist circumference at 4, 8, and 12 weeks. All subjects had a statistically significant mean circumferential reduction of −2.3 ± 2.9 cm from baseline at 12 weeks, with no significant differences among the five treatment groups. The study concluded that high-intensity focused ultrasound treatment using either a low or high fluence setting in a GR or SR method is effective for circumferential waist reduction, resulting in statistically significant results in all treatment groups (1b) [22].

Cryolipolysis

Cryolipolysis involves controlled application of cold to subcutaneous tissue to reduce adipose tissue [23, 24]. Although the mechanism of action is not completely understood, preclinical studies suggest that an inflammatory process culminating in necrotic cell death is initiated when fat cells are cooled to temperatures between −2 and 7 °C. This process begins within 3 days after treatment and peaks within 14 days, and from day 14 to day 30, macrophages and phagocytes engulf dead lipid cells and inflammation declines, and the lipids are safely metabolized within 90 days [25].

When cryolipolysis is performed, suction is used to draw the target tissue into a cup-shaped applicator, in which contact is established between the treatment area and two opposing cooling panels. Treatment duration using the first-generation applicators is 45–60 min per treatment site, with most patients receiving treatment at multiple sites. With the use of a novel contoured cup and medium-sized applicator, however, which increases tissue contact and reduces skin tension, treatment times have been reduced to almost 25 min (2b) [26]. Cryolipolysis side effects include pain, bruising, erythema, and numbness, and treatment may also cause mild to moderate short-term dysesthesia in peripheral nerves, but no long-term damage has been reported [27]. The destruction of adipocytes does not significantly affect serum lipid levels or liver function tests [23]. One of the most serious side effects associated with cryolipolysis is paradoxical adipose hyperplasia in which patients develop painless, firm, and well-demarcated tissue masses in the treatment areas approximately 3–6 months following cryolipolysis (4) [28, 29]. Although the pathogenesis is unknown, recent studies have demonstrated factors that increase the risk of paradoxical adipose hyperplasia such as the use of a large applicator and the male gender (5) [30, 31].

Several studies have demonstrated the safety and efficacy of cryolipolysis for fat reduction in several anatomic areas including the abdomen, back, flanks, arms, and submental area (2b) [32, 33]. In a study of 518 subjects treated with cryolipolysis, the procedure was well tolerated, with 89% of respondents reporting a positive perception of treatment duration and caliper measurements demonstrating 23% reduction in fat layer thickness at 3 months (2b) [34]. Aside from being safe and efficacious, cryolipolysis has proven to be a durable treatment with results lasting almost a decade as shown by a longitudinal study of two patients (4) [35].

Since cryolipolysis does not use heat to achieve fat reduction, it does not stimulate dermal remodeling. Thus, although skin tightening after cryolipolysis may occur from the normal elastic recoil properties of skin tightening, a skin-tightening procedure may be required after cryolipolysis.

Injectable Biologics

An emerging trend in the field of non-invasive fat reduction is injectable biologic agents with a lipolytic profile. Extensive preclinical safety testing and rigorous clinical trials demonstrating a favorable product profile using a pharmaceutical-grade formulation are required for regulatory authority approval, and two agents have made the most progress down that line: novel lipolytic (LIPO-102) and adipolytic (ATX-101) agents.

LIPO-102 is a combination of salmeterol xinafoate and fluticasone propionate that targets and stimulates adipocyte (intracellular) lipolysis to produce a nonadipolytic, nonsurgical fat tissue reduction. In clinical testing, 22 weekly abdominal injections of LIPO-102 (0.5 μg salmeterol and 1 μg fluticasone) in 20 subjects for 4–8 weeks produced rapid (within weeks) and significant reductions in abdominal circumference and volume versus placebo (20 subjects). Overall change in waist circumference was statistically significant at 6 weeks postdosing, but at the 12-week follow-up, failed to reach significance. There were no significant hematologic, cardiovascular, or dermatologic adverse effects (i.e., atrophy, pigmentation, nodularity, necrosis) and minimal difference in swelling, redness, irritation, or any other local injection site reactions between LIPO-102 and placebo. According to company press releases, LIPO-202 is currently in phase II trial for the reduction of central abdominal bulging, and a phase II proof-of-concept study of LIPO-202 for the reduction of localized fat deposits under the chin (submental fat) will be initiated by the end of 2016.

Another injectable biologic ATX-101 was approved in 2015 as a first-in-class injectable drug for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat. ATX-101 (deoxycholic acid) physically and preferentially disrupts the cell membrane of adipocytes causing cell death. ATX-101 has been evaluated in a clinical development program that included 18 phase I–III clinical studies to support the current indication. The efficacy of ATX-101 for reducing submental fat was evaluated across all phase III trials, and that showed significant reduction of fat 12 weeks posttreatment. Clinician and patient scale-based assessments of submental fat severity were utilized as well as calipers and MRI as an additional imaging-based objective assessment of the change in submental volume after ATX-101 treatment (5) [36].

Conclusion

Non-invasive techniques such as radiofrequency, laser, ultrasound, cryolipolysis, and injectable biologics have emerged as particularly appropriate options for nonobese patients requiring modest to moderate reduction in fat deposits.

All of these treatments can be administered in an outpatient setting with little or no need for anesthesia or analgesia and typically result in few, transient complications. With the exception of HIFU and cryolipolysis, these procedures require multiple treatments to achieve meaningful results and require maintenance sessions to sustain clinical outcomes. A table comparing the aforementioned strategies for fat reduction is presented in Table 14.2. In summary, non-invasive

Table 14.2 Summary of treatment options for non-invasive fat reduction

Approach	Level of evidence	Number of treatments	Treatment time	Safety/side effects
Radiofrequency	B	4–6	30–40 min	Erythema, pain
Ultrasound	A	1	40 min	Bruising, erythema, pain
Laser	C	4–6	20–40 min	Bruising, erythema, pain
Cryolipolysis	A	1–2	30–60 min	Bruising, erythema, pain, swelling, hyperplasia
Injectable biologics	A	2–6	10 min	Irritation at injection sites

fat removal in the carefully selected candidate is fully safe and attainable. Depending on the site of treatment, patient budget, and time constraints, the treating physician will be able to navigate the patient and recommend the most appropriate non-invasive fat removal strategy.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE Score: quality of evidence
Available scientific data demonstrate high level of evidence regarding the safety and efficacy of ultrasound and cryolipolysis and ATX-101 for fat reduction	A
Data for safety and efficacy of radiofrequency devices for fat reduction are moderate	B
There is still paucity and low-level evidence for laser devices being effective in reducing fat	C

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Self-Assessment Questions

1. Male with excess flank adiposities is requesting non-invasive fat reduction. Male self-reports a low pain threshold. Following the consultation would you recommend:
   (a) Cryolipolysis
   (b) HIFU
   (c) Radiofrequency
   (d) 1060 nm laser
   (e) Low-level laser therapy
2. Female with BMI of 17 is requesting fat removal for the medial arms. She self-reports feeling distress with the look of her extremities. She has previously undergone cellulite and skin tightening treatments. Would you recommend to the patient:
   (a) Cryolipolysis
   (b) Psychiatric evaluation for body dysmorphic disorder
   (c) ATX-101
   (d) HIFU
   (e) Radiofrequency
3. Female that had undergone liposuction 8 months ago is experiencing excess skin laxity with contour irregularities. She does not want to have additional surgery. Recommendation for her would include:
   (a) Cryolipolysis
   (b) Low level laser therapy
   (c) HIFU
   (d) Radiofrequency
   (e) Radiofrequency with vacuum
4. Male requests surgery alternatives to reduce his double chin. He has needle phobia and travels frequently so cannot engage in many treatments.
   (a) ATX-101
   (b) Cryolipolysis with the mini applicator
   (c) HIFU
   (d) Laser
   (e) Low-level laser therapy
5. Female presenting cellulite and excess fat in her inner thighs is requesting the best treatment approach. She has plenty of funds and time at her disposal. Treatment recommendations would be:
   (a) Radiofrequency coupled with IR and vacuum
   (b) Cryolipolysis
   (c) Laser
   (d) ATX-101
   (e) Surgery recommendations.

Correct Answers

1. d: Cryolipolysis in the flanks presents the risk of paradoxical hyperplasia. Low-level laser therapy would not be effective for large areas, and both HIFU and cryolipolysis may be deemed too painful by the patient.
2. b: At a BMI of 17, the patient is dangerously underweight. History of additional treatments and continued dissatisfaction is an indicator of an underlying mental health problem.
3. e: Both HIFU and cryolipolysis would treat the contour irregularities but not the laxity issue. Radiofrequency with vacuum would be the best choice to treat both the adiposities and the skin laxity.
4. b: ATX-101 would be effective, but since the patient has time constraints and needle phobia, this would not be a suitable treatment approach for him. Cryolipolysis would require one to two treatments without subjecting the patient to needles.
5. a: Cryolipolysis or laser would treat the excess fat but not the cellulite. Radiofrequency coupled with IR and vacuum would improve the appearance of cellulite and reduce the adipose tissue layer.

Noninvasive Skin Tightening

15

Eric C. Wilkerson and David J. Goldberg

Abstract

Nonsurgical techniques for rejuvenation have dramatically expanded in recent years and, with this, so have noninvasive techniques, technologies, and devices specifically directed toward tightening the skin. In general, the two technologies primarily utilized for skin tightening are ultrasound and radiofrequency. This chapter seeks to review the available literature discussing the indications, effectiveness, preoperative and postoperative considerations, treatment techniques, and safety of the presently available technologies and methods for noninvasive skin tightening. The available literature suggests noninvasive tightening modalities are generally safe and effective with little downtime and minimal side effects. However, of paramount importance are appropriate patient selection and managing patient expectations preoperatively.

Keywords

Tightening · Skin tightening · Radiofrequency (RF) · Ultrasound (US) · Safety · Noninvasive Microfocused ultrasound · Unipolar radiofrequency · Monopolar radiofrequency · Bipolar radiofrequency

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Indications for Noninvasive Skin Tightening

As the demand for nonsurgical skin rejuvenation continues to grow, it is no surprise that the available technology continues to increase and improve, including in the realm of skin tightening. Noninvasive skin tightening can be achieved via a variety of modalities to treat nearly every area of the body. Most commonly, tightening has focused on the face, neck, and abdomen, but, more recently, the décolletage, hands, flanks, thighs, buttocks, knees, and arms have increasingly become targets for tightening therapies. Transdermal radiofrequency (RF) and focused ultrasound (US) are two of the major technologies used primarily for skin tightening. Some laser and light modalities, fractionated and microneedle radiofrequency, and cryolipolysis have also been shown to promote skin tightening, but, since it is not their primary function, these will not be discussed in detail.

While minimal evidence exists to determine truly evidence-based treatment indications, across the spectrum, noninvasive skin tightening treatments are generally indicated for mild-to-moderate skin laxity with some specific variations for certain devices (4, 4, 5, 5) [1–4]. Otherwise, the US Food and Drug Administration (FDA)-approved indications can be mentioned for individual devices, although this is typically not the limit of a device's clinical potential or

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common uses. As each device or modality is introduced, its FDA-approved indications, as well as other off-label clinical applications, will be reported.

Effectiveness of Noninvasive Skin Tightening

In some cases, myriad reports and clinical trials exist in the literature on the modalities reviewed, so it would be impossible to discuss them all meaningfully. For some newer devices or treatments, significant studies are lacking. This review will focus on the best available literature; however, it is important to note that there are not many studies in this field with a high level of evidence. Finally, focus is given to trials specifically reporting on "tightening" or improvements in "laxity" rather than surrogates for tightening such as improvements in rhytids, elasticity, or skin quality.

Microfocused Ultrasound

Microfocused ultrasound (MFUS), or microfocused ultrasound with visualization (MFU-V), can target deep to superficial subcutaneous and dermal tissues depending on the transducer used. Ultherapy (Ulthera, Inc., Merz Device Innovation Center, Mesa, Arizona) is the major MFUS system available in the United States and has indications for brow lifting, lifting of the submental and neck tissue, and improving the rhytids of the décolletage. It was the first device to receive a noninvasive lifting indication from the FDA.

For skin tightening, microfocused ultrasound uses specially designed transducers to deliver focused intense ultrasound energy to varying depths in the dermis, subcutaneous tissue, and muscular fascia up to 4.5 mm without affecting other structures including the epidermis. Ultrasound energy is delivered by a selection of transducers operating at 4 or 7 MHz and at fixed depths of 1.5 mm, 3.0 mm, or 4.5 mm. Each transducer delivers a "line" up to 25-mm long of multiple intense, focused points of energy, each of which creates an ~1-mm^3 zone of thermal injury. Energy ranges from 0.75 to 1.2 J. This allows heating of this tissue to >60 °C, which is optimal for immediate collagen fibril contraction and denaturation and long-term neocollagenesis to induce skin lifting and tightening (5, 5, 4) [1, 5–7].

In the initial clinical trial examining MFUS treatment for brow lifting, investigators used the 7-MHz, 3.0-mm or the 7-MHz, 4.5-mm transducer on the neck, the 7-MHz, 4.5-mm transducer on the forehead and temple, and the 4-MHz, 4.5-mm transducer on the cheeks. On average, 110 lines were delivered to the face and neck. Photographs taken 90 days after the treatment of 30 patients were judged by blinded evaluators as having clinically significant improvement in brow lift, and there was a mean brow elevation of 1.7 mm above the pre-treatment baseline. The authors admit that the treatment was performed conservatively and that more aggressive treatment may or may not have yielded greater improvements (4) [8].

In a retrospective study, 45 women were treated on the face and upper neck using both the 4-MHz, 4.5-mm transducer and the 7-MHz, 3.0-mm transducer. On average, 370–420 treatment lines were delivered at the highest energy setting, and subjects were followed at 90 and/or 180 days after treatment. Blinded investigator assessment of improvement from baseline in the primary endpoint of skin laxity at 180 days determined 67% of subjects were improved. Global assessment of improvement by subjects and physician evaluators demonstrated 75% or more of the subjects were improved at 90 and 180 days [1].

Suh and colleagues treated 22 patients on the face and submentum with a single treatment involving multiple transducer depths and energies and an average of 200 treatment lines. Ninety-one percent showed improvement in two objective laxity scores, and the remaining subjects showed improvement in one objective score. Subjectively, 77% and 73% of subjects reported much improvement in the nasolabial folds and jawline, respectively. Histologic analysis showed increased dermal collagen and dermal thickness and straightening of elastic fibers [7].

In the largest trial of MFUS for lower face laxity, 93 patients treated with an average of 293 treatments lines were evaluated, and blinded reviewers reported improvement in 58% of the subjects at 90 days. Using quantitative measures, 64% of the subjects were found to be improved at 90 days. Subjectively, 66% of patients perceived improvement [2].

With proven efficacy on the face, MFUS was then investigated on other body areas. After a pilot study prospectively treating the décolletage of 24 patients showed promising results, Fabi and colleagues completed a prospective multicenter study treating 125 women to assess the treatment's ability to lift and tighten as well as improve lines and wrinkles. The treatment was administered with three different depth transducers (4.5 mm, 3.0 mm, and 1.5 mm) with approximately 280 treatment lines. Blinded assessments revealed 66% achieved improvement at 180 days. 45% of subjects noticed less sagging at 180 days. At 90 days and 180 days, 66% and 63% of subjects, respectively, were overall satisfied or very satisfied (4) [9, 10].

MFUS for lifting of the arms, thighs, and knees was examined in 18 women chosen to receive the treatments in one of these areas. Both sides were treated with the 4.5-mm depth transducer, and one side was randomized to receive a second treatment with the 3.0-mm depth transducer for a dual plane treatment. An average of 160 lines was delivered to the arms, 142 to the knees, and 157 to the thighs with the 4.5-mm transducer. An average of 153 lines was delivered to the arms, 136 to the knees, and 152 to the thighs with the 3.0-mm transducer. There was improvement in all areas by global assessment scores, and the knees and arms had better lifting/tightening than did the thighs on the dual-plane side but without significant difference on the single-plane side (2b) [11].

For the buttocks, a trial of dual plane treatment with the 4.5-mm depth and 3.0-mm depth transducers was conducted with an average of 973 lines delivered to a standardized square area of the left buttock of 30 patients. In assessing laxity, at 180 days, of 19 subjects available for evaluation, the physician global assessment was improved in 89.5% of patients, compared to 81.5% at 90 days. Subject global assessment was improved in 74.1% of the subjects at 90 days and in 89.5% of them at 180 days (2b) [12].

Radiofrequency

Radiofrequency treatments have been shown to induce skin tightening by effecting changes in the dermal collagen and elastin via heating to target temperatures of 40–45 °C. In general, radiofrequency technology produces energy in the electromagnetic spectrum at various frequencies to produce an electric current, with some variations (5, 2b, 4) [13–15]. Immediately, there is a thermally mediated collagen fiber thickening and denaturation with associated collagen fiber contraction, but the effect is temporary. Subsequently, more tightening occurs over time as the wound healing process initiates an inflammatory cascade leading to increased fibroblast activity and, thus, neocollagenesis and neoelastogenesis (5, 4) [4, 13, 16–20]. Many RF devices exist in the cosmetic market today, but only a few devices, which have been represented in the literature, will be discussed here (Table 15.1).

Monopolar RF

Monopolar RF (MRF) passes an electric current through the target tissues from the treatment electrode to a grounding electrode. The dermal and subcutaneous tissues have inherent resistance to the electric current, which creates heat, leading to volumetric heating of the dermal and subdermal tissues, including the fat and fibrous septae. The depth of treatment is typically greater for monopolar RF than other RF technologies and increases with the diameter of the electrode, and some have suggested the depth is approximately half of the electrode diameter [4, 13, 16–19].

Most clinical data, including efficacy, safety, and side effects, that exists for monopolar RF was obtained using the ThermaCool TC™ (Thermage Corp., Solta Medical, Hayward, CA) monopolar RF system since this device was the first of its kind. This system uses a stamping treatment technique with epidermal cooling. The device has

Table 15.1 Comparison of radiofrequency technologies

Type of RF	Electrode configuration	Energy type	Grounding requirement	Depth	Method of energy delivery	Cooling	Notes	Example devices
Monopolar	Single treatment electrode; one grounding electrode	Uses electric current	Requires grounding electrode	Generally deep; depth depends on size of electrode	Pulse or continuous motion	Some require cryogen cooling, topical cooling gel, or no epidermal cooling		ThermaCool, ThermiSmooth 250, Pellevé, Exilis, TruSculpt
Unipolar	Single electrode	Uses electromagnetic radiation	None	Generally deep; depth can be controlled	Continuous motion	None		VShape, Accent
Bipolar	One positive and one negative electrode on treatment probe	Uses electric current	None	Superficial; depth depends on distance between electrodes	Continuous motion	None	Variations include multipolar, fractionated, and microneedle fractionated	Innumerable
Multipolar	Multiple electrodes on the treatment probe	Uses electric current	None	Intermediate depth; depends on energy level and distance between electrodes	Continuous motion	None	Variation of bipolar	3Deep
Fractionated	Multiple electrodes on the treatment probe	Uses electric current	None	Depth depends on energy level	Pulse	None	Form of bipolar	eMatrix, Fractora
Microneedle RF	Multiple penetrating needle electrodes on the treatment probe	Uses electric current	None	Depth depends on penetrating depth of needles and energy level	Pulse	None	Form of bipolar	Infini, Intensif, Profound

FDA indications for the noninvasive treatment of periorbital wrinkles and rhytids including the upper and lower eyelids, noninvasive treatment of wrinkles and rhytids, and temporary improvement in the appearance of cellulite.

Fitzpatrick and colleagues treated 86 patients with the ThermaCool TC™ system at high fluence to determine brow lifting capacity and evaluated results at 6 months. Of 62 evaluable photographs, 61.5% of the brows were lifted at least 0.5 mm, while the average lift was 1.30–1.49 mm. In addition to tightening and lifting, 83.2% of treated periorbital areas had objective blinded wrinkle score improvements. At 6 months, 92.8% of treated areas had improved or remained the same, and improvement of at least one point on the Fitzpatrick Wrinkle Scale was noted in 28.9% of them. A total of 50% of the patients were satisfied with the results (4) [21]. Later, it was noted that this high fluence treatment resulted in scars and other textural adverse effects [17]. A subsequent study with lower fluence and more treatments decreased these effects (4) [22]. Details are discussed in the safety section.

A study examining the ThermaCool TC™ for neck and cheek laxity followed 50 patients with mild-to-moderate laxity. In 28 (93%) of the 30 patients whose cheeks were treated, objective clinical improvement on blinded assessment was noted in the nasolabial and mesolabial folds. On a four-point scale, at 6 months after treatment, the average improvement score was 1.53, where 1 = 25–50% improvement and 2 = 51–75% improvement. Seventeen (85%) of the 20 patients treated on the neck experienced objective improvement in submandibular and neck laxity with a score of 1.27 at 6 months (4) [23]. In another prospective study treating the lower face, 85 Japanese females were treated, and objective improvement in laxity was recorded with results better at 6 months than at 3 months. At 3 months, 50% or better improvement was observed in 70–78% of the subjects for jowls, nasolabial folds and marionette lines, and other facial folds. At 6 months, 84–89% of the subjects were improved by 50% or more (4) [24].

One of the newest monopolar RF devices is the ThermiSmooth® 250 (Thermi™, Irving, TX). It is indicated for the temporary reduction in the appearance of cellulite and used for tightening of the face and neck as well as various other body locations such as the abdomen, thighs, and arms. This system uses a probe in constant contact with the skin in constant motion and provides real-time cutaneous temperature feedback. In a preliminary study of efficacy and safety, 14 women with abdominal laxity received up to four treatments. Blinded objective evaluators found statistically significant improvement over baseline in the subset of 10 of 14 patients that the blinded evaluators correctly identified the before-and-after photos. A patient survey found that patients experienced an average tightening of 2.14 points on a four-point scale with 0 = lowest tightening and 4 = highest. Of 14 subjects, 8 would recommend it to a friend and 3 noticed looser clothing, indicating a slimming effect. This device can be used to treat the face, neck, and, potentially, any other body area, but further studies of efficacy are needed (4) [25].

In an initial study of the device that eventually became the Pellevé MRF system (Pellevé S5 Wrinkle Treatment Generator; Ellman International Inc., Oceanside, NY), 93 patients were treated, and patients noted subjective improvement in laxity and were quite satisfied. This device, indicated for nonablative treatment of mild to moderate facial wrinkles and rhytids, uses a generator and a handpiece in constant motion contacting the skin with topical cooling gel (4) [26]. Chipps and colleagues then examined the device for the treatment of rhytids and laxity of the face and neck. In general, they found objective improvement in global assessment scores by blinded investigators and subjective improvement in laxity by subjects (4) [27]. Another MRF device, (Exilis Elite, BTL Aesthetics, CITY), with FDA approval for the noninvasive treatment of wrinkles and rhytids, also has demonstrated efficacy in reducing skin laxity (4) [28].

Unipolar RF

Unipolar RF differs from other RF technologies in that it uses high-frequency electromagnetic radiation rather than an electric current to produce heat and does not require a grounding pad. The electromagnetic radiation produced causes

oscillations in water molecules that result in heat that can penetrate up to 20 mm in depth [13, 14].

A unipolar RF device (Accent™, Alma Lasers, Buffalo Grove, IL), indicated for the noninvasive treatment of wrinkles and rhytids, was used to treat 30 subjects with grades 3–4 upper thigh cellulite. Significant clinical skin tightening resulting in improvement of the cellulite as well as a decrease in thigh circumference of 2.45 cm on average with histologic evidence of dermal fibrosis after treatment was observed (4) [29].

Bipolar RF

Bipolar RF uses both a positive and negative electrode, which are both on the treatment probe. The current passes between these two electrodes, so these devices cannot penetrate to the depths of monopolar RF technology. There has been some suggestion that the depth of penetration is approximately half of the distance between the electrodes up to approximately 4 mm in depth. With such devices, energy distribution and heating are more controlled, and they require less energy and produce less discomfort [13, 14, 18, 19].

The Accent™ device has a bipolar handpiece in addition to the unipolar and has been studied for efficacy in treating 20 female subjects with mild-to-moderate laxity of the posterior thighs/buttocks. There was statistically significant improvement in laxity (up to 19% from baseline) and tightening (up to 15% from baseline) noted at week 4 and week 8 (2b) [30].

Bipolar devices are often combined with other laser and light-based devices such as an intense-pulsed light (IPL), an infrared light, or a diode laser or even with suction or mechanical massage (4, 3a-, 5) [31–33]. One example of such a device is the bipolar RF combined with IPL in the Aurora SR™ (Syneron Medical Ltd., Yokneam, Israel), which was used for facial rejuvenation treatments in 108 patients every 3 weeks for 5 treatments. Overall improvement was 75%, and laxity improved by 63%. Overall patient satisfaction was 92% (4) [34].

Multipolar RF

Multipolar radiofrequency is a variation of bipolar in which three or more electrodes are used, one of which acts as a positive electrode while the others act as negative electrodes (3a-) [35]. The Apollo™ device, FDA approved for the noninvasive treatment of mild-to-moderate facial wrinkles and rhytids (Pollogen Ltd., Tel Aviv, Israel) using TriPollar™ technology, is in this category and was used to treat 37 patients on the body and face. Weekly treatments, 7 on average (range 2–15), resulted in immediate and long-term skin tightening on the body and face as well as a reduction in body circumference and cellulite and improvement in facial rhytids (4) [36].

The 3DEEP™ technology on the EndyMed Pro (EndyMed Medical Ltd., Caesarea, Israel) is a proprietary multisource RF system indicated for the noninvasive treatment of mild-to-moderate facial wrinkles and rhytids. In one study, investigators examined the results of a series of treatments on 33 subjects with abdominal skin laxity. After six treatment sessions to the abdomen, patients returned for evaluation at 6, 9, and 12 months. Two clinical evaluators rated improvement in laxity on a five-point scale, where 5 = "significant change," with resulting values of 3.2–3.5 after the last treatment and 2.9–3.2 at 12 months, indicating an observed improvement of "visible change" or "slightly better." Patients rated efficacy and satisfaction on a five-point scale, where 5 = "highly satisfied, significant change." Immediately after the last treatment, the score given was 3.4 and then 3.1 at 12 months, corresponding to "somewhat satisfied, visible change." Results were better, on average, when higher final temperatures were achieved as well as when higher temperatures at 20 minutes were achieved. Subject weight was not significantly changed during the study (4) [37]. The same device has shown efficacy in treating facial laxity as well as clinical benefit treating the abdomen and thighs, achieving improvement in laxity, cellulite, and circumference (2b, 4) [38, 39].

Preoperative Evaluation

Evidence-based conclusions regarding the optimal patient for treatment and various other pretreatment considerations are nearly nonexistent.

Most recommendations are based on experience, common sense, common practice, and other "expert" opinion. The limited available evidence and some common practices will be discussed.

Microfocused Ultrasound

Patient Selection

In regards to patient selection, specifically considering lifestyle and patient characteristics, Fabi and colleagues found no evidence that age, skin type, alcohol intake, or major illness had any impact on treatment efficacy. However, for undetermined reasons, subjects reporting high levels of stress had higher physician assessment scores of aesthetic improvement. Subjects with lower BMI ($\leq$25 kg/m^2) had higher self-assessment improvement scores [1].

Along the same lines, Oni and colleagues found that subjects with BMI > 30 kg/m^2 had less subjective and objective improvement after treatment of the lower face than those with lower BMI. They surmised this may be due to excess fat or excessive laxity in the higher-BMI patients [2].

Fabi notes absolute contraindications include broken skin, severe or cystic acne, and implants such as pacemakers and defibrillators. Other situations requiring caution include treatment over keloids, implants, permanent dental fillers, and any other situation that could affect wound healing. These common practice elements have not specifically been tested in any clinical trials (5) [40].

Analgesia

Microfocused ultrasound treatments can be variably uncomfortable. Some clinicians routinely provide patients with an analgesic regimen. Though there is no evidence basis, in Baumann's study, 89% of the subjects received a combination of 2–3 analgesic medications: hydrocodone/acetaminophen, ketorolac, acetaminophen, naproxen, tramadol, and any of several benzodiazepines (4) [41]. In another study, most patients received a combination of a topical anesthetic, oral diazepam, and intramuscular meperidine and hydroxyzine [1].

Monopolar RF

Patient Selection

In Abraham's study, the opinion was given that the ThermaCool RF procedure is best for patients with earlier signs of aging, lacking significant underlying structural insufficiency. Therefore, patients with mild-to-moderate rhytids and laxity in their mid-30s to early 50s or older patients with a prior facelift procedure are likely to be ideal candidates. Those with significant laxity and redundancy are likely to have limited results [3]. Sukal expands this assessment to include benefit in patients even in the mid-60s as well as any patients who could benefit from a degree of brow and forehead lifting [4].

Abraham's report also discussed contraindications to the procedure, which can likely be generalized to all RF procedures. Specifically, any patient with an implanted device such as a pacemaker, defibrillator, or neurological stimulator may not be a candidate or may need clearance to have the device temporally deactivated if they are not completely dependent on it. Additionally, patients with acute or chronic active dermatologic conditions, collagen-vascular disorders, or autoimmune conditions should undergo directed screening and thorough consideration to ensure candidacy for the procedure. Valacyclovir should be used when needed for herpes prophylaxis [3].

Further evidence-based preoperative considerations are lacking in the literature.

Best Techniques and Performance

While each study in the literature uses specific and, typically, unique treatment parameters and techniques, studies directly comparing the efficacy of those parameters and techniques are rare. Therefore, it is difficult to provide an evidence basis for the use of any specific settings, passes, or other parameters being superior to other variations. In most cases, it can only be stated that the results in any given study were achieved with the particular treatment as it was executed in that study. Furthermore, it is important to note that treatment parameters, outcomes, and side effects

are often device specific rather than modality specific, and there can also be significant variability even with the same device based on how treatments are performed. The limited available comparative evidence will be discussed.

Microfocused Ultrasound

Investigating a multi-depth approach, in a study treating 64 patients, Baumann and Zelickson randomized subjects to one of three different treatment groups for treatment of the neck. Efficacy and patient satisfaction were greater in the group treated with both a deep (4.5-mm depth) and superficial (3.0-mm depth) pass versus a single deep pass [41]. Alster and colleagues found slightly higher clinical improvement scores at all sites (upper arms, medial thighs, and knees) treated on the dual-plane side compared to the single-plane (deep) side, but differences were not statistically significant [11]. Sasaki and Tevez determined from their prospective study that areas treated with more lines, higher energies, and at dual depths demonstrated greater lifting (2b) [42].

Based on clinical experience, but without objective prospective or retrospective analysis, Brobst and colleagues suggest that more treatment lines result in better results as does a multi-depth approach (5) [43].

Based on experience, Fabi suggests a treatment algorithm for the treatment of the full face and upper neck based on degree of laxity: 500–600 lines for mild laxity, 600–700 lines for moderate laxity, and 800 lines for severe laxity [40].

Radiofrequency

Initially, the ThermaCool device treatment algorithm involved a single pass at high energy. This resulted, at times, in inconsistent results and significant treatment pain [33]. The first step to improve the treatment algorithm was a small histologic study of three patients treated with one or multiple passes and low or high energies. Multiple-pass algorithms produced ultrastructural collagen changes similar to the more painful single-pass high-energy treatment (5) [44]. This, then, spawned several clinical investigations.

Analyzing a survey of physicians performing 5700 treatments with the ThermaCool device, Dover and a 14-physician consensus panel determined a low-energy, multi-pass technique yielded "substantial and consistent results." Compared to the initial single-pass treatment, the new multiple-pass algorithm resulted in greater immediate tightening, greater tightening at 6 months, much less pain, and an increased frequency of meeting patient expectations. Furthermore, the panel established "patient feedback on heat sensation is a valid and preferred method for optimal energy selection" and visible tightening is a valid clinical endpoint, predictive of results (5) [45]. Similarly, as Dover reports, Geronemus and Koch found a multiple-pass technique (thus using a higher number of pulses) yielded superior results when they treated 45 patients with varying pulse number ranges [45]. Though not directly comparing to the former single-pass technique, Bogle and colleagues also found a multiple-pass, lower-energy technique effective in the treatment of 66 subjects. They concluded this method is ideal to achieve results with the fewest side effects and that the endpoint in treatment is visible tightening (4) [46].

Fritz, Counters, and Zelickson randomized 20 subjects to receive either one or two treatment sessions using the same device and concluded that improvement was significantly greater in those treated with two sessions. Both groups had greater improvement 4 months after treatment than at 1 month after, and both had relatively high patient satisfaction (4) [47].

In a study of the EndyMed multisource RF device, it was determined that there is a greater degree of clinical improvement in subjects when surface temperatures increased more than 11.5 °C by the end of the procedure and remained increased greater than 4.5 °C 20 minutes after the procedure [37].

Further studies are lacking to provide evidence for specific treatment parameters with other devices and modalities.

Safety

A review of the available literature suggests that noninvasive skin-tightening treatments are vastly safe procedures.

Microfocused Ultrasound

No long-term side effects from MFUS treatments have been reported in the literature to date.

Hitchcock and Dobke performed an exhaustive literature review of MFUS (Ulthera) safety encompassing all available studies and trials in the literature as well as postmarket reports to the manufacturer (3a-) [48]. At the time of the review, an estimated 350,000 treatments had been performed worldwide. The most commonly reported side effects include transient erythema (which commonly occurs in all or nearly all patients treated), tenderness, and edema. Ecchymoses, numbness/tingling, and welts/wheals/striations (most likely due to inadequate transducer contact) are less common. Rare events include postinflammatory pigment changes and paresis. All side effects and rare adverse events have been temporary and resolved without sequelae. In a summary of 769 treated subjects in 22 clinical trials, tenderness/soreness occurred in 1.6%, welts/lines in 1.2%, and bruising in 0.4%. Other effects beyond the typical common adverse events occurring in less than 0.4% included moderate pain, nerve irritation, numbness/paresthesia, lumps, swelling, tingling, itchiness, redness, hives/rash, headaches, and swollen throat during treatment. All were mild except the moderate pain, hives/rash, and swollen throat which were moderate. All were temporary [48].

In a large European review of 318 treatments, beyond the expected, known adverse events as discussed, there were four unexpected side effects attributed to or possibly attributed to a poor treatment technique. These were a moderate submental burn leaving a "very small scar" (22 days to resolution), a severe mentalis nerve irritation (47 days to resolution), a 2 × 1-cm firm lump on the neck (91 days to resolution), and a moderate motor nerve deficit of the depressor angulis oris muscle (90 days to resolution) [48].

Another large European systematic survey examined side effects treating 233 patients. Transient erythema (<1 h) occurred in 100%. Other erythema (12–24 h), eyelid edema (<3 days), superficial ecchymosis (duration not specified), and moderate continuous pain (<3 weeks) occurred in 2.2–3% of patients. Vesicles and papules lasting <8 days occurred in 9.4%, and transient numbness occurred in 2.6%. Hitchcock and Dobke concluded that the treatment is safe and effective typically with only mild and transient side effects. Unexpected and rare adverse events are often attributed to poor technique and most can be avoided. Generally, all side effects have resolved [48]. No significant differences in safety have been reported since their review in 2014.

A 2015 study of the treatment of 52 patients with Fitzpatrick III to VI revealed a similar safety profile with only three adverse events: mild edema or welts in two subjects and severe prolonged erythema with mild scabbing in one subject. All resolved within 90 days, and the authors concluded the treatment is safe in all skin types (4) [49].

Radiofrequency

Monopolar RF

In the initial study using monopolar RF, Fitzpatrick and colleagues reported data on pain and adverse events. Of 86 subjects, 22 of whom received nerve blocks and all of whom received topical anesthesia, 3% reported no pain, 45% reported mild pain, 35% reported moderate pain, 13% reported severe pain, and 3% reported intolerable pain. The treatment energy was reduced when needed per patient's pain tolerance. The most frequent side effects were erythema (present immediately in 36% and present in 17% within 72 h) and edema (14% immediately and 6.4% within 72 h). Scabbing occurred in 7.7% within 72 h but was not present immediately. Other events occurring with an incidence of 5% or less included abrasion, blistering, blanching,

bruising, crusting, hyperpigmentation, oozing, purpura, and ulcer. Scarring had an incidence of 6.3% by 4 months and 3.6% by 6 months. Textural changes were noted to reach an incidence of 2.4% by 6 months without data beyond that point. Other than scarring and textural changes, most events resolved by 1 month, still others by 4 months, and all others by 6 months. There were 15 subjects with at least 1 area of second-degree burn for a total of 21 second-degree burns out of 5858 RF exposures, resulting in an incidence of 0.36%. They noted the overall high level of safety with this device to be "impressive" and that burns were likely due to user technique as well as some correlation between higher energies resulting in more burns [21].

Alster's study of 50 treated patients also found the procedure to be safe with limited adverse effects. Subjects described the procedure as moderately uncomfortable. All had erythema lasing 2–12 h. 56% reported soreness in the treated area. Erythematous papules that resolved in 24 h occurred in 6%, and one patient described dysesthesia along the mandible that resolved within 5 days. There were no pigmentary changes, blistering, or scarring [23].

Narins and colleagues investigated overtreatment with the ThermaCool RF device causing "delayed contour irregularities." Although most adverse reactions with this monopolar RF device are limited to superficial burns and these delayed contour irregularities are, overall, quite rare, with an incidence lower than that of the adverse events of many other surgical and nonsurgical treatments, they are thought to occur secondary to deeper tissue overheating. Using data tabulated from all contour irregularities reported by clinicians to the manufacturer, it was determined that this occurred with an incidence of 0.23% during the 18 months prior to a modification in the manufacturer's treatment guidelines to address this concern. After modification, the incidence declined to <0.04% during the subsequent 6 months. Furthermore, 70% of the cases prior to the treatment modification occurred when nerve blocks, tumescent anesthesia, and/or intravenous sedation impeded the patient pain perception and reporting. By following a modified treatment algorithm consisting of multiple passes at lower energies, patient feedback as a guide, and a delay between passes to allow tissue cooling, complications should be fewer [22].

In the prospective trial treating 49 subjects with the Pellevé system, there were no adverse events reported and no post-procedure recovery time or pain [27]. Vega's group also reported only mild-to-moderate discomfort during the treatment and no adverse events in their prospective trial using this system to treat the hands of 28 patients (4) [50].

The newer ThermiSmooth 250 monopolar RF system uses a probe with constant motion in constant contact with the skin that provides real-time surface temperature feedback to control energy delivery and does not require a cooling mechanism. In the preliminary prospective study treating 14 subjects, Key did not report any adverse events [25].

Overall, microfocused US and monopolar RF treatments present an excellent safety profile (B).

Unipolar, Bipolar, and Multipolar RF

Many studies using various systems have consistently reported a post-treatment transient erythema typically lasting 15–30 min up to 120 min in all or nearly all patients. None found any other significant adverse events such as blistering, scarring, or pigmentary changes (4) [14, 29, 30, 36–39, 51, 52].

Postoperative Care and Follow-Up

There are no specific evidence-based recommendations for particular follow-up intervals or monitoring. Anecdotal recommendations exist suggesting follow-up treatments at anywhere between 6 and 24 months. It should be noted that they are not at all evidence based.

Alternative Procedures and Modifications

Noninvasive skin tightening techniques can serve as the structural backbone for a comprehensive, multiple-modality approach to rejuvenation to

correct rhytids, photodamage, volume loss, and contour irregularities. Once the skin has been tightened and lifted, fillers, neurotoxins, superficial and deep resurfacing, as well as other vascular and pigment targeting lasers and intense-pulsed light can be combined as needed for correction of the aging skin.

Alternatively, more profound lifting from minimally invasive techniques such as absorbable suture lifts or even invasive lifting such as facelifts can be initially performed. Then, the results can be improved, maintained, and finessed with noninvasive tightening techniques as discussed.

A couple of minimally invasive energy-based techniques exist as alternatives to the tightening provided by the external tightening modalities reviewed: laser lipolysis and subdermal monopolar radiofrequency treatments.

Laser lipolysis has been shown in multiple studies to achieve skin tightening. Two large studies >40 patients, for example, showed tightening at all body areas treated including the neck and extremities in addition to the abdomen. While one study used measurements of circumference as proof of tightening, the other used skin caliper measurements (4) [53, 54]. Circumference measurements could be confounded by the volume loss from the lipolysis procedure. Complications were minimal to none. When present, they consisted of only prolonged edema in some patients [53, 54]. It is unclear if common and expected side effects occurred but were not reported.

In a study of subsurface monopolar radiofrequency treatment, 35 subjects were treated in the submental region. Subject graded improvement scores showed improvement in 84% at 90 days and 77% at 180 days. At 90 days, 68% of subjects were satisfied, and 64% of subjects were satisfied at 180 days. Adverse events included tenderness, edema, bruising, numbness, and nodules and induration. Two subjects experienced temporary marginal mandibular nerve palsy resolving within 14 days. One had a transient burn (4) [55].

While not discussed in detail, other radiofrequency technologies, devices, and techniques have also been shown to induce skin tightening. While they tend to be used primarily for other indications, fractionated bipolar RF and microneedle fractionated bipolar RF have been shown to induce skin tightening (5 [56], 4 [57–64]) [13, 35, 56–64]. Thus, skin tightening can be a secondary benefit to the use of these devices, or these treatments can be employed primarily for their tightening effect, usually on the face and neck.

Other noninvasive devices and treatment modalities have been shown to produce tightening effects as well. While used more commonly for resurfacing and photodamage, fully ablative lasers, fractional ablative lasers, fractional nonablative lasers, various nonablative laser wavelengths, infrared devices, and intense-pulsed light have all been shown to produce some degree of skin tightening, as has cryolipolysis. (4 [65–73], 2b [74–78], 5 [79, 80]) [17, 65–80]. Picosecond systems with nonablative laser wavelengths are being studied for photorejuvenation including skin tightening as well. These modalities can be employed in place of or in addition to the other tightening technologies discussed as needed for each patient.

Other body contouring procedures and noninvasive fat reduction procedures can be complementary to skin tightening procedures. These include other contouring lasers such as the 1060-nm body sculpting laser, the multipolar contactless RF field treatment, intense-focused ultrasound devices, and acoustic pulse therapy devices.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
The noninvasive skin tightening techniques, modalities, and devices as discussed are generally safe and effective means for achieving nonsurgical tightening results with minimal downtime and minimal side effects	B
Careful patient selection matching severity of laxity and goals of treatment with the appropriate device and referring for invasive treatments when necessary are both important	D
Of paramount importance is ensuring patients completely understand the expectations of the treatment and potential results	D
Microfocused ultrasound, various radiofrequency technologies, ablative fractional and full-field resurfacing, nonablative fractional resurfacing, various laser wavelengths, and cryolipolysis have shown evidence of various degrees of skin tightening. Often this may be dependent upon treatment technique, patient characteristics, and the modality employed, but studies affirming optimal treatment parameters are generally lacking	B-C
Microfocused ultrasound, various radiofrequency technologies, ablative fractional and full field resurfacing, nonablative fractional resurfacing, various laser wavelengths, and cryolipolysis have shown evidence of various degrees of skin tightening	B-C
Radiofrequency, microfocused ultrasound, and nonablative laser wavelengths in the infrared spectrum are generally safe for the treatment of all Fitzpatrick skin types when used appropriately	B
Younger patients with mild-to-moderate laxity are likely to see more improvement than older patients or those with significant redundancy, particularly as studied for radiofrequency modalities	C
This may be generalizable to the other noninvasive tightening modalities	D
As studied in microfocused ultrasound, subjects with BMI ≤ 25 kg/m^2 are likely to see better results compared to those with higher BMI	C
Additionally, studies suggested a dual-plane treatment algorithm likely improves results	C
It seems a greater number of treatment lines might as well	D

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Self-Assessment Questions

1. Which of the following types of radiofrequency technology does not use an electric current to create heat in the skin?
   (a) Bipolar RF
   (b) Fractionated RF
   (c) Monopolar RF
   (d) Multipolar RF
   (e) Unipolar RF
2. Which of the following lifestyle or patient characteristics has been shown to affect the final outcome from microfocused ultrasound treatments?
   (a) Age
   (b) Alcohol consumption
   (c) BMI
   (d) Illness
   (e) Skin type
3. Which of the following treatment algorithms was determined best to avoid delayed contour irregularities from the original monopolar RF treatment device:
   (a) Single pass, higher energy
   (b) Single pass, higher energy with tumescent anesthesia of the entire treatment area.
   (c) Single pass, lower energy
   (d) Multiple passes, higher energy
   (e) Multiple passes, lower energy
4. A device of which of the following technologies has an FDA indication for brow lifting?
   (a) 1550-nm fractional laser
   (b) Bipolar RF
   (c) Microfocused ultrasound
   (d) Monopolar RF
   (e) Multisource RF
5. Which of the following is true of bipolar RF compared to monopolar RF?
   (a) In bipolar RF, one electrode is located in the treatment probe, and the other is a grounding pad.
   (b) In bipolar RF, the presence of both the negative and positive electrode in the treatment probe results in a generally deeper treatment.
   (c) In bipolar RF, the presence of both the negative and positive electrode in the treatment probe results in a generally more superficial treatment.
   (d) Monopolar RF is typically delivered in a fractionated pattern.
   (e) Monopolar RF uses high-frequency electromagnetic radiation instead of an electric current to produce a thermal effect.

Correct Answers

1. e: Unipolar RF uses a single electrode to deliver electromagnetic radiation to the skin, which results in oscillation of water molecules to produce heat. Other forms of RF use two electrodes to deliver an electric current. Fractionated RF and multipolar RF are a form and variation of bipolar RF, respectively.
2. c: BMI $\leq$ 25 kg/m^2 was shown to result in higher self-improvement scores, and BMI > 30 kg/m^2 was shown to have lower subjective and objective improvement scores when using microfocused ultrasound [1, 2].
3. e: After the initial treatment protocol using the first monopolar RF treatment device with epidermal cooling and a "stamp" treatment technique called for a single high-energy pass, there was a small incidence of delayed contour irregularities. A multiple-pass, low-energy algorithm was determined to be safest to avoid contour irregularities as well as to yield superior results. Additionally, upon review, it was determined that local anesthesia prevented appropriate patient feedback for safety [22, 45].
4. c: A microfocused ultrasound device has an FDA indication for brow lifting.
5. c: The short distance between electrodes in bipolar RF limits the depth of treatment.

16 Vascular Laser and Light Treatments

Brent C. Martin and Kristen M. Kelly

Abstract

This chapter provides an overview of vascular targeting light treatments applied to treatment of commonly encountered cutaneous vascular lesions, specifically port wine birthmarks (PWBs), infantile hemangiomas (IHs), and telangiectasias. Evidence-based recommendations are provided regarding light-based treatment effectiveness, preoperative evaluation, treatment techniques, safety, and postoperative management. We also discuss device and drug combinations which have been utilized including photodynamic therapy or laser in combination with antiangiogenic agents for PWBs and beta-blockers with lasers for IHs. This chapter provides a practical, concise, and evidence-based guide for the utilization of vascular-specific laser treatments available today.

Keywords

Pulsed dye laser · Nd:YAG · Intense pulsed light (IPL) · Alexandrite · Port wine birthmarks/stains · Infantile hemangiomas · Telangiectasias

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Introduction

One of the first applications of lasers in dermatology was the treatment of port wine birthmarks (PWBs). Vascular-specific lasers such as argon lasers were used in the 1960s and improved PWBs but caused an unacceptably high incidence of scarring, due to the relatively non-specific heating of skin. Anderson and Parrish published their landmark paper on selective photothermolysis [1] in 1983, which proposed a way to confine thermal injury to the target of interest, while minimizing damage to surrounding tissue, reducing scarring and pigmentary change. Three laser parameters are important to selective photothermolysis: laser wavelength, pulse duration, and fluence. The wavelength should have preferential absorption for the targeted chromophore. In the case of vascular lesions, this is oxyhemoglobin, which has the greatest absorption peaks at 418, 542, and 577 nm (Fig. 16.1). Pulse duration should be matched to the target size with short durations for smaller targets and longer pulse durations for longer targets. In the case of vascular lesions, blood vessels are relatively large targets, and millisecond pulse durations are used. Fluence is the energy per unit area and must be adequate to cause damage to the target, but not excessive, which could result in nonselective injury.

The pulsed dye laser (PDL) (577–600 nm) was developed in the 1960s and provided the

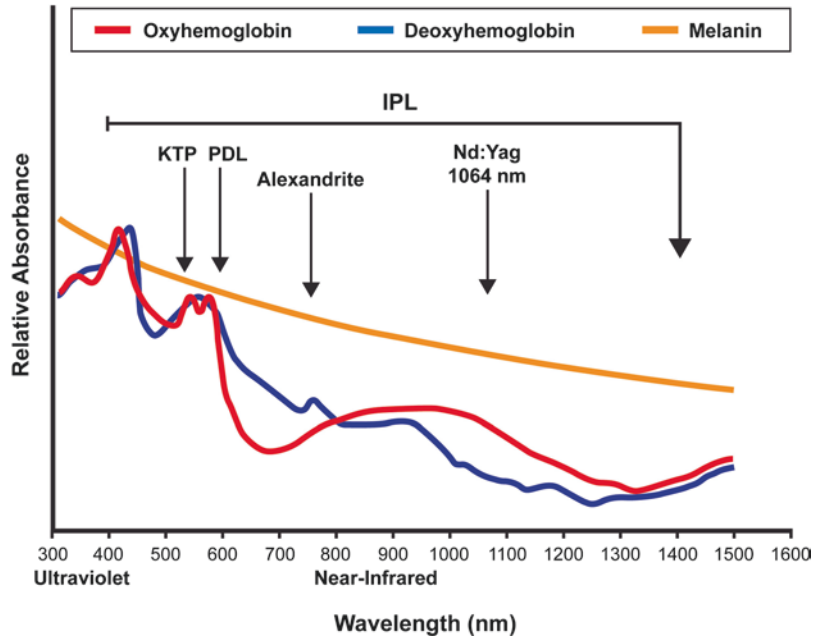

Fig. 16.1 Relative absorbance curves of vascular lasers and light

necessary components for selective photothermolysis to target vascular lesions. Several advancements were made in this device over subsequent decades. PDLs with longer wavelengths (585 and 595 nm compared to the original 577 nm) allow for slighter greater depths of penetration. The ability to use longer pulse durations (3–40 ms as compared to 1.5 ms or less) allows treatment for some lesions such as telangiectasias with minimal purpura, which is advantageous for cosmetic treatments [2 (2b)].

Epidermal cooling was introduced in the 1990s to protect the skin surface and to minimize pigmentary change and scarring, while reducing patient discomfort. Use of epidermal cooling is especially advantageous in patients with dark skin types, where increased epidermal melanin prevents penetration of light to targeted dermal tissues. Epidermal cooling also allows the use of higher fluences to improve tissue effect. The three types of epidermal cooling used are cryogen spray cooling, contact cooling, and air cooling.

Other devices have also been used for vascular lesion treatment. Potassium titanyl phosphate (KTP) lasers use a neodymium:yttrium aluminum garnet (Nd:YAG) crystal frequency doubled with a KTP crystal to emit a wavelength of 532 nm. The depth of penetration is slightly less than that of PDLs given the shorter wavelength. There is also increased melanin absorption at the 532 nm wavelength. Longer wavelength lasers can penetrate up to 50–75% deeper into the skin and can be used to treat deeper lesions. The alexandrite laser at 755 nm is a good choice to treat deeper, more resistant venous lesions, as its wavelength is close to the deoxyhemoglobin absorption peak (Fig. 16.1). Near-infrared diode (800–810 nm, 940 nm) devices are also used successfully for vascular targeting. The Nd:YAG laser can be used to treat vascular lesions by targeting the secondary, lower peak for the absorption of light by oxyhemoglobin (Fig. 16.1). It is important to note that the absolute absorption of hemoglobin is lower, requiring the use of higher fluences, which increases the risk of tissue damage and scarring. As such, these devices should be used with caution and are best used by clinicians with extensive experience. Intense pulsed light (IPL) devices emit polychromatic noncoherent broadband light from 420 to 1400 nm with varying pulse durations. Filters are implemented to remove unwanted shorter wavelengths to treat

vascular lesions with blue-green to yellow wavelengths. Dual wavelength or energy devices such as PDL combined with Nd:YAG (595 and 1064 nm) and PDL combined with radiofrequency energy are also available.

When selecting a device and treatment parameters, the user should keep in mind the type of lesion, the depth of the lesion, and the patient characteristics such as skin type. As an example, since the PDL penetrates 0.5–1.2 mm into the skin, it is efficacious for treating vascular lesions in the superficial dermis [3] and is most easily used in patients with lighter skin types, although settings can be adjusted (e.g., lower energies and longer pulse durations) for patients with dark skin types. Near-infrared and infrared wavelengths can be used to treat deeper lesions; however, as noted above, there is increased risk.

Indications for Vascular Lasers and Light Treatments

A diverse range of cutaneous vascular lesions can be treated with light-based devices. We describe some specific indications below.

Port Wine Birthmarks

Port wine birthmarks (PWBs) are congenital capillary malformations characterized by erythematous to violaceous patches. PWB vessels vary in size from 7 to 300 μm, with older patients tending to have larger vessels. PWBs are found in approximately 0.3% of newborns. They are commonly found on the head or neck, but can occur anywhere throughout the body. Over decades, lesions may thicken and develop papules and nodules [4, 5 (4, 4)]. Tissue hypertrophy, which can occasionally occur at birth, has been associated with 60–70% of lesions by the fifth decade of life. PWBs can be associated with various syndromes such as Sturge–Weber syndrome, which involves a facial PWB with associated ophthalmologic and/or neurologic abnormalities including glaucoma, seizures, and developmental delay. PWBs can also occur in association with arteriovenous malformations in Klippel–Trénaunay–Weber and Parkes Weber syndromes as well as in capillary malformation–arteriovenous malformation syndrome. Many patients seek treatment for these lesions due to the psychosocial or functional impact. Laser therapy is the standard of care treatment for PWBs.

Infantile Hemangiomas

Infantile hemangiomas (IHs) are the most common benign vascular tumors in children, occurring in 4–10% of infants. IHs are three times more common in females. Lesions are present at birth or become evident during the first several weeks of life. Sixty percent of lesions arise on the head and neck. Hemangiomas are characterized as localized or segmental, and as superficial (red papules or plaques), deep (blue or skin colored nodules), or mixed [6 (2a)]. Associated syndromes need to be considered when evaluating patients with IHs. PHACES syndrome needs to be considered in large segmental facial IH and involves posterior fossa malformations, IH, arterial anomalies, coarctation of the aorta, eye abnormalities, and sternal or supraumbilical raphe. LUMBAR syndrome includes **l**ower body infantile hemangiomas with **u**rogenital anomalies and **u**lceration, **m**yelopathy, **b**ony deformities, along with **a**norectal, **a**rterial, and **r**enal anomalies. Diffuse neonatal hemangiomatosis involves multiple skin hemangiomas and an associated risk of visceral hemangiomas.

Most IHs proliferate, often rapidly, until 6–9 months of life. Lesions then stabilize and begin to regress, with the majority of lesions regressing by 9 years of age, although recent studies suggest this may occur sooner [7 (1a)]. Some IHs leave behind residual fibrofatty tissue, atrophy, or telangiectasias. Small, non-ulcerated lesions in a non-cosmetically sensitive area may not require treatment. Treatment is needed for lesions that affect an important function (vision, feeding etc.), ulcerated lesions (as these are very painful), and for lesions that are in cosmetically sensitive areas and are likely to

result in scarring. Common locations of IHs that are indicated for treatment include lesions on the face or in the anogenital region. Treatment should be aimed at stopping progression of lesions early on to minimize tissue damage and therefore avoiding the need for long-term treatment in the future. Topical therapies (such as topical timolol), systemic medications (especially beta-blockers such as propranolol), and occasionally surgical intervention are used for lesions that ulcerate or impact functionality, such as feeding or vision. Beta-blockers are currently the standard of care for IHs, for which treatment is recommended. Laser therapy may be beneficial, especially for superficial or ulcerated lesions. Laser therapy is often used in combination with topical or systemic medications. Vascular targeting and fractioned lasers are commonly used to remove residual skin changes after involution.

Telangiectasias

Telangiectasias are common lesions that present as 0.1–1-mm diameter vascular dilatations that are visible on the skin anywhere on the body but especially on the face, around the nose, the cheeks, and the chin. They may occur in an acquired fashion in the setting of other conditions including cutaneous photodamage, rosacea, connective tissue or liver disease, radiation dermatitis, and post-long-term topical corticosteroid therapy [8 (2a)]. Numerous congenital conditions are associated with telangiectasias including hereditary hemorrhagic telangiectasia (HHT), Osler-Weber-Rendu syndrome, and ataxia-telangiectasia. Facial redness is a common complaint in patients with many telangiectasias.

Telangiectasias and resultant facial redness often do not require treatment from a medical standpoint, but some lesions, especially those associated with syndromes, may bleed. Telangiectasias can be treated for cosmetic purposes. Lasers provide quick and effective therapy. New telangiectasias often develop with time, and repeat treatments are often beneficial.

Effectiveness of Vascular Laser and Light Treatments

Port Wine Birthmarks

PDLs are commonly used to treat PWBs, with many studies demonstrating efficacy [9–14 (2b, 2b, 3b, 2b, 2b, 4)]. Multiple treatments are required to achieve maximum lightening of PWBs (15–20 or more are not uncommon), and complete clearance is uncommon [9–11 (2b, 2b, 3b)]. In 1 study of 76 patients, 79% clinical improvement was reported over an average of 9 PDL treatments [12 (2b)]. Factors that lead to improved response to PDL treatments of PWBs include small size (<20 cm^2), a location directly above a bony area (particularly the central forehead), and treatment at a young age [13 (2b)]. One study on 49 infants, all of whom started laser treatment before the age of 6 months, found an average clearance of nearly 90% after 1 year [14 (4)]. Additional studies have also indicated that earlier treatment of PWBs might allow for better results with fewer total treatments [15–18 (2b, 2b, 2b, 3b)]. Greater efficacy of treatment in young children may be related to increased hemoglobin concentration in the first 6–12 months of life and the presence of thinner skin and smaller lesion vessels in infants as compared to older individuals. Studies have shown that PWBs located on the trunk, extremities [19 (2a)], and central face (medial cheek, upper lip, nose) [20], and those lesions that are violaceous or nodular [21 (2b)], are more difficult to treat.

Lesions may recur after treatment. In a 10-year follow-up study of 51 patients treated with PDLs for PWBs, lesions were found to be significantly darker at follow-up than at the time of the last treatment. Lesions did remain significantly lighter than prior to initial therapy [22 (4)].

Infantile Hemangiomas

As noted above, beta-blockers are currently the standard-of-care treatment for IHs. When lasers are used, PDLs are a common laser used for the treatment of infantile hemangiomas. Study results

vary on the efficacy of treatment. Variability in study results is likely due to the natural course of these lesions (regression with time) and the range of laser parameters that have been used. Recent studies that suggest early treatment with PDLs can halt further growth and facilitate a transition to the involution phase, with minimal risk of adverse effects, when appropriate settings are used and patients are selected correctly. In a retrospective study of 90 patients, treatment with a 595-nm PDL with cooling led to 85% clearance of color and 64% resolution of thickness [23 (2a)]. Superficial IHs, as compared to deeper lesions, respond better. This is due to the limited depth of penetration of PDL light. A prospective study of 165 patients showed complete clearance of superficial IHs, while no mixed superficial-deep lesions exhibited complete clearance [24 (2b)].

PDL is also beneficial for treatment of ulcerated hemangiomas, especially in the anogenital area. A study on 78 patients with ulcerated hemangiomas showed that 91% improved after a mean of 2 PDL treatments [25 (2b)].

Propranolol can be used in combination with PDL. A retrospective study showed that complete clearance occurred more commonly when IHs were treated with propranolol and PDLs concurrently compared with IHs treated with propranolol followed by PDLs and IHs treated with propranolol alone [26 (2a)]. The same study also showed that clearance occurred at 92 days with combined therapy as opposed to 288 days for propranolol alone.

Telangiectasias

Many different light sources are effective in treating telangiectasias including PDLs, long-pulsed 532-nm lasers and intense pulsed light. PDL treatment with shorter pulse durations generally results in temporary purpura. Longer pulse durations, greater than 6 ms, can decrease resultant purpura, but more treatment sessions are usually needed. Two studies involving patients with facial telangiectasias and erythema showed that fluences that induce purpura were more effective at reducing the appearance of telangiectasias, although subpurpuric fluences did reduce surrounding erythema [27, 28 (3b, 2b)]. Vessels around the nasal ala are more difficult to treat. One study showed that cautious stacking of non-purpuric PDL settings resulted in successful resolution after PDL alone [29 (3b)]. Follow-up treatments are often required as telangiectasias can recur or new lesions develop with time.

Preoperative Evaluation

An initial consultation is important to determine the correct diagnosis, to assess if additional work-up is needed, and to discuss treatment options. If laser therapy is planned, expectations for treatment, the need for multiple sessions, and risks of treatment as well as benefits should be discussed. It also needs to be determined whether anesthesia will be used for the procedure, and if so, anesthesia options should also be discussed. Expected post-treatment effects including erythema, purpura, and swelling should be described and aftercare, including sun protection and avoidance of trauma should be addressed. Photos should be taken prior to each treatment to check and assess improvement.

As mentioned earlier, associated syndromes need to be considered when evaluating patients with PWBs, infantile hemangiomas, and telangiectasias. For PWBs, if Sturge-Weber syndrome is suspected, then ophthalmology and neurology referrals may be appropriate. Imaging studies including ultrasound (in the first year of life) or magnetic resonance imaging (MRI) may also be appropriate to assess central nervous system involvement. For large facial IH, features of PHACES syndrome should be assessed through utilization of imaging studies including echocardiogram and brain MRI/MR angiogram. An eye exam by an ophthalmologist may be warranted. If hemangiomas of the beard area (mandibular innervation area of the trigeminal nerve) are seen, referral to an otolaryngologist is warranted to assess for upper airway hemangiomas, which can cause airway obstruction. Urologic workup including imaging (ultrasound, MRI) of the pelvis and perineum to assess for abnormalities in the kidney, urinary tract, and genitalia should be considered if

LUMBAR syndrome is suspected. Work up is not generally required for telangiectasias unless a genetic syndrome such as HHT is suspected.

Prior to treatment, the question of whether to use local/general anesthesia or pain medications should be addressed. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they inhibit clotting and can minimize treatment effects. Topical anesthetics can be used, but vasoconstriction and lesion blanching may occur with some topicals, which could potentially decrease the efficacy of treatments. Injected anesthesia, nerve blocks, and local injections can be considered [30 (2a)]. One study showed that complete nerve block, when utilized for laser treatment of cutaneous lesions, led to excellent pain control in 96% of cases, while complications, including vasovagal syncope, swelling, and neurapraxia occurred in only 1.1% of cases and were generally mild and transient [31 (2b)]. Early treatment of PWBs and IHs is often beneficial, and general anesthesia may be considered for treatment of infants and young children as treatments are uncomfortable and require eye protection and limited movement of the patient. In our clinic, general anesthesia is used in some children over 6 months of age; it offers the advantage of minimizing fear and pain in children who will need lengthy and/or multiple procedures for large lesions. One study reported no serious adverse events in 881 dermatologic procedures performed on children with an age range of 2 months to 18 years [32 (2b)]. Other studies have shown little risk during the procedure if general anesthesia is performed with pediatric anesthesiologists [33, 34 (2b, 2b)]. In recent years, the risk of developmental delay when general anesthesia is used in children less than 3 years of age has been a concern. Some of the concerns were based on animal studies. The US Food and Drug Administration (FDA) recently released a warning [35] as these animal research studies have shown that there may be risks, including neurodegenerative changes in the developing brain, with general anesthesia in the first few months to a year of life. At the current time, the FDA states that there is insufficient data to determine the clinical relevance of these findings and further studies are needed to assess the long-term effects. There have been some recent large clinical studies, which did not find significant increased risk of development delay associated with general anesthesia procedures in young children [36, 37 (2b, 1b)], but additional studies are pending. However, all potential risks should be discussed with parents, so informed decisions can be made.

Immediately following laser treatment for vascular lesions, local swelling and pain similar to a sunburn is common. Aftercare including elevation, ice application, over-the-counter oral analgesics (if not contraindicated acetaminophen is preferable to NSAIDs as the latter could affect treatment effects and increase bruising), mild topical emollients (such as petrolatum), sun avoidance/protection, and avoidance of trauma all are beneficial for decreasing the likelihood of patient discomfort, hyperpigmentation, and scarring [38 (2a)].

Best Techniques and Performance

Use of lasers always requires appropriate eye protection. All present in the room must wear appropriate goggles. Patients can wear goggles if non-facial areas are treated, if goggles of the correct size are available, and if the patient is unlikely to remove them. Young children often require more secure eye protection, such as laser safe eye pads (adhesive pads with metal to protect the eyes) and gauze or securely placed overlying metal eye shields. If the skin inside the orbital rim is to be treated, corneal shields are needed. These can be placed using anesthetic drops approved for ophthalmologic indications and lubricant. Use of lubricant may cause post-procedure blurriness, so patients should have an accompanying driver or make sure lubricant is rinsed out prior to driving. There is a small risk of corneal eye injury with placement of these shields, so this should be done with care.

Laser parameters vary based on type of lesion, lesion characteristics and location, and patient skin type. Large spot sizes offer the advantage of minimizing light scatter and allows for increased penetration of light. It may be advisable to use

lower fluences and longer pulse durations in those with darker skin types. Epidermal cooling techniques are used concurrently for all laser treatments of vascular lesions.

Port Wine Birthmarks

PDLs are commonly used for PWBs. An example of parameters include [39 (2a)]:

- Wavelength: 585–595 nm
- Pulse duration: 0.45–10 ms
- Fluence: 4.5–12 J/cm^2 (settings need to be individualized for each device; lower energies are generally used with larger spot sizes)
- Spot size: at least 7 mm
- Appropriate epidermal cooling

Treatment parameters for PWBs with PDLs vary to some degree with each specific device. Appropriate initial PDL fluence settings vary largely due to individual patient characteristics including skin color, lesion morphology, and lesion location. Lower initial fluences are typically used for young children, individuals with dark skin (due to risks of hyper/hypopigmentation), and lesions in areas at higher risk for cutaneous damage, such as the neck or eyelid. Fluences can be increased by 0.5 J/cm^2 during subsequent treatment visits, if adequate response has not been obtained and there are no adverse effects [38 (2a)]. It is important to know desired treatment end points for all laser treatments. For PDL treatment of PWBs, purpura without cutaneous whitening or graying is the desired endpoint.

Other devices can also be used. The 532-nm frequency-doubled Nd:YAG is one option. In one study, the 532-nm Nd:YAG (9.5–20 J/cm^2, pulse duration 15–50 ms, 2–6 mm spot size, unspecified integrated cooling system utilized) generated 50% improvement from baseline in PWBs resistant to other laser treatments [40 (2b)]. Another study found that lesion color improved at least 25% in 53% of patients after treatment with a 532-nm frequency-doubled Nd:YAG (5–50 J/cm^2, pulse duration 1–50 ms, variable spot sizes, cooling method unspecified) [41 (2b)].

Near-infrared lasers including the alexandrite and 1064-nm Nd:YAG lasers are helpful for violaceous, nodular, or hypertrophic lesions [42, 43 (3b, 4)]. Scarring is more likely to occur, as higher fluences are needed to target the vasculature. This is especially true of the Nd:YAG laser which preferentially targets arterial blood, as opposed to the venous blood which is present in PWBs. Studies of the Alexandrite 755-nm laser have demonstrated good efficacy for hypertrophic PWBs resistant to PDLs, with clinical observations showing mild-to-moderate PWB lightening (40–100 J/cm^2, pulse duration 1.5 ms, 8 mm spot size, dynamic cooling device utilized), (35–100 J/cm^2, pulse duration 3 ms, 8–12 mm spot size, forced cold-air cooling) [44, 43 (5, 4)]. One study demonstrated good to excellent improvement with only a few treatments using the long-pulsed 1064-nm Nd:YAG laser in most patients treated for hypertrophic PWBs (100–240 J/cm^2, pulse duration 30 ms, 5 mm spot size, liquid cooling via stainless steel hand piece). Lesion hypertrophy responded better than color, and authors recommended combining with PDL treatment to further improve coloration of lesions [45 (2b)].

IPLs can also be utilized to treat PWBs. A study by Faurschou et al. found that both PDLs and IPLs lightened PWBs and could be used safely without adverse events (595-nm PDL, 7–14 J/cm^2, pulse duration 0.45–1.5 ms, 7–10 mm spot size; dynamic cooling device at 30-ms spray duration and 20-ms delay; IPL, 500–1400 nm, 22–46 J/cm^2, pulse duration 5–10 ms; handpiece equipped with sapphire contact cooling). In this study, more patients experienced better clearance rates with PDL (75%) as compared to IPL (30%) [46 (1b)]. Another study showed that in a group of 15 patients with PDL-resistant PWBs, 40% achieved more than 75% clearance with IPL (555–950 nm, 13–22 J/cm^2, pulse duration 8–30 ms, optical coupling gel utilized) [47, (3b)]. IPL was found to be safe and efficient in the treatment of PDL-resistant PWBs, except for those located in the V2 type distribution of the face as these lesions in the central part of the face are located deeper in the skin, and thus insufficient energy may have reached these areas. Furthermore, shorter pulse durations may be ben-

eficial for these lesions given the average size of vessels.

PWB treatment sessions are typically scheduled at 4–6-week intervals, and ten or more treatment sessions are often required. Shorter intervals can be considered as described in a retrospective study of 24 infants with facial PWBs where treatment intervals of 2, 3, or 4 weeks were effective and were well-tolerated [48 (3b)]. Darker skin types or lesions in the extremities may require longer intervals between treatments, ranging from 6 to 8 weeks.

Pulses can be overlapped by 10% [38 (2a)]. Multiple passes during the same treatment session may benefit PWBs [49] but should be approached with caution as this approach can increase the risk of adverse effects including pigmentary change (which can be permanent) and scarring.

Infantile Hemangiomas

As noted above, PDLs are the most common lasers used for the treatment of IHs. Commonly used parameters include (parameters vary by device):

- Wavelength: 585–595 nm
- Fluence: 5–7.5 J/cm^2
- Pulse duration: 0.45–6 ms
- Spot size: 5–10 mm

The growth phase of the IH must be taken into account. Proliferating lesions have a higher risk of ulceration and lower fluences must be used during this period. Lower fluences are also advisable in darker skin types and areas of thin skin, such as the eyelids. As mentioned earlier, skin cooling techniques are vital as they allow for higher fluences while minimizing the risks of epidermal damage. Multiple treatments are usually required and may be done at 2–4-week intervals for rapidly proliferating/ulcerated lesions or 4–6-week intervals for stable/involuting lesions.

Other laser options that have also been implemented to successfully treat IHs include frequency-doubled Nd:YAG. A retrospective study of 50 infants were treated with a 585 nm PDL (5.3–6.8 J/cm^2, pulse duration 0.3–0.45 ms, 7 mm spot size, chilled tip cooling utilized) or a 532-nm frequency-doubled Nd:YAG (20 J/cm^2, pulse duration 1–50 ms, 5 mm spot size, chilled tip cooling utilized). PDL was found to be more effective, where cessation of growth or improvement occurred in 93% (average of 3 treatments) of lesions compared to 70% (average of 2.6 treatments) of lesions using the 532-nm Nd:YAG laser [50 (2b)]. The 1064-nm Nd:YAG has been suggested for use with thicker hemangiomas given its greater depth of penetration. An uncontrolled study showed that sequential 595-nm PDL (7–15 J/cm^2, 10–40 ms pulse duration, variable spot sizes, unknown if cooling utilized) with 1064-nm Nd:YAG (50–100 J/cm^2, 10–40 ms pulse duration, variable spot sizes, cooling not described) treatments led to excellent improvement in the majority of hemangiomas involving the head and neck [51 (3b)]. There is a high risk of scarring with the 1064-nm Nd:YAG, and the authors never use this device for IHs and would recommend that use of this device only be considered by experienced users. For IHs with a superficial and deep component, beta-blockers in combination with PDLs may be a good option.

After involution, IHs can leave behind telangiectasias or residual fibrofatty tissue. Telangiectasias can be treated with PDL, and texture changes have been shown to improve with ablative or non-ablative fractional resurfacing (NAFR). A case report showed excellent skin texture improvement along with a substantial decrease of residual tissue bulk using NAFR (fractionated 1440-nm erbium-doped fiber laser, 25 J/cm^2, 15 mm spot size, forced air device cooling utilized) [52 (5)]. A series of case reports have shown that ablative fractional CO_2 lasers have promise in the flattening of fibrofatty residual tissue with 50–75% improvement in color, texture, and overall appearance (ablative fractional CO_2 laser, 20–40 J/cm^2, 15 mm spot size) [53 (5)].

Telangiectasias

Lasers are the most common treatment for multiple or large areas of telangiectasias and can also

be used when other modalities, such as electrocautery, have failed. Multiple treatments (2–4) are often required to achieve the best results, especially when non–purpuric settings are utilized [27, 28 (3b, 3b)].

Commonly used parameters for PDL include (parameters vary by device):

- Wavelength: 595 nm
- Fluence: varies depending on spot size and pulse duration
- Pulse duration: 1.5–20 ms
- Spot size: 7–12 mm
- Appropriate epidermal cooling

Multiple passes or pulse stacking can be considered when longer pulse durations are used [49, 54 (3b, 2b)]. Telangiectasias respond in fewer treatment sessions when purpuric settings are used, but cosmetic patients often prefer to avoid purpura. Vessel clearance and purpura indicate appropriate end points of therapy. Follow-up treatments are usually necessary.

The 532-nm frequency-doubled Nd:YAG laser is also commonly used and effective. The 532-nm laser can be used to treat facial telangiectasias with minimal to no purpura. In a study of 66 patients with facial telangiectasias, a 532-nm Nd:YAG laser (16–22.5 J/cm^2, pulse duration 15–30 ms, 5–7 mm spot size, cooling not specified) resulted in 75–100% clearance of telangiectasias in >90% of subjects after one treatment [55 (2b)]. A disadvantage of this laser is increased melanin absorption, resulting in a greater risk for adverse effects in darker skin types.

IPL can also be used very successfully for telangiectasias. One study showed that IPL-treated telangiectasias (570 nm cut-off filter, 40–43 J/cm^2, 4 ms pulse duration, ice application for 10 min following procedure) achieved 75–100% clearance with minimal purpura. Results correlated with operator experience [56 (2b)].

The long pulsed 1064 nm Nd:YAG laser can also be used for facial telangiectasias. One study demonstrated 95–100% clearing of facial telangiectasias after only one treatment (100 J/cm^2, 10 ms pulse duration, 2.5–7 mm spot sizes, external epidermal cooling device utilized) [57 (2b)]. Again there is an increased risk of scarring with the device, and it should be used cautiously by operators experienced with 1064-nm Nd:YAG use and end points.

Safety

Lasers are safe for use in patients of all ages, including young infants. Knowledge about desired end points and careful monitoring of the skin during and after the procedure are the best ways to avoid undesired adverse effects [58 (4)]. When using the PDL, temporary purpura is expected when treating PWBs and IHs. Purpura usually resolves within 7–14 days [39 (2a)]. A gray color may indicate epidermal damage, and treatment should be stopped or settings adjusted. The 755-nm alexandrite laser has a treatment end point of a transient gray discoloration of the skin followed by purpura. Persistent gray discoloration is not desired and may result in adverse effects including scarring.

Potential adverse effects of laser therapy include blistering, erosions or ulcerations, scarring, and hyper- or hypopigmentation. There is low risk of pigment changes and scarring with yellow wavelength lasers, particularly if appropriate cooling and longer pulse durations are implemented as mentioned above [59 (2b)]. Darkly pigmented skin and extremity lesions have a higher risk of adverse effects. As noted above, proliferating IHs are at increased risk for ulceration, which often results in scarring, and treatment at this stage needs to be approached with caution [60 (4)]. Laser treatment of vascular lesions with longer wavelengths, especially the 1064-nm Nd:YAG, carries increased risk of ulceration and scarring and should be considered only by more experienced laser surgeons.

Hair loss can occur with any millisecond laser or IPL, especially in patients with darker hair, and as such, hair-bearing areas are generally avoided. Applying aloe vera gel or Vaseline to the eyebrows and eyelashes when treating near these areas can help protect the superficial follicles that are most susceptible to hair loss during laser treatment.

Appropriate eye protection as described above is essential and allows avoidance of eye injury.

Postoperative Care and Follow-Up

Laser treatment sessions for PWBs are typically scheduled at 4–6 week intervals, and many treatments are often required [38 (2a)]. Multiple treatments are also required for IHs and may be done at 2–4 week intervals for rapidly proliferating/ulcerated lesions or 4–6-week intervals for stable/involuting lesions. Multiple treatments may also be required to achieve the best results for telangiectasias and can be performed at 4–6-week intervals.

During follow-up visits, patients or their parents should be asked about bruising or blistering, and the skin should be evaluated for scarring, atrophy, and dyspigmentation. As previously noted, patients with darker skin tones are at greater risk for pigmentary change and scarring. Daily application of a bleaching cream, such as hydroquinone 4%, after the resolution of any purpura and between treatment sessions can be used to decrease this risk or to treat post-inflammatory hyperpigmentation. Sun protection for treatment areas before and after treatment can decrease melanin and improve treatment results (greater efficacy with diminished risk of adverse effects).

Alternative Procedures and Modifications

Port Wine Birthmarks

Lasers and light-based devices are clearly the standard of care for PWBs in the United States and Europe. Photodynamic therapy (PDT) has also been used to treat PWBs. It is most commonly used in China. One study found PDT to be at least as effective as PDL in terms of blanching rate and side effects for the treatment of neck and upper arm lesions [61 (3b)]. Another study determined that fewer treatment sessions were required using PDT for PWBs compared to PDL for the successful treatment of superficial lesions and improvement of thick lesions [62 (3b)]. PDT has rarely been used in the United States as the administration of systemic photosensitizers results in prolonged photosensitivity for weeks after the procedure, and there is a risk of multiple side effects including deep vascular injury, which can result in significant scarring [62 (3b)]. Optimization of the parameters of PDT or its combination with PDL may improve the utility of PDT for PWBs [63–65 (2b, 3b, 3a)].

Angiogenesis inhibitors, such as rapamycin, in combination with PDL, have also been evaluated. This is an off-label use of rapamycin. Topical and oral formulations of rapamycin have been studied; use of topically applied medication has the benefit of minimal systemic absorption and few side effects. Multiple studies have demonstrated that topical rapamycin can suppress angiogenesis pathways induced by PDL [66, 67 (1b, 5)] and that the combination of topical rapamycin and PDL can, at least in some cases, provide improved treatment results. Further studies are necessary to determine the effectiveness of combined device/antiangiogenic agents and to find an optimal combination and protocol.

Infantile Hemangiomas

Oral propranolol has been established as a safe and effective treatment and is the first-line therapy for IHs. Clinicians treating IHs must be familiar with and consider the option of beta-blockers for IHs. In a meta-analysis, propranolol showed superior reduction in IH size compared to observation, placebo, and oral corticosteroids [68 (2a)]. A recent randomized, controlled trial on 460 infants showed propranolol to be effective in doses up to 3 mg/kg/day for 6 months [69 (1b)]. Side effects of nonselective beta-blockers include dizziness, weakness, trouble breathing, shortness of breath, chest pain, changes in heart rate, and seizures. Beta-blockers are generally well tolerated in infants for which there are no contraindica-

tions for treatment. Topical beta-blockers are another option and have also been demonstrated to provide benefit in treatment of IHs. A randomized controlled trial using topical timolol gel on superficial hemangiomas on 41 infants aged 5–24 weeks showed significant color change and reduction in size after 24 weeks of treatment with minimal variation in blood pressure or heart rate [70 (1b)]. Another randomized controlled trial using atenolol, a cardio-selective beta-blocker with less respiratory comorbidities than propranolol, showed that oral atenolol was at least as effective as oral propranolol in the treatment of IH [71 (2b)].

Combining beta-blockers with laser may achieve enhanced results compared to either treatment option alone. A study by Reddy et al. showed that facial IH treated with both oral propranolol and PDL showed more complete resolution with propranolol treatment needed for a shorter period of time (595-nm PDL, 8.5–12 J/cm^2, pulse duration 0.45–1.5 ms, 7 mm spot size, dynamic cooling device spray duration of 30 ms and delay of 30 ms) [72 (2b)]. In another randomized, controlled trial, timolol plus PDL was superior to PDL alone in effecting resolution of IHs (585-nm PDL, 9 J/cm^2, pulse duration 0.45 ms, 5 mm spot size, no cooling) described [73 (1b)].

Telangiectasias

Telangiectasias often do not require treatment. Laser therapy is a quick and effective treatment, when desired. Electrocautery can be considered as an alternative when there are a small number of superficial lesions and/or a laser is not available.

Observations and Recommendations (Table 16.1)

Table 16.1 Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Vascular lesions including PWBs, IHs, and telangiectasias are among the most common indications for laser treatments	B
Epidermal cooling techniques minimize pigmentary changes and scarring and are important to use during laser treatment of cutaneous vascular lesions	B
The risk of scarring and pigmentary change is increased in patients with darker skin tones and when using deeper penetrating lasers	C
Port wine birthmarks	
PDLs are commonly used for PWBs, but multiple vascular targeting devices can be used	B
Resistant, nodular and/or hypertrophic lesions can be treated with deeper penetrating lasers but should be used cautiously by experienced clinicians due to increased risk of adverse effects	C
Multiple treatments are required and some recurrence is common	C
Treatment at an early age may enhance response	C
Infantile hemangiomas	
Infantile hemangiomas that are superficial are the best candidates for laser therapy	C
PDL is the most common laser used for treatment	C
Combining beta-blockers with laser therapy should be considered and may achieve quicker and more complete response	B
Telangiectasias	
Laser therapy is an effective, and when performed correctly, safe treatment for telangiectasias	B
Multiple devices can be used including PDL, 532-nm lasers, and IPL	B
Development of new lesions is common	B

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Self-Assessment Questions

1. Which of the following increases the potential for side effects including discoloration, ulceration, or scarring when treating vascular lesions?
   (a) Use of longer wavelength lasers (such as 1064 nm)
   (b) Use of small spot size with high fluences
   (c) Turning off epidermal cooling
   (d) Treatment of patients with darker skin types
   (e) All of the above
2. All are factors that portend to an improved response to PDL treatment of PWBs except:
   (a) Small size (<20 cm^2)
   (b) Nodular lesions
   (c) Treatment at a young age
   (d) Lesion above a bony area
   (e) Lesion near the peripheral face
3. Which of the following statements regarding laser treatment of PWBs is false?
   (a) A desired end point is purpura without cutaneous whitening/graying.
   (b) The 755-nm alexandrite laser can be used for hypertrophic lesions resistant to PDL treatment.
   (c) Both PDL and IPL treatments have been shown to produce good clearance rates of PWBs.
   (d) Lesions may recur after treatment.
   (e) None; all of the above statements are true.
4. All of the following are indications to treat IHs early except for:
   (a) Lesions in the anogenital region
   (b) Lesions near the mouth
   (c) Non-ulcerated lesions near an extremity
   (d) Ulcerating lesions
   (e) Lesions near an eye
5. Which of the following is/are false regarding the treatment of IHs?
   (a) Propranolol used in combination with PDL for IH has been shown to be as efficacious as propranolol alone.
   (b) It has been shown that topical timolol plus PDL is superior to PDL alone.
   (c) PDL is the first-line therapy for IH.
   (d) Mixed superficial–deep lesions treated with PDL have not been shown to exhibit complete clearance.
   (e) a and c.
6. Which of the following devices can be used to treat telangiectasias?
   (a) PDL
   (b) Long-pulsed 532-nm laser
   (c) IPL
   (d) Long-pulsed 1064-nm laser
   (e) All of the above

Correct Answers

1. e: Risks of discoloration and scarring are higher with longer wavelengths such as the 1064-nm Nd:YAG and 755-nm alexandrite lasers. The use of large spot sizes, low fluences, and epidermal cooling techniques helps to minimize the risk of ulceration and scarring. Patients with darker skin types have increased melanin and are at higher risk of adverse effects.
2. b: Factors that lead to improved response to PDL treatments of PWBs include small size (<20 cm^2), a location directly above a bony area (particularly the central forehead), and treatment at a young age. Studies have shown that PWBs located on the trunk, extremities, central face (medial cheek, upper lip, nose) rather than on other facial areas, and those lesions that are violaceous or nodular are more difficult to treat.
3. e: For PDL treatment of PWBs, purpura without cutaneous whitening or graying is the desired end point. Other laser therapies can be utilized in patients who fail to improve with PDL therapy alone. Near-infrared lasers including the 1064-nm Nd:YAG and 755-nm alexandrite lasers have been shown to improve the appearance of hypertrophic PWBs, particularly lesions resistant to other laser treatments. More patients have experienced better clearance rates with PDL compared to IPL, but clearance rates following both treatments have shown good results. Lesions may recur after treatment. In a 10-year follow-up study of 51 patients treated with PDLs for PWBs, lesions were found to be significantly darker at follow-up than at the time of the last treatment, although the lesions did remain significantly lighter than prior to initial therapy.
4. c: Treatment of IH should be aimed at stopping progression of lesions early on to minimize tissue damage and therefore avoiding the need for long-term treatment in the future. Intervention is recommended for lesions that ulcerate or impact functionality, such as feeding or vision.
5. e: Propranolol can be used in combination with PDL. A retrospective study showed that complete clearance occurred more commonly when IHs were treated with propranolol and PDLs concurrently compared with IHs treated with propranolol followed by PDLs and IHs treated with propranolol alone. In a randomized, controlled trial, timolol plus PDL was superior to PDL alone in effecting resolution of IHs. Oral propranolol has been established as a safe and effective treatment and is the first-line therapy for IH (not PDL). In a meta-analysis, propranolol showed superior reduction in IH size compared to observation, placebo, and oral corticosteroids. Superficial IH, as compared to deeper lesions, responds better to PDL treatment. This is due to the limited depth of penetration of PDL light. Studies have shown complete clearance of superficial IH, while mixed superficial-deep lesions exhibited less complete clearance.
6. e: All of the above devices can be used to treat telangiectasias. Lasers are the most common treatment for multiple or large areas of telangiectasias and can also be used when other modalities, such as electrocautery, have failed. Treatment/device selection and settings should be individualized to conform to patient's skin type, vessel characteristics, and healing time tolerance.

17 Pigment Lasers and Light Treatments

Daniel A. Belkin and Roy G. Geronemus

Abstract

Altered or uneven pigmentation is a common reason to present to a dermatologist or laser surgeon. Modalities available for treating pigmentary alterations include medication, destruction, excision, resurfacing lasers, and lasers specifically targeted to pigment. The last modality will be the focus of this chapter.

Keywords

Hyperpigmentation · Q-switched lasers · Picosecond lasers · Tattoo lasers · Light treatments

Introduction

Altered or uneven pigmentation is a common reason to present to a dermatologist or laser surgeon. Modalities available for treating pigmentary alterations include medication, destruction, excision, resurfacing lasers, and lasers specifically targeted to pigment. The last modality will be the focus of this chapter.

The principle of treatment with pigment lasers involves the photothermolysis of pigment, whereby absorption of light energy by the chromophore produces heat, fragmentation, and destruction. In most cases, the chromophore is melanin. In cases of exogenous sources of pigmentation, such as a tattoo, other pigments are targeted. Melanin is one of the main endogenous chromophores of the skin and is most concentrated at the basal layer [1]. It has a broad absorption spectrum, from 250 to 1200 nanometers (nm) [1], absorbing light avidly in ultraviolet wavelengths, less so in visible light wavelengths, and still less in the infrared range (Fig. 17.1). Conversely, depth of penetration of laser light into the skin increases with increasing wavelengths in this range. In general, the appropriate wavelength for the condition at hand should balance the avidity of melanin absorption with the depth of penetration of light.

Laser media used for the purpose of treating pigments produce light that falls in the visible and near-infrared spectra. Lasers include the ruby (producing light at 694 nm), alexandrite (755 nm), neodymium-doped yttrium aluminum garnet (Nd:YAG; 1064 nm), and the Nd:YAG that is frequency-doubled with a potassium titanyl phosphate (KTP) crystal (532 nm). These lasers can be used in their "long-pulsed" forms, which produce pulses in the millisecond range,

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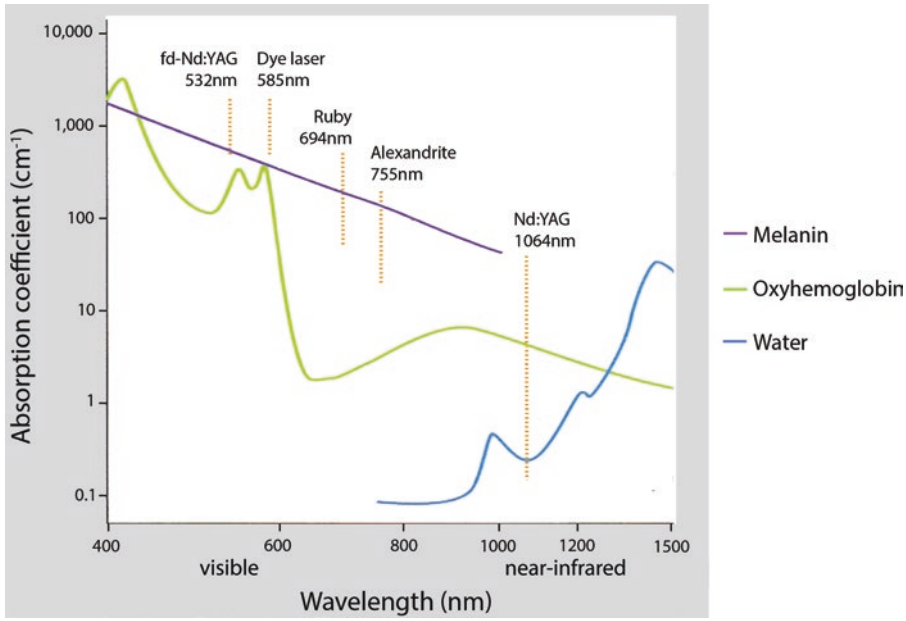

Fig. 17.1 The absorption spectra of three important skin chromophores with superimposed wavelengths of common pigment lasers. (Adapted from Roy G. Geronemus, *Lasers & Related Technologies in Dermatology*, McGraw-Hill 2013)

and in their "quality-switched" (Q-switched) forms, which traditionally produce pulses in the nanosecond range. More recently, picosecond devices are available that produce extremely short pulse widths in the picosecond range. Because melanosomes and tattoo pigments are small targets with short thermal relaxation times, short pulse durations are required, so Q-switched and picosecond lasers are most frequently used. Long-pulsed lasers with pulses in the millisecond range are used for larger chromophores that require wider heat damage, such as the hair bulb in laser hair removal or vessels in vascular lesions.

Although this chapter will attempt to organize and synthesize the current evidence regarding the use of pigment lasers and light therapies, it is important to remember that evidence is limited in this area. In large part, this field has relied on expert opinion, case reports, and case series. Furthermore, laser surgeons have techniques that are non-standardized, and laser devices, settings, and protocols vary across available studies. However, reviewing the available evidence should give the reader a general sense of the current state of the art.

Q-switched Pigment Lasers

Melanosomes have a thermal relaxation time that ranges from 50 to 500 ns [2]. Q-switched lasers, traditionally with nanosecond pulse widths, can selectively target melanosomes with minimal diffusion of heat and thermal damage [3]. These are therefore the "go-to" lasers for pigmentary disorders. Vejjabhinanta and colleagues treated freckles with Q-switched 532-nm light, with 10-ns pulse width, and long-pulsed 532-nm light, with 10-ms pulse width; they found that the Q-switched laser produced immediate whitening and good efficacy, while the long-pulsed setting did not (4) [1]. Since they are targeted toward the pigment, Q-switched lasers also tend to be more effective than nonspecific resurfacing. Schoenewolf and colleagues compared Q-switched ruby laser with fractional ablative carbon dioxide (CO_2) laser for the treatment of solar lentigines on the dorsal

hands of 11 patients and found the Q-switched ruby laser significantly more effective (4) [4].

Conditions that may respond to Q-switched lasers include those of increased epidermal or dermal melanin, such as solar lentigo, lentigo simplex, café au lait macule (CALM), dermal melanocytosis (including nevus of Ota, nevus of Ito, and Hori's nevus), and post-inflammatory hyperpigmentation (PIH). Besides the condition to be treated, the most important variable in determining the appropriate treatment settings is the Fitzpatrick skin type (FST) of the patient. Darker skin types are more challenging to treat, because higher pigment content in background skin competitively absorbs laser energy [5]. Not only is there increased epidermal melanin in darker skin, but there are larger and more widely distributed melanosomes and a more labile melanocytic and fibroblast response [6]. Due to these features, there is both an increased prevalence of pigmentary disorders in nonwhite individuals and a greater risk of post-procedure pigmentary alteration [6]. Among individuals with skin of color, those with Asian type IV skin are well-represented in the literature. There are few studies in those of African ancestry or type V and VI skin [6].

Q-switched Ruby and Alexandrite

The red lasers ruby, at 694 nm, and alexandrite, at 755 nm, are highly effective for disorders of hyperpigmentation. Red light can penetrate relatively deep in the dermis compared to the green light of 532 nm and is absorbed by melanin with high avidity compared with the near-infrared light of 1064 nm.

Ruby has been used for multiple disorders in both white skin and skin of color, though it tends to produce more pigmentary side effects in the latter. Multiple case series report success in treating lentigines, CALMs, and nevus of Ota. Sadighha and colleagues ran a controlled comparison study in 91 patients with FST II-IV with solar lentigines and found that one or two treatments with Q-switched ruby laser cleared all lesions (2b) [7]. It caused post-inflammatory pigmentary alteration, mainly hyperpigmentation, in 7.8% of FST II patients, 9.8% of FST III patients, and 16.6% in FST IV patients, all of whom improved over 6 months [7]. Mucosal pigmented lesions respond very well to ruby laser as well (5) [8].

Treatment of nevus of Ota is frequent in the literature given it is relatively common, cosmetically disfiguring, and challenging to treat. It is characterized by excess dermal pigment, and it tends to occur in FST IV or higher; this combination makes safe treatment more difficult, and hyper- and hypopigmentation are common side effects. Kang et al. reported PIH in 55% of Asian patients treated with Q-switched alexandrite for nevus of Ota, though all were resolved within 4 months (4) [9]. Suh reported hyper- or hypopigmentation in about 25% of 87 Asian patients with nevus of Ota treated with alexandrite, though all cases were mild and transient (4) [10]. In 81 Korean patients, most patients achieved at least 50% clearance, though 40% had transient hyperpigmentation lasting for 2–6 months (4) [11]. In a study of 102 Japanese patients with nevus of Ota treated 12 months prior with Q-switched ruby laser, 16.8% had persistent hypopigmentation and 5.9% had persistent hyperpigmentation, suggesting that though ruby is effective, pigmentary alterations can be permanent (4) [12].

Despite higher incidences of pigmentary side effects in skin of color, many have reported good results with ruby and alexandrite. A large retrospective study in China with 602 patients confirmed good efficacy of Q-switched alexandrite laser for nevus of Ota, with only seven cases (1%) of transient hypopigmentation and only five cases (1%) of hyperpigmentation (2b) [13]. In 114 Japanese patients, ruby was safe and effective for lightening nevus of Ota, generally by more than 70% in patients who had four to five treatments, with only eight patients (7%) having transient PIH [14]. In one of our early studies using Q-switched ruby to treat nevus of Ota in mostly skin of color, all patients had at least 50% clearance with two of 15 (13%) having pigmentary alteration post-procedure (4) [15]. Alster and Williams reported seven patients with skin of color, five of which had 100% clear-

ance of nevus of Ota, with no incidence of pigmentary complications with Q-switched alexandrite (4) [16]. One case report showed effective treatment with no post-procedure pigmentary alteration in the treatment of facial lentigines in an Afro-Caribbean woman with inherited patterned lentiginosis after four sessions of the Q-switched ruby laser (4) [17]. Treating with Q-switched laser earlier in childhood seems to reduce risk of complications. In a study of 46 children and 107 adults who had achieved 75% clearance or more, complications were only 4.8% in the younger group compared with 22.4% in the older age group (2b) [18]. Unfortunately, it is likely that even after complete clearance of nevus of Ota, recurrence can occur (4) [19].

Alternatives have been tried in skin of color in hopes of producing fewer side effects, such as the Q-switched Nd:YAG, intense pulsed light (IPL), and picosecond devices. Because the Q-switched Nd:YAG at 1064 nm penetrates deeper and is absorbed by melanin less avidly, it provides some inherent epidermal protection. However, Q-switched ruby seems to produce better results. Chang and colleagues performed a retrospective review of 94 patients of Asian descent with nevus of Ota treated with Q-switched ruby laser or Q-switched Nd:YAG and found that clearing and fading was clinically and statistically significantly better in subjects treated with ruby [20]. Post-inflammatory hyperpigmentation (PIH) was comparable in both groups and transient [20]. Chan et al. compared the efficacy of Q-switched alexandrite and Q-switched Nd:YAG in Asian patients with nevus of Ota and though there was a trend toward lower efficacy and more complications with alexandrite, the difference was clinically minimal (4) [21]. In our work in nevus of Ota, we have seen good efficacy and safety using Q-switched ruby in FST IV and Q-switched 1064 nm in FST V and FST VI. In 24 children with skin of color and nevus of Ota treated in this way, there was over 50% improvement in 86% of patients with minimal lasting pigmentary alteration [22]. In a comparison between Q-switched alexandrite and intense pulsed light (IPL) for ephelides and lentigines in Asian patients, results differed based on the lesion type (2b) [23]. Alexandrite was superior to IPL for both ephelides and lentigines, but while safe in ephelides, it caused PIH in nearly half of patients with lentigines. The authors concluded that Q-switched alexandrite was better for ephelides but that because of safety, IPL should be used for lentigines. Finally, in comparison with picosecond devices, our group found that while Q-switched lasers seemed to fare better than picosecond in the clearance of pigmentary disorders in FST III–VI, they caused a high rate of side effects in darker-skinned groups (4) [24]. Sixteen percent of patients treated with Q-switched laser had lasting dyspigmentation, and all were FST V or FST VI [24]. Pigmentary side effects with 755 nm picosecond laser, on the other hand, were temporary and resolved with no intervention [24].

One of the most challenging conditions in dermatology to manage is melasma. Though our group favors low-density low-energy nonablative resurfacing for this condition, others have tried Q-switched laser with variable outcome. Jang et al. showed mild efficacy of low-dose Q-switched ruby laser in 15 Korean patients with melasma (4) [25]. Q-switched ruby combined with intense pulsed light (IPL) was used by Park et al. in treating Asian patients with a variety of types of complex dyspigmentation, including melasma, solar lentigines, ephelides, and Hori's nevus (4) [3]. Sixty percent of patients achieved 76–100% improvement with minimal side effects. Three patients had transient PIH (12%) and one patient (4%) had hypopigmentation. Our group frequently uses low-density low-energy 1927 nm fractional resurfacing for the treatment of melasma in all skin types. In a series of 23 patients treated with this method, 10 of which had melasma and the rest with PIH or other photo-induced pigmentation, we found an increase in improvement with each treatment session, with an average of moderate to marked improvement seen after the sixth visit [26]. There was transient PIH in one (4%) patient. In clinical practice, we tend to combine laser therapy with adjunctive topical depigmenting agents or oral tranexamic acid.

An important pigmentary abnormality in Asian patients is Hori's nevus, also known as acquired bilateral nevus of Ota-like macules. It is notoriously difficult to treat, and laser treatment frequently leaves PIH. Lee and colleagues treated 82 patients with either Hori's nevus or nevus of Ota with Q-switched alexandrite laser and found more post-procedure erythema and PIH in the Hori's nevus group (2b) [27]. Interestingly, they found that the rate of complications seemed to correlate with the extent to which dermal melanocytes resided in a perivascular distribution on histologic examination, which was more often the case in Hori's nevus. In contrast, in nevus of Ota, dermal melanocytes were more frequently scattered throughout [27]. In another study by Lam et al., Q-switched alexandrite, though achieving decent clearance, produced high numbers of pigmentary alteration in 32 Chinese women (4) [28]. Though more than 80% of patients had more than 50% clearance, 12.5% had hyperpigmentation and 50% had hypopigmentation [28]. Some feel that in this condition and perhaps in other conditions of complex dyspigmentation, it is helpful to remove epidermal pigment before treating dermal pigment with laser. Two studies combining Q-switched ruby laser with topical bleaching agents (tretinoin and hydroquinone) achieved successful results with less PIH than is often seen when treating Hori's nevus (4) [29, 30]. Similarly, epidermal ablation prior to Q-switched ruby laser with one pass of a scanned carbon dioxide laser was significantly more successful in 13 Thai women with Hori's nevus (2b) [31].

Q-switched Nd:YAG

Q-switched Nd:YAG at 1064 nm is frequently used to treat pigmented lesions in darker skin types, because the longer wavelength is associated with less epidermal absorption and greater safety. Melasma, nevus of Ota, Hori's nevus, and PIH are four pigmentary disorders that are particularly problematic in darker-skinned individuals and where this laser has frequently been used. Alexis has the following recommendations for treating darker skin types: (1) use longer wavelengths; (2) use lower fluences and longer pulse durations; (3) emphasize pre- and post-treatment sun protection; (4) consider pre- and post-treatment bleaching agents; (5) optimize epidermal cooling; and (6) consider topical steroids post-procedure (5) [6].

Reports of treating melasma with this laser are conflicting [2, 32]. In a study of 22 Asian patients with melasma treated with low-fluence 1064 nm Nd:YAG, all patients had recurrence of melasma despite temporary improvement, three (14%) developed hypopigmentation, and four (18%) developed rebound hyperpigmentation (4) [2]. The authors therefore concluded that Q-switched Nd:YAG treatment for melasma in Asians was not worth doing. In another study of 25 Asian patients with melasma, 72% had at least 50% improvement with low-fluence Q-switched 1064 nm laser, with only two patients suffering from post-treatment pigmentary alteration. The authors here felt that the treatment is effective (4) [32]. Vachiramon et al. studied this laser in 12 Asian men with melasma, randomized to five sessions of Q-switched Nd:YAG plus 30% glycolic acid peel on one side and the laser alone on the other (2b) [33]. The adjunctive glycolic acid peel was intended to allow lower fluence and lesser frequency of laser treatments. While there was a significant improvement in the combined group (and none in the monotherapy group), there were two cases of hyperpigmentation and one case of guttate hypopigmentation that did improve in the study period. The authors did not feel the risk of side effects was worth the short-lived benefits of this treatment [33]. The same group also studied 20 women with melasma, comparing laser plus IPL with laser alone in the same split-face method, with better improvement on the combined side and without pigmentary complications (2b) [34]. The authors emphasize the importance of low fluence; here it was 2.6–2.8 J/cm [2]. Low-dose Q-switched 1064-nm Nd:YAG may fragment melanosomes without being strong enough to destroy cells [2]. Still others have shown that low-flu-

ence Q-switched Nd:YAG is of benefit (4) [35, 36]. Choi et al. combined Q-switched Nd:YAG with long-pulsed Nd:YAG in 30 patients with melasma aggravated from prior laser treatment with very good results (4) [37]. Eighty percent had 76–100% improvement, and the rest had over 50% improvement. The authors note that the addition of the long-pulsed Nd:YAG may prevent rebound hyperpigmentation, and the combination is a safe and effective salvage treatment for those whose melasma has worsened from prior laser treatments.

In nevus of Ota, Q-switched Nd:YAG is somewhat less efficacious but may reduce risk. In our practice, we use this laser for FST V and FST VI while using ruby for most FST IV as described above. In a large series of 171 patients with nevus of Ota by Chan et al., there was no significant difference in the complication rate between Q-switched Nd:YAG and Q-switched alexandrite, but there was a significantly higher incidence of complications, mainly hypopigmentation, in patients who had received both treatments (4) [38]. In Hori's nevus, Q-switched Nd:YAG was modestly effective with 50% of patients achieving good to excellent results in a series of 66 patients (4) [39]. The authors noted better clearance is seen when this laser is used for nevus of Ota. Ee et al. showed that Q-switched 1064-nm treatment alone is not as effective for Hori's nevus than when combined with Q-switched 532 nm (2b) [40]. Though combined treatment produced higher incidence of mild PIH, it was resolved at 2 months and felt by the authors to be worth the increased efficacy.

PIH can be challenging to treat. In our practice, similar to melasma, we use low-energy low-density 1927 nm fractional nonablative resurfacing along with topical bleaching agents. A prospective randomized controlled trial by Kim and Cho found that low-fluence Q-switched Nd:YAG was clinically and statistically significantly more effective in reducing PIH in type IV and type V Korean patients than acne surgery with intralesional corticosteroids (2b) [41]. Interestingly, it was also more effective at reducing inflammatory acne. In our group, we have also noticed the benefit of Q-switched 1064 nm, together with long-pulsed Nd:YAG, for inflammatory acne.

Q-switched Frequency-Doubled Nd:YAG

In our practice, we use the Q-switched frequency-doubled 532 nm Nd:YAG for superficial pigmentary abnormalities, such as solar lentigines, in skin of color (Fig. 17.2). Though this wavelength is absorbed avidly by melanin, it penetrates superficially. Furthermore, the shape of the beam is flat-topped, rather than Gaussian, which minimizes nonspecific heat injury (from personal conversations; 5). Others have used 532 nm

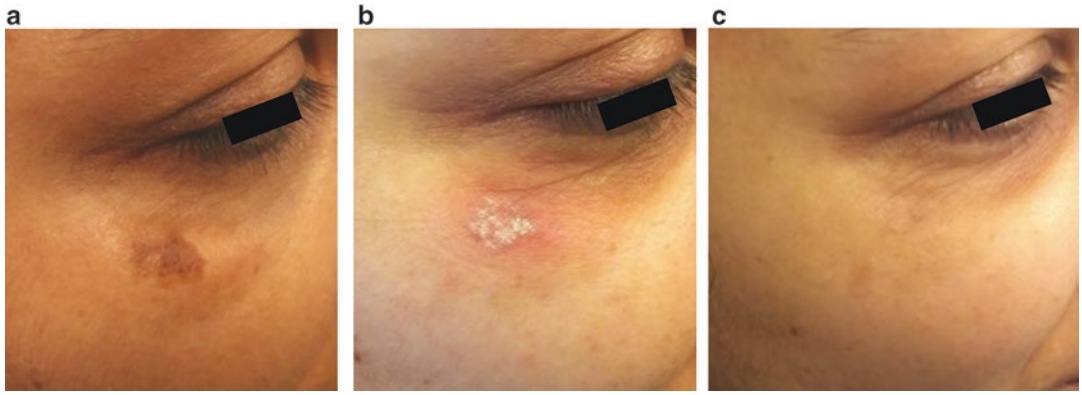

Fig. 17.2 A solar lentigo in a patient with Fitzpatrick type V skin at baseline (**a**), immediately after a subsequent treatment with appropriate whitening response (**b**), and 1 month after three treatments with a Q-switched 532-nm laser (**c**)

for Asian patients with good efficacy, though with some sacrifice in efficacy compared to the ruby. Noh et al. ran a randomized, split-face, double-blinded comparative study to assess a Q-switched 532 nm Nd:YAG against a Q-switched 660 nm ruby-like laser for solar lentigines in Asian women and found similar improvement with both lasers (2b) [42]. However, there was a trend toward better efficacy of the 660 nm laser, and the improvement was longer lasting with 660 nm. The authors proposed that this was perhaps due to slightly more PIH in the 532 nm group due to superficial vascular damage caused by absorption of 532 nm light by hemoglobin [42]. We have not noticed this phenomenon in our practice. Tse et al. noticed similar findings when comparing ruby to Q-switched 532 nm in 20 patients with several types of pigmented lesions including lentigines, CALMs, and nevus of Ota; both achieved significant lightening but with a slightly better response with the ruby (4) [43]. Hereditary lentigines such as those associated with Peutz-Jeghers syndrome have also been treated with Q-switched frequency-doubled Nd:YAG. Ge et al. found excellent response with more than 75% lesion clearance in 8 of the 11 patients and at least 50% clearance in the rest after 2–6 treatments (4) [44].

Several investigators have added adjunctive treatments to further improve efficacy or safety. Park et al. investigated whether a cream containing epidermal growth factor (Easydew Repair Control, Daewoong Pharmaceutical Co, Seoul, Korea) twice daily postoperatively could prevent PIH after treatment with Q-switched 532 nm for lentigines in 25 Asian patients (2b) [45]. They found that PIH was significantly less in those who applied the cream, with 7.7% incidence, compared with those who applied a control cream, with 50% incidence [45]. Another group ran a split-face controlled study on Q-switched 532 nm laser alone for solar lentigines in Asian patients versus laser plus an Erbium-doped YAG "micropeel" (2b) [46]. They found that though both techniques reduced pigment, adding the epidermal ablation significantly increased PIH and should not be used.

Picosecond Lasers

For Pigmentary Disorders

All the benefits of the picosecond devices are still being elucidated. Our group evaluated 755 nm picosecond laser as part of a chart review of 42 patients with skin types III through VI treated with pigment lasers (4) [24]. Though clearance was generally better with Q-switched lasers, the picosecond laser was safer, with only transient post-procedure dyspigmentation compared with some in Q-switched lasers that was not seen to resolve. Among conditions treated, picosecond seemed to be most consistently effective for nevus of Ota, with similar efficacy to Q-switched lasers. It is likely that with picosecond devices, photomechanical effects enhance clearance of melanin beyond classic photothermal effects, decreasing adverse effects [24]. Interestingly, some of the picosecond subjects had initial apparent exacerbation at 1 month with subsequent improvement at about 3 months. This may be due to aggregation of melanin particles after rupture of melanosomes and then delayed clearance by dermal macrophages and fibroblasts [24]. Chan also found the 755 nm picosecond laser to be highly effective for benign pigmented lesions in Chinese patients, especially nevus of Ota, with lower risk of PIH than Q-switched technology (4) [47]. CALMs responded fairly well, but Hori's nevus was fairly resistant. There was no PIH and only transient hypopigmentation in 2 of 13 (15%) patients [47]. Our group has also studied 532 nm picosecond laser for lentigines on the dorsal hands in Caucasian skin types, with slow but excellent results; this modality seems to be highly effective and extremely safe (unpublished results; Fig. 17.3).

Our group also showed that the picosecond laser with the diffractive lens array ("Focus" handpiece) is safe in skin of color [48]. A retrospective review identified 56 patients with skin types IV to VI who had undergone treatment for various conditions, about 10% of which were pigmentary abnormalities. Six patients reported hyperpigmentation that resolved within a few days to 2 weeks, and two patients reported hyperpigmentation that took 1 month to resolve (4) [48].

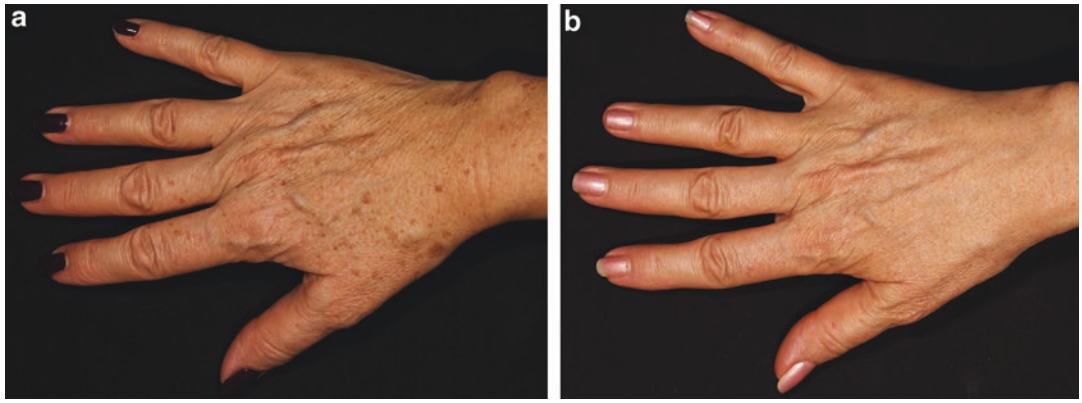

Fig. 17.3 Solar lentigines in a patient with Fitzpatrick type II skin at baseline (**a**) and 3 months after four treatments with a 532-nm picosecond laser (**b**)

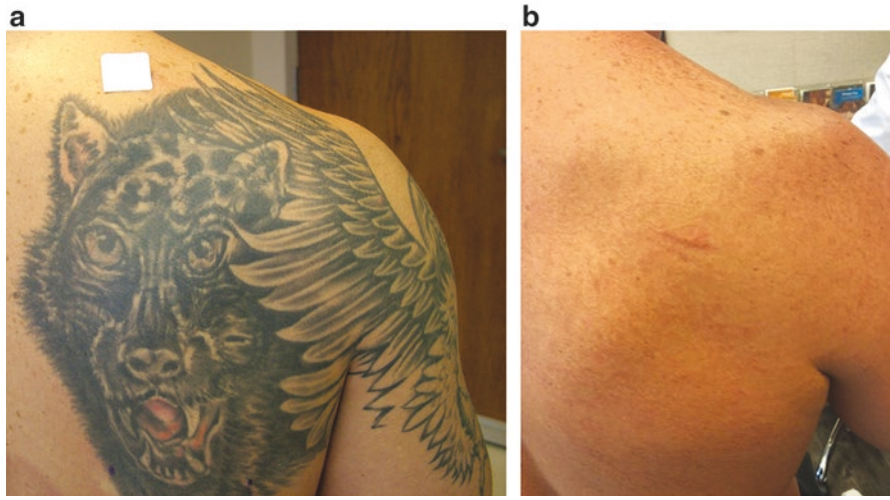

Fig. 17.4 A large predominantly black tattoo at baseline (**a**) and after 12 treatments with a 755-nm picosecond laser (**b**)

Tattoo Lasers

It is generally agreed that picosecond lasers are superior to Q-switched lasers for tattoo removal (Fig. 17.4). Q-switched lasers rely on photothermal damage as the main mechanism of pigment destruction, so adverse reactions from thermal damage can occur, especially in darker skin types. This manifests as pigmentary alteration, textural change, and scarring. Hypopigmentation has been reported in up to 50% of patients treated with Q-switched alexandrite and textural changes reported in up to 12% (3a) [49].

With picosecond devices, photoacoustic fragmentation enhances photothermal effect, which increases efficacy while reducing nonspecific heat damage. The extremely short pulse durations create acoustic waves that further fracture pigment particles. Computer simulations support this [50]. Studies have shown that tattoo particles are more effectively cleared with picosecond pulses compared to nanosecond (2b) [51, 52]. Saedi et al. found that in 12 patients, a 755-nm picosecond device was able to achieve 75% clearance in all patients with black or blue tattoos at an average of 4.25 treatments with most having near-complete

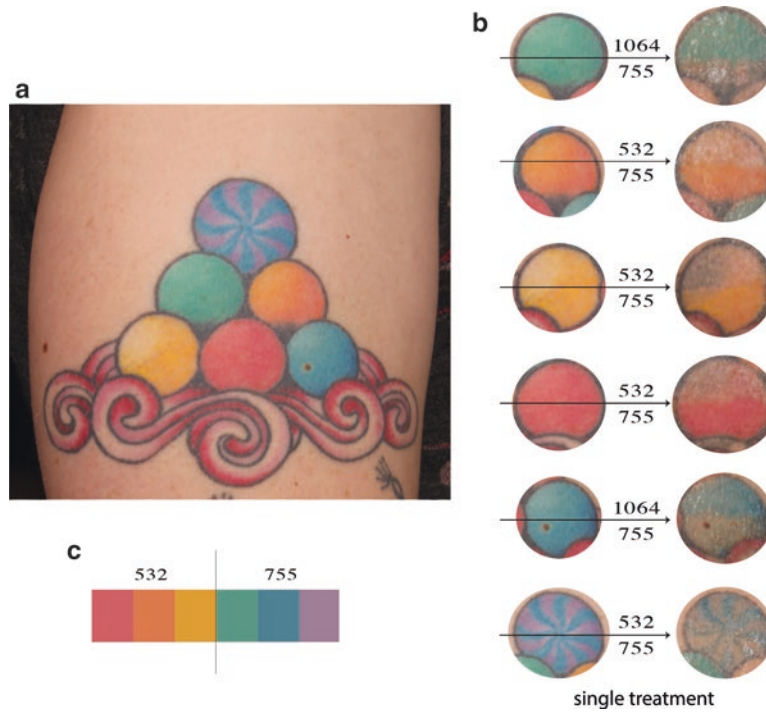

Fig. 17.5 A multi-colored tattoo (**a**) demonstrates variable efficacy of picosecond laser by color. For green and blue, 755 nm and 1064 nm were compared, and for orange, yellow, red, and purple, 532 nm and 755 nm were compared (**b**). In a single treatment, red, orange, and yellow responded best to 532 nm whereas green, blue, and purple responded best to 755 nm (**c**)

clearance (4) [53]. Compared to historical controls, picosecond treatments appear to be more rapid with Q-switched devices taking on average 8–9 treatments for 95% clearance [53].

The type of laser used for tattoo removal depends on the color of the targeted pigment. Our group demonstrated successful treatment of green and blue tattoos using the picosecond alexandrite [54]. Clearance of at least 75%, and in most cases near-complete clearance, was achieved after only one or two treatments (4) [54]. In practice, we have found picosecond technology to be a major game-changer when it comes to green and blue tattoos, which were previously quite difficult to remove. Our group also showed that yellow tattoos can be cleared relatively easily with picosecond technology, in this case a frequency-doubled Nd:YAG at 532-nm wavelength (4) [55]. Six patients achieved over 75% clearance of yellow tattoos with two to four treatments [55]. We are currently running a trial using a 1064 nm picosecond device to clear black tattoos in FST V and FST VI. In our experience, 755 nm is the most effective device for blue, green, purple, and black ink, and 532 nm is the most effective device for red, yellow, and orange ink (Fig. 17.5).

Other Treatments

IPL and pulsed dye laser (PDL), though not generally considered pigment lasers, have been used for pigmented lesions. IPL is not a laser, as it uses a polychromatic light with a broad band of wavelengths. Filters allow the exclusion of lower wavelengths to restrict output and to some extent mimic laser therapy. PDL is a laser comprised of yellow light at 585 nm or 595 nm, which corresponds with a peak in the absorption spectrum of oxyhemoglobin and is therefore used most commonly for vascular lesions. Because melanin does avidly absorb light at this wavelength, epidermal protection is built into these devices with either dynamic or contact cooling.

IPL with a cut-off filter of 560 nm in 3–5 treatments was used for solar lentigines and ephelides in 18 Japanese patients (4) [56]. There was modest efficacy, with 28% of patients "markedly improved" and the rest with no to slight improvement. There

were no side effects. In another study in 60 Japanese patients with the same protocol, there was modest efficacy, with only about half achieving 50% improvement, though with no side effects. Interestingly, when broken down, those with ephelides did much better with 70–75% of patients achieving 50% improvement (4) [57]. Though these studies showed no pigmentary side effects, IPL should be used cautiously in skin of color and perhaps avoided altogether in FST V and FST VI, due to the risk of hyperpigmentation (5) [6].

PDL has also been studied for treating lentigines in Asian skin. In 18 patients, treatment was compared between Q-switched ruby laser and PDL with diascopy to prevent absorption by oxyhemoglobin (4) [58]. PDL was safer and more effective, with 83% clearance compared with 70% and with no side effects compared with four cases of PIH with Q-switched ruby. A larger series in 54 patients using PDL with diascopy to prevent oxyhemoglobin absorption showed excellent response in 70% and good response in 26%, with PIH occurring in only one (2%) patient (4) [59]. Ho and colleagues compared four lasers for the treatment of lentigines and ephelides in 40 Asian patients, the 595 nm PDL, the 755 nm long-pulsed alexandrite, the 532 nm long-pulsed Nd:YAG, and the Q-switched 532 nm Nd:YAG (4) [60]. All but the long-pulsed alexandrite produced improvement, and though there was 10% incidence of PIH with the Q-switched Nd:YAG, there was none with PDL. They concluded that long-pulsed lasers may be safer in darker skin types.

Conclusion

Treating pigment with laser technology is powerful, but technique- and operator-dependent, and the evidence reflects this. There is a large number of case series, but they use different devices, settings, and treatment protocols, and most lack controls. However, general themes do emerge from the data and give laser practitioners a good idea of what is available and useful.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Q-switched lasers, with nanosecond pulse widths, are the preferred modality for treating disorders of basal layer hyperpigmentation	B
Q-switched ruby is safe and effective for epidermal pigmented lesions, such as solar lentigines, in Caucasian skin	C
Q-switched ruby is effective for nevus of Ota in Asian skin, but the incidence of post-procedure hyper- or hypopigmentation is relatively high	B
Q-switched 694 nm, 1064 nm, and 532 nm appear to be safer than Q-switched alexandrite for treating lentigines in Asian skin	C
Picosecond laser is generally less effective than Q-switched lasers for disorders of endogenous hyperpigmentation but appear to be safer for skin of color	C
Picosecond laser may approach efficacy of Q-switched lasers with nevus of Ota	C
Hori's nevus is more effectively treated with the Q-switched ruby laser when it is combined with either adjunctive bleaching agents or light epidermal ablation	C
If Q-switched lasers are to be used on melasma, low-energy Q-switched 1064 nm appears to be the safest but still with unpredictable results	B
Adding a cream containing epidermal growth factor twice daily post-procedure may help prevent PIH when treating lentigines in type IV skin with Q-switched 532 nm	C
Picosecond laser with diffractive lens array is safe in skin of color	C
Picosecond devices are safer and more effective for tattoo removal than Q-switched devices	B
Yellow, green, and blue tattoos, which were traditionally very difficult to remove, are highly responsive to picosecond lasers	C
Long-pulsed PDL and cautious use of IPL may be useful for lentigines and ephelides in Asian patients	C

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Self-Assessment Questions

1. Why are quality-switched (Q-switched) lasers frequently used for pigmented lesions?
   (a) Because they are higher quality than other laser devices
   (b) Because they produce light in the ultraviolet range
   (c) Because they penetrate deeper than other types of lasers
   (d) Because the thermal relaxation time of melanosomes is in the nanosecond range
   (e) Because the thermal relaxation time of melanosomes is in the millisecond range
2. The following laser does *not* fall in the visible light spectrum:
   (a) Nd:YAG (1064 nm)
   (b) Frequency-doubled Nd:YAG (532 nm)
   (c) Pulsed dye laser (595 nm)
   (d) Ruby (694 nm)
   (e) Alexandrite (755 nm)
3. All of these are benefits of picosecond lasers *except*:
   (a) They produce more rapid clearance of tattoos than Q-switched lasers
   (b) They produce more rapid clearance of pigmented lesions than Q-switched lasers
   (c) They seem to be safer in skin of color than Q-switched lasers
   (d) Photoacoustic effect of short pulse width enhances fragmentation of pigment
   (e) Tattoo colors previously difficult to treat such as green and yellow are now much easier to remove
4. The following are general strategies to increase safety in skin of color *except*:
   (a) Use longer wavelengths
   (b) Use higher fluences
   (c) Use longer pulse widths
   (d) Treat slower
   (e) Consider perioperative bleaching agents
5. Nevus of Ota is treated with all of the following *except*:
   (a) Q-switched ruby laser
   (b) Q-switched alexandrite
   (c) Q-switched 1064-nm Nd:YAG
   (d) Picosecond 755 nm
   (e) Q-switched 532 nm frequency-doubled Nd:YAG

Correct Answers

1. d: Q-switched lasers create pulse widths in the nanosecond range, which corresponds to the thermal relaxation time of melanosomes. They are not necessarily higher quality than other devices, and they generally produce light in the visible and near-infrared spectra. Depth of penetration is more a function of wavelength and fluence.
2. a: Nd:YAG produces laser light at 1064 nm, which falls in the infrared spectrum and cannot be seen by the human eye. Frequency-doubled Nd:YAG produces light at 532 nm, which is a green light. Dye laser produces light at 585 or 595 nm, which is yellow. Ruby and alexandrite produce light at 694 nm and 755 nm, respectively, which are red lights.
3. b: Picosecond technology allows for extremely short pulse durations, which cause fragmentation via photoacoustic effect in addition to photothermal effect. They have changed the treatment of tattoos, allowing for more rapid treatment and treatment of previously difficult colors. For pigmented lesions, case series suggest that though picosecond lasers cause less post-procedure pigmentary alteration, Q-switched lasers still have better efficacy.
4. b: There are several strategies to decrease risk of post-treatment pigmentary alteration in skin of color. Longer wavelengths penetrate more deeply and are absorbed by melanin relatively less, thereby providing some epidermal protection. Longer pulse widths deliver the same energy over more time and can avoid unwanted destruction of melanosomes, which have short thermal relaxation times. Treating slower prevents bulk heating and allows for effective epidermal cooling. Perioperative bleaching agents can help prevent PIH. Lower fluences, not higher fluences, should be used in darker skin types, to prevent nonspecific thermal damage.
5. e: Because nevus of Ota is a disorder characterized by dermal melanocytes, laser light must be able to penetrate into the dermis. The green light of 532 nm will not penetrate far beyond the epidermis. However, the red and near-infrared light of the other options penetrate well into the dermis and will have efficacy for dermal disease.

18 Nonablative Fractional Energy Treatments

Stephanie D. Gan and Jeffrey S. Orringer

Abstract

Nonablative lasers heat but do not vaporize the skin. Many nonablative devices emit light in the infrared portion of the electromagnetic spectrum, including traditional intense pulsed light (IPL, 500–1200 nm) devices, neodymium/yttrium-aluminum-garnet (Nd/YAG, 1064 and 1320 nm), and diode lasers (980 and 1450 nm). The fractionated nonablative resurfacing lasers include the 1550-nm erbium-doped, 1540-nm erbium glass (Er/glass) lasers, and several others. The energy emitted by these nonablative lasers is absorbed by dermal water, leading to tissue heating and subsequent dermal remodeling. In contrast, the ablative devices, such as the carbon dioxide (CO_2) and Erbium/YAG (Er/YAG) lasers, remove the epidermis and dermis during treatment (see Chap. 19). While the results of ablative treatments may be impressive, there is a significant degree of associated postoperative morbidity. By completely preserving the stratum corneum and precisely confining epidermal and dermal coagulation, nonablative fractionated laser (NAFL) treatments often offer satisfactory clinical results with much less postoperative morbidity (roughly 3 days of downtime versus 7) as compared to their ablative counterparts (5) (Hantash and Mahmood, Dermatol Surg 33(5):525–534, 2007). Results from an individual NAFL treatment, as expected, are less dramatic than those from traditional resurfacing lasers, but the side effect profile is significantly more favorable. Due to these advantages, the nonablative methods for skin resurfacing have become a mainstay treatment.

Keywords

Nonablative fractional energy treatments · Nonablative lasers · Nonablative devices · Fractional laser device · Fractional photothermolysis (FP)

Introduction

Nonablative lasers heat but do not vaporize the skin. Many nonablative devices emit light in the infrared portion of the electromagnetic spectrum, including traditional intense pulsed light (IPL, 500–1200 nm) devices, neodymium/yttrium-aluminum-garnet (Nd/YAG, 1064 and 1320 nm), and diode lasers (980 and 1450 nm). The fractionated nonablative resurfacing lasers include the 1550-nm erbium-doped, 1540-nm erbium glass (Er/glass) lasers, and several oth-

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ers. The energy emitted by these nonablative lasers is absorbed by dermal water, leading to tissue heating and subsequent dermal remodeling. In contrast, the ablative devices, such as the carbon dioxide (CO_2) and Erbium:YAG (Er:YAG) lasers, remove the epidermis and dermis during treatment (see Chap. 19). While the results of ablative treatments may be impressive, there is a significant degree of associated postoperative morbidity. By completely preserving the stratum corneum and precisely confining epidermal and dermal coagulation, nonablative fractionated laser (NAFL) treatments often offer satisfactory clinical results with much less postoperative morbidity (roughly 3 days of downtime versus 7) as compared to their ablative counterparts (5) [1]. Results from an individual NAFL treatment, as expected, are less dramatic than those from traditional resurfacing lasers, but the side effect profile is significantly more favorable. Due to these advantages, the nonablative methods for skin resurfacing have become a mainstay treatment.

The first fractional laser device was the Fraxel SR750 Laser™ (Solta, Hayward, CA), a 1550-nm erbium-doped fiber laser system that could be adjusted to vary both depth of laser penetration and the percentage of skin surface area coverage. This allowed for the safe treatment of various skin types. A later model, the Fraxel Re:Store™ (formerly called the SR1500™), was capable of delivering higher fluences (up to 40 J/cm^2), along with the production of wider and deeper zones of thermal injury (up to 40% of surface area coverage and a depth of 1.114 mm). Since then, several companies have produced fractional lasers, such as the Fraxel Re:fine™, an erbium fiber that delivers a 1410-nm wavelength; Fraxel Re:Store Dual,™ combining the 1550-nm erbium-doped fiber laser with a more superficial thulium of 1927-nm wavelength; the Palomar Lux 1540™ (Cynosure, Westford, MA) with an erbium/glass laser; Sciton Halo™ (Sciton, Palo Alto, CA), a hybrid fractional laser combining the 1470-nm diode with the 2940-nm ablative Er/YAG laser; and the ResurFX™ module of the M22 platform (Lumenis, San Jose, CA) with a 1565-nm wavelength, among other devices. These devices deliver energy either via a stamping scanner or a rolling scanner handpiece.

In contrast to traditional full-field lasers that cover 100% of the skin surface, fractional photothermolysis (FP) creates numerous discrete epidermal and dermal microscopic treatment zones (MTZs) that cover a fraction (generally 20–35%) of the skin surface while sparing adjacent skin (5) [2]. The intervening surrounding normal skin acts as a structural reservoir facilitating rapid wound healing through migration of untreated viable tissue. These findings correlate with short-lived post-procedure erythema and edema and limited social downtime.

Histologic examination demonstrates well-defined cylindrical zones of necrosis in the papillary and reticular dermis with an intact stratum corneum, termed microscopic epidermal necrotic debris (MEND). These MENDs contain substantial pigment and epidermal dyskeratotic cells that act as a "melanin shuttle," promoting extrusion of pigment within 1 week after FP. Cellular markers of dermal wound healing and neocollagenesis such as heat shock protein (HSP) 70, matrix metalloproteinase-1, collagen I and III, and procollagen I are expressed within the treatment areas. HSP 47 is required for collagen remodeling and maturation. It becomes generalized throughout the dermis at 1 month and may persist for up to 3 months, indicating ongoing tissue remodeling (5) [1, 3–5]. Given their frequently excellent cosmetic outcomes, favorable safety profile, and shortened recovery time, the NAFL has become a workhorse technology in skin resurfacing.

Indications for Nonablative Fractional Energy Treatments

NAFL technologies have successfully improved photodamage, dyspigmentation, skin texture, rhytides, striae distensae, and scars (5) [6]. Table 18.1 summarizes the main indications of the NAFL and their efficacy. Due to the preservation of the epidermis which facilitates rapid wound healing, NAFL treatments have a favorable safety profile in all skin types, ages, and

Table 18.1 Clinical indications for nonablative fractional energy devices

Indication	Efficacy
Acne scars	Excellent
Surgical, traumatic, and hypertrophic scars	Excellent
Dyschromia or photodamage, facial	Good
Dyschromia or photodamage, non-facial	Good
Melasma	Mixed
Striae distensae	Mixed
Deep or perioral rhytides	Poor

anatomic sites (1a) [7]. Commonly treated areas for photorejuvenation include the face, neck (5) [8], décolletage (5) [9], and dorsal hands (5) [10].

Multiple studies have demonstrated relatively consistent results in the treatment of a variety of scars, including acne, surgical (1a) [11], traumatic, burn, and hypertrophic scars. The 1540-nm laser improves atrophic acne scars (1b) [12–14]. Specifically, boxcar scars reportedly respond better than rolling and ice-pick scars after six treatments with the 1540-nm device (2b) [15].

Treatment of melasma using NAFL devices must be done cautiously with conservative settings, as there is a propensity for developing a rebound effect (4) [16–22].

Less commonly, granulomatous conditions such as lupus miliaris disseminatus faciei are treatable with the 1565-nm NAFL, when other topical therapies, oral medications, and laser devices have failed (4) [23].

Effectiveness of Nonablative Fractional Energy Treatments

In general, the results of NAFL treatments for some indications are often difficult to assess and even more challenging to quantify, although attempts have been made to do so. Correction of photodamage is one of the most common aesthetic indications for the NAFL. Improvements in texture, rhytides, and dyspigmentation are safe even in darker Fitzpatrick skin types (III–IV) (1b) [24–26]. Off-face applications of the NAFL, including addressing poikiloderma of Civatte (5) [27] and dyschromia of the hands and chest, are notable areas that are otherwise treated with caution with the fractionated ablative device due to concerns of scarring. When treating non-facial locations, post-treatment redness usually persists longer, approximately 1 week (5) [28]. The NAFL is not a first-line treatment for deeper rhytides that may be better addressed with a fractionated ablative laser. Similarly, perioral laxity and rhytids commonly demonstrate only mild-to-moderate improvement after NAFL and often require a multimodal approach in conjunction with neuromodulators, soft tissue filler, and ablative fractional laser therapy.

The thulium 1927-nm laser is ideal for treating superficial lesions, including lentigines, actinic keratoses (AKs), macular seborrheic keratoses (4) [29], and some syringomas (4) [30]. Its higher absorption coefficient of water allows for more superficial penetration compared to that of other NAFL wavelengths. The 1927-nm laser reverses clinical photodamage as demonstrated by an 86.8% clearance of actinic keratoses 6 months following four monthly treatments (2b) [31]. In contrast, the deeper penetrating 1550-nm fractionated laser is not an adequate single-treatment modality for actinic keratoses. Six months after a series of five 1550-nm laser treatments, histologic evidence of AKs persisted even though clinically apparent facial AKs were reduced by an average of 55% (2b) [32].

Outcomes with NAFL treatments for melasma have been mixed, with the risk of exacerbation an ongoing concern (4) [16–22]. Formation of MENDs and subsequent pigment extrusion via the "melanin shuttle" is the most likely mechanism for clinically apparent lightening of lentigines and melasma (5) [33]. Despite significant short-term improvement, recurrence rates of melasma are high. In particular, darker skin type patients tend not to respond as favorably. Patients currently taking an oral contraceptive pill should be advised to switch to a low-estrogen type, as this could be contributing to the melasma. A paradoxical exacerbation of melasma diffusely throughout the face after NAFL is possible and patients should be counseled about this potential side effect. In general, a gentle treatment approach (e.g., low laser fluence/energy density,

fewer passes) is recommended. Lastly, a Consensus Group recommends decreasing cooling levels to avoid overcooling the skin. This could increase dermal-epidermal junction inflammation and consequently result in post-inflammatory hyperpigmentation (PIH) (5) [28]. Treatment success rates for treating melasma patients with skin phototypes V–VI are low given the higher risk of PIH. Physicians should be cautious when treating melasma in this select patient population.

Repigmentation in areas of post-inflammatory hypopigmentation may also reportedly be induced following serial 1540- and 1550-nm laser treatments alone or in combination with topical bimatoprost and tretinoin or pimecrolimus (4) [34–36]. In a prospective case series, seven patients with hypopigmented facial scars received 2–4 treatments every 4 weeks with the 1550-nm NAFL. Treatment settings ranged from 7 to 20 mJ and density of 1000–2500 MTZ/cm^2. Independent physician assessment 1 month after the final treatment demonstrated a 51–75% improvement in hypopigmentation in six of seven patients (2b) [36]. The mechanism of repigmentation may rely on melanocyte recruitment from the periphery of the hypopigmented scar.

The NAFR is a first-line treatment for noninvasive scar revision. A randomized, prospective, split-lesion study of hypertrophic scars treated with four monthly treatments using the 1540-nm fractional laser demonstrated a statistically significant improvement in patient scar assessment after 1 ($p = 0.006$) and 3 ($p = 0.02$) months; however, physician global assessments could not confirm clinical efficacy (1b) [37]. Second- and third-degree burn scars demonstrated improvements in skin texture, dyschromia, and degree of hypertrophy/atrophy 3 months after five 1550-nm NAFL treatments according to independent investigators. Patients' self-reports revealed moderate-to-excellent improvements in burn scar areas and significant improvement in self-esteem ($p = 0.03$) (2b) [38]. Uniquely, NAFL can lead to improvement in cosmesis and functionality in contracted scars. A 28-year-old woman with a 1-year-old traumatic scar of her right lower extremity received two treatments with the 1927-nm laser (10 mJ, 30% density, 8 passes) and four treatments with the 1550-nm laser (40 mJ, 17–26% density, 8 passes) spaced 4–8 weeks apart. There was objective improvement in range-of-motion measurements for plantar flexion (15°), inversion (10°), eversion (6°), and dorsiflexion (5°) as well as a 60–75% patient- and clinical-rated improvement in both texture and pigmentation (3b) [39]. NAFL treatments address a variety of scar types from both an aesthetic and functional perspective by inducing collagen turnover and remodeling.

In addition to hypertrophic and contracted scars, patients with atrophic scars may also benefit from a series of NAFL treatments (5) [11]. A series of laser treatments are often followed by injection of soft tissue fillers directly into the atrophic scars to provide additional volume. Atrophic acne scars have shown significant improvement (50% or greater) after a series of treatments using either the fractionated diode (1410-nm) laser, the 1550-nm laser, or the 1540-nm laser (1b) [40–44], and these devices are safe to use in patients with Fitzpatrick skin types IV–VI (1b) [45]. Interestingly, post-inflammatory erythema within acne scars also demonstrated statistically significant improvement that is comparable to that of the pulsed dye laser (PDL) (1b) [46].

The fractional 1540- and 1550-nm laser has been shown to safely and effectively improve the appearance of striae rubra and alba in Fitzpatrick skin types II–IV (1b) [47–51]. Before the patient commits to a series of treatments, a test spot treatment may be performed first. After several weeks, if there is improvement, the patient can proceed with a series of roughly five treatments. Striae rubra, in particular, may benefit from a combination of both PDL and NAFL treatments in order to address the underlying hypervascularity component (5) [28].

Preoperative Evaluation

The ideal candidate for nonablative skin resurfacing is relatively young (25–65 years of age) and has minimal facial skin sagging. Patients who

want to minimize treatment discomfort and downtime tend to favor nonablative over ablative treatments. They should be made aware that skin texture irregularities and fine lines will improve but will not be completely eliminated. Furthermore, since the effects of treatment are cumulative, it is important to reiterate that multiple treatments, typically from three to six or more, will be more beneficial than a single treatment. Since changes occur gradually, patients should not expect immediate results and they should understand that final results may take months to develop following the final treatment session (5) [52].

All patients should be screened for a history of prior facial herpes simplex virus (HSV). The energy from the procedure can cause a reactivation of dormant HSV with the potential for scarring. If the patient has a known strong history of HSV, the authors prophylactically treat with a 5-day course of valacyclovir 500 mg orally every 12 h starting the day before the procedure. Despite adequate prophylaxis, HSV reactivation may still occur. In a large retrospective chart review of 961 successive 1550-nm laser treatments, 6 of 86 treatments (7%) preceded with adequate antiviral prophylaxis still resulted in an HSV outbreak (2b) [53]. Widespread use of antiviral prophylaxis regardless of HSV history, however, is not recommended.

Historically, it is believed that laser procedures should not be performed until 6–12 months after completion of a course of isotretinoin (13-*cis*-retinoid acid; 4) [54]. This rationale is extrapolated from data on keloids induced after dermabrasion or argon laser treatment when carried out during or within 6–12 months of isotretinoin treatment (4) [55–57]. Isotretinoin may impair wound healing through alterations in pilosebaceous units and inhibition of collagenase, thus increasing the risk for scarring (5) [58]. However, recent evidence suggests that wound healing after laser treatments sooner than 6 months after completion of a course of isotretinoin does not necessarily lead to adverse events (2b) [59–62]. A patient on high-dose isotretinoin was treated with the nonablative fractional 1540-nm laser, ablative fractional 2940-nm laser, and fully ablative 2940-nm laser. At 6-month follow-up, both the fractional nonablative and ablative treatment sites did not develop scarring. Therefore, the authors concluded that at least the fractional lasers may be relatively safe to use during isotretinoin therapy (5) [63]. A retrospective study evaluated 20 patients who received fractional ablative CO_2 laser therapy for facial acne scars and had completed isotretinoin (10–60 mg/d) within 1–3 months of laser treatment (2c) [64]. Six-month follow-up evaluations showed normal reepithelialization in all patients. No side effects, such as prolonged, persistent, and intense erythema, or development of hypertrophic scars, or keloids occurred. Conservative management with a minimum 6-month wait after completing isotretinoin therapy before any NAFL treatments is advisable, although shorter periods prior to initial laser treatment may not lead to any long-term adverse events.

For all patients, a topical pretreatment regimen should include a broad-spectrum sunscreen with a minimum SPF of 30 as well as strict sun avoidance. Although there is no consensus regarding a specific topical pretreatment regimen for preventing PIH in skin types IV–VI, a review panel recommends prescribing topical tretinoin and hydroquinone (HQ) for several months before treatment. Tretinoin should be discontinued 1 week before laser treatment and HQ discontinued 3 or 4 days before (5). [28] A specific protocol described by Clark et al. recommends topical HQ 4% to the entire face or treatment area 2 weeks prior to the laser treatment, followed by transient discontinuation for 7 days post-laser and then subsequent topical HQ 4% for 4 weeks thereafter (5) [65]. Adequate pre-procedure prophylaxis with sunscreens and lightening agents may reduce the risk of PIH, particularly in those with darker skin types.

Pretreatment photographs using a high-resolution, reproducible digital photography system such as the Visia (VISIA GmbH, Stuttgart, Germany) or Canfield (Canfield Scientific Inc., Fairfield, NJ) systems allow for more precise monitoring of results.

Due to the nonablative nature of this type of laser and light-based technology with only

minimal risk and downtime, only a few contraindications exist for this treatment. Patients on chronic systemic corticosteroids or those with serious underlying illnesses should be evaluated by their primary care physician before undergoing this procedure. Contraindications include unrealistic expectations, active or latent HSV infection, and isotretinoin use within 6 months. Relative contraindications include an active collagen vascular disease, poor wound healing, a history of drug reactions to or use of medications that may interact with topical anesthetics, and intolerance to the intraoperative discomfort associated with nonablative resurfacing. Moreover, those with a predisposition for excessive scarring, pigmentary changes, and/or keloid formation may be at an increased risk of developing these changes after therapy and should be made aware of these possibilities beforehand (5) [28]. Finally, there are no studies available on the safety and efficacy of treatment in pregnant or lactating women; therefore, treatment of these individuals should generally be avoided.

Best Techniques and Performance

Topical anesthesia may be used to provide intraoperative comfort. Topical anesthetic agents are often applied from 20 min to 1 h prior to the procedure and then removed immediately before treatment. There are several preparations available, including 5% lidocaine, 7% lidocaine/7% tetracaine, 23% lidocaine/7% tetracaine, and 30% lidocaine. Although only 5% lidocaine and 7% lidocaine/7% tetracaine have FDA-approved preparations, stronger preparations are available through compounding pharmacies. Limiting the treatment area to 300–400 cm^2 and using the lowest dose of lidocaine that will achieve adequate anesthesia are important to minimize the risk of lidocaine toxicity from the topical anesthesia. Symptoms of lidocaine toxicity include perioral paresthesias, lightheadedness, dizziness, tinnitus, and at higher doses, slurred speech and seizures. If patients are still uncomfortable despite topical anesthesia, regional nerve blocks may be helpful. To further reduce discomfort, 800 mg of ibuprofen can be taken orally 45 min prior to the procedure. Anxiolytics are generally not required.

Concomitant application of handheld forced cool air or direct contact cooling has been demonstrated to significantly reduce pain and increase patient comfort during fractional laser treatments. Fisher et al. conducted a study of 20 patients to rate their pain level with and without cooling; 19 of 20 noted a mean improvement of 2.8 +/− 1.8 on a pain scale of 1–10 with the addition of handheld forced air cooling (4) [66]. Moreover, forced cool air is recommended to prevent bulk heating of the skin, thereby reducing the risk of hyperpigmentation and blistering. However, Laubach and colleagues found that cooling decreases the size of the MTZ and may interfere with treatment efficacy [33]. In the authors' experience, alternating treatment sides with intervening chilled ice pack applications also aids in patient comfort. Adjuvant direct cooling is important for improving patient comfort and reducing side effects, such as hyperpigmentation and scarring.

Fractionated laser treatments are delivered using either a stamping or rolling scanner handpiece. The procedure requires multiple, generally 3–8, passes. Treatment zones using the stamping method should be overlapped and laid down in the same direction. When treating the entire face, sequential treatment by cosmetic subunits—forehead, temples, cheeks, upper cutaneous lip, chin, and nose—is an organized approach to reduce application technique error. To minimize bulk heating and reduce pain, passes should be applied in a proximal-to-distal format for two passes and then lateral to medial for two passes. Brief pauses between passes allow for adequate cooling. Simply rolling the handpiece back and forth without changing planes does not allow for sufficient cooling and risks significant pain, blistering, and potentially scarring [28]. Ice packs should be applied for at least 15 min post-procedure followed by a broad-spectrum sunscreen SPF 30+. Table 18.2 reviews a proposed treatment protocol for the NAFL.

Tissue effect for a given laser is determined by the laser wavelength, the fluence or energy per focal spot area, the density or fixed percentage of surface

Table 18.2 Proposed treatment protocol for patients undergoing fractional laser resurfacing

1. Pretreatment in those predisposed to post-inflammatory hyperpigmentation with topical hydroquinone and/or tretinoin to the entire treatment area for at least 2 weeks prior to laser treatment, followed by discontinuation for 7 days post-laser therapy. Restart topical therapy for 4 weeks thereafter
2. Patients with a history of herpes labialis should be prophylaxed with a 5-day course of valacyclovir 500 mg twice daily starting the day prior to the procedure
3. Photographs and written consent prior to each treatment
4. Topical anesthetic (23% lidocaine, 7% tetracaine cream) applied to the treatment area 60 min before each treatment
5. Continuous forced air chiller use intraoperatively
6. Post-procedure cooling with ice packs to the treatment area for approximately 15 min
7. Post-procedure application of a broad-spectrum SPF 30+ sunscreen and written posttreatment handout given to patient

area of coverage, and the number of passes delivered. Increasing fluence produces a greater depth of dermal penetration and tissue effect, while increasing density also serves to increase clinical effect (5) [67]. Increasing these treatment parameters may produce more patient discomfort and pain. Slowing down the handpiece speed, increasing the handheld cooling device level, or decreasing the density or MTZs/cm^2 in each pass can optimize patient comfort at higher treatment levels.

To define optimal NAFL parameters to treat photoaged skin, Orringer et al. examined molecular changes in expression of selected genes and proteins after high (70 mJ) and low (15 mJ) fluence treatments. Photodamaged forearms of subjects were treated with the 1550-nm NAFL, and serial skin biopsies were obtained up to 28 days posttreatment. As expected, the high-fluence NAFL produced a more intense inflammatory response. Interestingly, both treatments produced similar patterns of molecular changes, and only minimal differences were observed between lower- and higher-energy settings (5) [3]. The data suggest that lower-fluence/higher-density settings which are generally better tolerated by patients may yield similar dermal changes to that of higher-energy/lower-density parameters.

Optimal treatment settings for scar management appear to be low-density and high-fluence treatment settings as extrapolated from the fractional ablative laser literature (2b) [68]. Similar comparative studies adjusting the fluence and density variables have not been reported with the NAFL. Lin et al. examined the effect of density settings using the 1550-nm laser in a prospective, randomized split-scar study. Half of 20 linear hypertrophic scars were treated with either a low-density (14% coverage; treatment level 5) or high-density setting (26% coverage; treatment level 9) at a fluence of 40 mJ every 2 weeks for four treatments. Subjects in the low-density treatment arm rated the treated side with higher scores compared to internal controls than those in the high-density arm (p = 0.001; 1b, B) [69]. In lower-density NAFL, significant improvement over control was seen at both 1 and 3 months post-NAFL. Subjects in the high-density treatment arm experienced significantly more side effects, including erythema, exfoliation, and pain (p = 0.05, 0.02, and 0.01, respectively), as compared to those in the low-density treatment arm. The low-density NAFL treatments demonstrated better clinical efficacy with fewer side effects, compared to the high-density NAFL treatments.

The ideal time to first start treating a new scar is still unclear. In one study, younger scars <2 years old responded better to NAFR as compared to scars >6 years old (5, D) [69]. Early intervention may be key in the treatment of scars.

The fractional 1927-nm NAFL is an option for treating photopigmentation. A prospective multicenter study demonstrated moderate-to-significant improvement in facial lentigines and ephelides in 82% of subjects at 1 month and 69% at 3 months after two treatments with the 1927-nm laser. Subjects with skin types I–IV were treated at a fluence of 10 mJ, density of 40%, and 4–6 passes. Independent physician assessment of photos demonstrated a durable response at 3-month follow-up (A) [26]. The fractional thulium laser produced moderate-to-marked improvement in overall appearance and pigmentation with high patient satisfaction.

There are limited comparative trials of the various nonablative fractional devices. A small

trial compared the efficacy and safety of a 1540-nm NAFL and a 1410-nm NAFL for the treatment of abdominal striae distensae. After six treatment sessions, all nine subjects experienced improvement at 3-month follow-up visits both histologically with an increased epidermal and dermal thickness and elevated collagen and elastin density compared to baseline and clinically with blinded photographic evaluation. These differences were not statistically significant (2b) [70]. Clinical experience suggests that when used optimally, results among the nonablative devices appear to be similar (5) [71].

Safety

The biggest advantage of nonablative fractional laser systems is their relatively low incidence of adverse effects and minimal postoperative recovery periods. In a retrospective review of side effects and complications of the NAFL from 961 treatment sessions in 422 patients, 73 (7.6%) complications were documented: 18 acneiform eruptions, 17 herpes simplex outbreaks, 13 erosions, 8 cases of prolonged erythema, 7 cases of PIH, 6 cases of prolonged edema, 2 cases of dermatitis, and 1 case each of impetigo and purpura [53]. Common adverse events include pain during the procedure and posttreatment erythema, edema, crusting, and scaling (2b) [72]. Longer duration of erythema is expected when a higher fluence is used (2b) [73]. Typically, facial erythema lasts for 2–5 days and patients are able to return to work the next day with minimal post-laser skincare (5) [74]. The nonablative lasers are often favored by patients who are unwilling or unable to schedule the requisite time for recovery required by the ablative modalities.

Herpes simplex virus (HSV) infection is the most common infectious complication following NAFL treatment with an incidence of up to 2% (2b) [75]. Antiviral prophylaxis can minimize the rate of reactivation to less than 0.5% and should be administered in patients with a history of facial HSV. In contrast, the incidence of bacterial infection after fractionated laser treatment is extremely low with an incidence of 0.1% in all treated cases (4) [53, 76]. Antibacterial prophylaxis is not typically necessary for nonablative treatment; however, it is sometimes recommended for ablative fractionated laser resurfacing [77].

Transient acneiform eruptions after fractional skin resurfacing occur in 2–10% of patients and are particularly common in those who are acne-prone (2b) [7, 53, 78]. Avoidance of occlusive moisturizers and use of noncomedogenic equivalents are recommended for preventing milia development [78, 79].

Pigmentary alterations including PIH have been observed in 1–32% of patients, depending on the device used, parameters applied, and skin phototype treated (2b) [43, 80–82]. Patients with a darker phototype (Fitzpatrick III–VI) have a greater likelihood of developing PIH. Higher density, rather than higher fluence, has been shown to increase the risk of PIH [80]. To minimize such risk, patients should avoid significant sun exposure at least 2 weeks before and after the resurfacing procedure (5) [80, 83]. Although it often resolves without treatment within 6–12 months, application of topical bleaching and mild peeling agents (e.g., retinoic, azelaic, ascorbic, and glycolic acid) and liberal use of sunblock may hasten its resolution (5) [84]. There have been no reported cases of iatrogenic hypopigmentation following nonablative fractionated laser therapy.

Hypertrophic scarring is a relatively uncommon complication of the NAFL. The use of excessively high treatment densities, lack of adequate cooling during and between passes, and postoperative infection are potential causes for scarring. Furthermore, non-facial sites including the neck and chest are more prone to develop scars. With fewer pilosebaceous units and a less rich vasculature, two factors that greatly impact wound healing (5) [85], these scar-prone anatomic sites and the periorbital area and mandibular ridge, require more conservative laser parameters. Early treatment of hypertrophic scarring may include the use of topical or intralesional steroids and silicone gel products. The KTP or pulsed dye laser is also a helpful adjuvant therapy for treating any underlying erythema (5) [86, 87].

Rarely, development of low-grade malignant skin tumors called keratoacanthomas may follow the 1550-nm laser resurfacing of photodamaged skin of the legs (4c) [88]. Trauma to the follicular unit could be a possible mechanism for keratoacanthoma development.

Other uncommon side effects include a transient and benign heat-induced recall phenomenon (4c) [89]. An irritant contact dermatitis may be induced by topical natural or herbal remedies used in the perioperative treatment regimen [53]. Topical anesthesia-induced toxicity rarely occurs but has been reported after 30% lidocaine gel was not removed before fractional laser treatment (2b) [90].

Postoperative Care and Follow-Up

After treatment, ice packs may be applied for comfort and acetaminophen can be taken for pain. The patient can wash his or her face with a gentle cleanser and lukewarm water. A noncomedogenic moisturizer should be used instead of an occlusive ointment, such as petroleum jelly, as the latter may lead to post-treatment acne. Avoidance of prolonged direct exposure to sunlight as well as wearing a broad-spectrum sunscreen with SPF 30 or higher is recommended. Resuming topical bleaching agents in darker skin types may help reduce the risk of PIH.

Mild erythema and edema are expected to occur immediately post-procedure. This typically resolves within 1–5 days. Fine desquamation lasting for 1–3 days is common during the week after treatment. Patients should expect a rough skin texture and dryness during this time period and often require extra moisturizer use. The use of oral corticosteroids posttreatment is controversial. There is evidence that they may speed up recuperation. However, they may also impede the inflammatory response, thus negatively impacting collagen synthesis and reorganization.

Because nonablative lasers have limited thermal tissue effects, a series of three to six treatments performed at 3–6-week intervals may be recommended for optimal results (2) [52, 71, 79, 91]. Significant, long-lasting effects are rarely achievable following a single treatment [28]. Improvements continue to develop months after the final treatment.

Similar to the fractional, infrared-domain millisecond nonablative lasers mentioned previously, laser therapy with the fractional nonablative Qs 1064-nm Nd/YAG laser requires a series of treatments at approximately 2–4-week intervals. Treatments may improve hyperpigmentation, telangiectases, skin laxity, tactile roughness, and actinic keratoses (2b) [92]. The fractional Qs 1064-nm laser demonstrated efficacy in both patient self-assessment and objective melanin index scores when treating melasma in patients with skin types III and IV. No adverse events were reported (4) [93]. With its excellent safety profile even on areas at higher risk of scarring such as the neck and chest, no downtime, and no minimal pain, the fractional nonablative Qs Nd/YAG laser is a reasonable option for treating superficial rhytides and photoaging (2b) [94, 95]. The frequency-doubled Qs Nd/YAG (532 nm) laser has also been reported to successfully treat a café-au-lait macule with less downtime as compared to conventional laser treatments (3b) [96]. Post-procedure care and follow up with these devices are similar to those outlined earlier for more conventional NAFL treatments.

Alternative Procedures and Modifications

Alternative treatments that target wrinkles, acne scars, and pigmented lesions include the fractional ablative devices (Chap. 19) and picosecond lasers with a fractional diffractive lens array (DLA) (4) [97–99]. The picosecond laser delivers short-pulse bursts of energy to the skin in the picosecond range, effectively targeting pigment and melanin. The DLA is an optical attachment composed of 120–130 tightly packed diffractive lenses that evenly distribute energy in high-energy pulses. By redistributing energy, multiple passes may be used to safely treat a specific area. Within each localized zone, Tanghetti et al. described histologically unique intra-epidermal cavities (5) [100].

These cavities result from an electron avalanche breakdown, alternatively termed "laser-induced optical breakdown" (LIOB). The number and size of cavities depend on the amount of melanin in the epidermis (melanin index) and laser energy used. Once formed, LIOBs absorb most of the subsequent incoming laser irradiation. Excessive radiation does not reach the dermoepidermal junction, protecting pigment and minimizing collateral damage. These focal areas of injury form MEND zones that exfoliate over the subsequent 2–4 weeks. LIOBs can directly stimulate an epidermal repair mechanism that results in improvement in dyspigmentation and new collagen, elastin, and mucin formation. The 755-nm picosecond alexandrite laser with DLA was reported to be a safe treatment of atrophic and hypertrophic scars, pigmented lesions, and striae in skin types IV–VI (2b) [101]. The most common side effects in this study were mild swelling, pain, redness, and crusting. Three of 56 patients developed hyperpigmentation that was resolved without any intervention. A total of 2–3-week treatment intervals were found to expedite results without increasing side effects when using the 755-nm picosecond laser with the fractional DLA to treat facial pigmentation and wrinkles (2b) [102].

Dyspigmentation can alternatively be addressed with Quality-switched (Qs) or the newer picosecond lasers (see Chap. 17. "Pigment lasers and light treatments"). Both nanosecond and picosecond lasers have been observed to produce a photomechanical effect that causes fragmentation of tattoo ink or pigment. The latter technology can be used to deliver lower fluences to affect tattoo pigment particles and melanosomes. These very small chromophores or targets have a thermal relaxation time of less than 10 nanoseconds (5) [103]. In a retrospective analysis, the Qs 694-nm ruby, Qs 532-nm KTP, and Qs 1064-nm Nd/YAG nanosecond lasers and the 755-nm alexandrite picosecond laser were noted to be safe and effective modalities for removing lentigines in skin types III–VI if used appropriately (2b) [104]. Notably, the risk of PIH in darker skin types may be decreased with the use of a picosecond laser as compared to the Qs lasers. Evidence of PIH was noted in only 2 of 255 total treated lentigines following laser therapy in patients with skin type IV using the 532-nm picosecond laser. The patient who developed PIH admitted to picking the treated area and potentially confounding results (2b) [105]. Similarly, a 755-nm picosecond laser demonstrated efficacy for the treatment of benign pigmentary lesions in Asians with only 2 of 13 patients developing transient hypopigmentation and none developing hyperpigmentation (4) [106]. The picosecond laser appears to more efficiently clear pigmentation than the Qs lasers with fewer treatments necessary. After only one picosecond laser treatment, 78% of lentigines improved by 75–100% [105]. Split-face studies comparing the picosecond and Qs lasers are needed.

As mentioned previously, melasma is a challenging condition to treat with the NAFL due to the high risk of a rebound effect and potential for exacerbation. Topical skin brighteners including bleaching creams and strict sun protection with a broad-spectrum sunscreen SPF 30 or higher can be used synergistically with the NAFL (4) [28, 79, 107]. Pretreatment for at least 2–4 weeks followed by posttreatment for 2–6 months with a bleaching agent is recommended to prevent hyperpigmentation particularly in skin types III–IV.

Fractional ablative laser therapy is an alternative treatment to address photoaging. In a comparative study using the fractional ablative 2940-nm (Er/YAG) laser versus the 1550-nm nonablative fractional laser to treat photoaging in Asian skin, Moon et al. found that a reduction in pigment, uneven tone, and erythema scores was significantly greater with the use of the Er/YAG ablative laser, while wrinkle score reduction was significantly greater using the 1550-nm NAFL (1b) [108]. Moreover, recalcitrant perioral and deeper rhytides tend to respond better to the fractional ablative lasers than the NAFLs (5) [6].

Scar revision often requires a multimodal approach to address the textural and vascular components of an individual scar. Hypertrophic erythematous scars are best addressed using a combination approach with PDL followed by the 1540-nm or 1550-nm laser (5) [11]. In a meta-analysis of keloidal and hypertrophic scars treated with intralesional steroids alone or in combination with 5-Fluorouracil, the combination treatment arm demonstrated statistically significantly greater efficacy based on patient satisfaction scores, observer assessment, and scar height (1a) [109]. When performed on the same day, intralesional injections should be performed after NAFL to avoid ulceration from bulk heating secondary to an increase in the aqueous target of NAFL (3b) [110].

Microneedling therapy and fractional needle radiofrequency treatments are alternative techniques that may be used for the treatment of scars. The process of microneedling involves the use of small, minimally invasive microneedles that break the collagen bundles in the superficial layer of the dermis that is responsible for scars, leading to a subsequent induction of more collagen immediately below the epidermis (5) [111].

Fractionated radiofrequency devices deliver sub-ablative energy that induces coagulative damage to the dermis. With relative sparing of melanin, the risk of dyspigmentation may be minimized with these devices. Studies in patients with skin types I–IV demonstrated favorable results in treating atrophic acne scars (1b) [112–124], periorbital wrinkles (2b) [125], and photoaging (2b) [126]. The use of fractional needle radiofrequency devices alone or in combination with microneedling has shown promising results in smaller studies in the treatment of scars and photoaging; however, there is still a need for larger comparative trials against the gold standard ablative and nonablative lasers.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Nonablative fractional energy devices are safe and effective options for the treatment of a variety of conditions	B
Nonablative fractional energy devices offer the advantages of rapid recovery, minimal side effects and complications, and the ability to treat all skin types	B
Disadvantages of nonablative fractional energy devices include the requirement of multiple treatment sessions to achieve a clinical endpoint due to the lower efficacy per treatment compared to ablative resurfacing lasers	B
Nonablative fractional energy devices demonstrate consistent clinical efficacy in treating photoaging, rhytides, and scars on both facial and non-facial anatomic locations, including the neck, chest, and hands	B
Perioperative care includes herpes simplex virus prophylaxis if there is a positive history, photoprotection with a broad-spectrum sunscreen, sun avoidance, and topical hydroquinone and/or tretinoin for those predisposed to developing post-inflammatory hyperpigmentation	D

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Self-Assessment Questions

1. Which of the following conditions is NOT ideally treated using a nonablative fractional laser?
   (a) Rhytides
   (b) Dyspigmentation
   (c) Telangiectases
   (d) Striae distensae
   (e) Scars
2. Which of the following is NOT a symptom of lidocaine toxicity?
   (a) Seizures
   (b) Perioral paresthesias
   (c) Hearing loss
   (d) Slurred speech
   (e) Lightheadedness and dizziness
3. Which of the following is the most common infectious complication of nonablative fractional laser resurfacing?
   (a) Staphylococcus aureus
   (b) Candida albicans
   (c) Streptococcus
   (d) Human papilloma virus
   (e) Herpes simplex virus
4. Which of the following fractional nonablative lasers is best for treating superficial conditions such as actinic keratoses?
   (a) 1410-nm erbium laser
   (b) 1550-nm erbium-doped laser
   (c) 1540-nm erbium glass laser
   (d) 1927-nm thulium laser
   (e) 10,600-nm CO_2 laser
5. Which of the following patients would be the most ideal candidate for the nonablative fractional 1550-nm/1927-nm laser?
   (a) An 80-year-old woman with deep rhytides and severe photodamage
   (b) A 32-year-old pregnant woman with melasma
   (c) A 16-year-old man with boxcar acne scars on the cheeks who finished a course of isotretinoin 2 months ago
   (d) A 25-year-old man with a traumatic scar on his upper lip who also has on closer inspection grouped vesicles on an erythematous base
   (e) A 45-year-old woman with mild-to-moderate facial rhytides and mild skin laxity

Correct Answers

1. c: Telangiectases. Nonablative fractional lasers target the chromophore water. Vertical columns of thermal damage induce microscopic epidermal necrotic debris that stimulates collagen formation and produces the melanin shuttle in which pigment is extruded through the epidermis. Therefore, rhytides, dyspigmentation, striae distensae, and scars are treatable with the NAFL. Telangiectases are best treated with lasers targeting the chromophore hemoglobin within red blood cells such as the 532-nm KTP and 585–595-nm-pulsed dye lasers.
2. c: Hearing loss is not a sign of lidocaine toxicity. Symptoms of lidocaine toxicity include perioral paresthesias, lightheadedness, dizziness, tinnitus, and at higher doses, slurred speech and tonic-clonic seizures.
3. e: Herpes simplex virus infection is the most common infectious complication with an incidence of up to 2% [75]. Antiviral prophylaxis can minimize the rate of HSV reactivation to less than 0.5% and should be administered in patients with a history of facial HSV.
4. d: The 1927-nm thulium laser is best for treating superficial lesions such as actinic keratoses. Its high absorption coefficient of water allows for more superficial penetration compared to that of other NAFL wavelengths. The 1927-nm fractional laser produced an 86.8% clearance of actinic keratoses 6 months following four monthly treatments [31]. In contrast, the deeper penetrating 1550-nm fractionated laser is not an adequate single-treatment modality for actinic keratoses. Six months after a series of five 1550-nm laser treatments, histologic evidence of AKs persisted, although clinically apparent facial actinic keratoses (AKs) were reduced by an average of 55% [32]. The 10,600-nm laser is an ablative device.
5. e: The ideal candidate for the nonablative fractional resurfacing procedure is a relatively young (25–65 years of age) patient with minimal facial skin sagging and realistic expectations. Deep rhytides and significant photodamage are better treated with an ablative fractional device. Women who are pregnant or nursing should not be treated with these lasers. A recent history isotretinoin use (</= 6 months) should preclude the laser resurfacing procedure. Laser treatment should be avoided in a patient with an active herpes simplex virus infection. Moreover, this patient should be given antiviral prophylaxis prior to each laser treatment, given his high risk of viral reactivation.

Medium to Deep Chemical Peels

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Suzan Obagi

Abstract

Prior to the development of laser resurfacing, chemical peels were among the sole methods by which to resurface the skin. For decades, medium and deep peels have been used to treat a number of skin conditions in ethnically diverse patients. Despite the growing popularity of lasers, peels continue to rank among the most popular cosmetic procedures performed today showing a 4% increase to 1.36 million procedures in the USA during 2016. The two most commonly used acids for medium and deep peels are trichloroacetic acid (TCA) and phenol. The most common indications for chemical peels are actinic keratosis, photodamage, ephelides/lentigines, rhytides, post-inflammatory hyperpigmentation, certain types of acne scars, and melasma. By varying the concentration of the solution or the peeling agent, peels can be used to treat the skin of the neck, chest, and upper extremities.

Keywords

Peel · Phenol peel · TCA peel · Trichloroacetic acid peel · Scar · Acne scar · Melasma · Dyschromia · Actinic keratosis · Chemical peel dyschromia · Chemical peel melasma · TCA melasma · Phenol melasma · TCA acne scars · CROSS TCA · CROSS peel

Introduction and Indications for Medium to Deep Chemical Peels

Prior to the development of laser resurfacing, chemical peels were among the sole methods by which to resurface the skin. For decades, medium and deep peels have been used to treat a number of skin conditions in ethnically diverse patients. Despite the growing popularity of lasers, peels continue to rank among the most popular cosmetic procedures performed today [1] showing a 4% increase to 1.36 million procedures in the USA during 2016. The two most commonly used acids for medium and deep peels are trichloroacetic acid (TCA) and phenol. The most common indications for chemical peels are actinic keratosis, photodamage, ephelides/lentigines, rhytides, post-inflammatory hyperpigmentation, certain types of acne scars, and melasma. By varying the concentration of the solution or the peeling agent, peels can be used to treat the skin of the neck, chest, and upper extremities.

Chemical peeling agents can be classified as protein denaturants (TCA, phenol) or as keratolytic agents (glycolic acid, lactic acid, salicylic acid, and low strength phenol). It is the protein

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denaturing property that is desired in medium and deep peeling to achieve wounding through the epidermis and into different levels of the dermis. Medium depth peels penetrate through the epidermis and into the papillary dermis level while deep peels penetrate through all the layers of the skin and reach the upper reticular dermis. Extremely deep peels into the mid reticular dermis can be performed but the risk of hypertrophic scarring, hypopigmentation, and permanent textural change make that type of peel very risky.

What Accounts for Chemical Peel Penetration?

A lot of importance is given to acid concentration when it comes to phenol and TCA peels. However, peel depth penetration is determined by more than just acid concentration. TCA is hydrophilic; therefore oily skin would serve as a barrier to peel penetration. Phenol is lipophilic and will penetrate through the skin very quickly. Furthermore, we now understand the important role croton oil plays in driving phenol peels deeper.

The Following Factors Influence Peel Penetration

Concentration

Higher concentration of TCA or phenol will penetrate through the skin to a deeper level than the same volume of a lower concentration TCA or phenol. The higher the acid concentration, the more protein coagulation that occurs. Thus, the acid will reach a deeper depth with each application.

Volume

As TCA and phenol acids penetrate the skin, their effect stops once enough protein coagulation has occurred to negate the acid that was applied. Thus, further peel penetration would require more acid be applied to the skin to drive the peel deeper. Therefore, thicker skin would require more acid volume than thinner skin to achieve a peel to the same depth.

Body Surface Area

Body surface area (BSA) is another factor. A fixed volume and concentration of peel solution will penetrate more deeply if the entire volume is applied over a small area of skin as opposed to the same volume being applied to a larger surface area.

Skin Thickness

Epidermal and dermal thickness varies by patient age, gender, anatomic location, and ethnicity. Chemical peel solutions will reach the dermis more quickly in thinner skin patients than those with thicker skin. Therefore, the physician will need to adjust either the volume or concentration of the peeling solution.

Skin Oiliness

Sebum and thicker, oilier skin is more challenging for TCA penetration. Properly degreasing the skin will allow TCA to penetrate more deeply than it would otherwise. Patients with oily skin will require either more volume of TCA or a higher concentration of TCA to penetrate through the sebum. Alternatively, patients who are very oily may require systemic therapy with isotretinoin for a month or two to reduce sebum production prior to the peel. However, if a patient is treated with isotretinoin, a waiting period of 3 months before peeling of the skin may be suggested to ensure proper wound healing.

Croton Oil Concentration

The most recognized formula for deep phenol peeling is the Baker & Gordon formula in which patients were peeled to the mid reticular dermis. While the results were dramatic, the risk of scarring and permanent hypopigmentation greatly reduced the number of patients that could or would undergo this procedure. Two researchers, Stone (2b) [2] and Hetter(2b) [3], studied the peel depth penetration achievable by varying either the phenol acid or croton oil concentration.

Other Factors Influencing Peel Depth

Pre-peel thinning of the stratum corneum with topical retinoids or fruit acids will help the peel solution penetration more easily. Furthermore, the amount of rubbing or pressure applied to the

skin when performing the peel will also drive the solution deeper.

Effectiveness of Chemical Peels for Treating Melasma

Melasma is one of the most common complaints of patients presenting to the dermatologist. It remains a challenging condition to treat. Many modalities, while giving initial improvement, are associated with a significant relapse rate.

Kumari and Thappa (2b) [4] looked at glycolic acid (GA) versus TCA peels in patients with melasma. Forty patients with epidermal (78%) or mixed melasma (22%) (epidermal and dermal) were randomized into two groups. "Most" patients were phototype IV–VI. All patients had baseline melasma area and severity index (MASI) scores calculated. The GA group received pretreatment with 12% GA cream and a sunscreen SPF 15 to use daily for 2 weeks prior to the peel. The TCA group was given 0.1% tretinoin nightly and sunscreen SPF 15 daily starting 2 weeks before the peels. Patients were then peeled every 2 weeks with escalating concentration or contact time to the peel solutions. Peel 1: 20% GA or 10% TCA left on for 2 min. Peel 2: 20% GA or 10% TCA for 4 min. Peel 3: 35% GA and 20% TCA for 2 min. Peel 4: 35% GA or 20% TCA for 4 min. More peels were performed after these initial four if patients showed slow or inadequate response. At the conclusion of all the peels, patients were treated with 2% hydroquinone cream nightly and an SPF 15 daily to maintain the results. The study showed that the GA group had MASI score reductions from 26.6 to 5.6 (79%) and the TCA group showed a reduction from 29.1 to 8.2 (73%). The difference between the GA and TCA group was not statistically significant. Similarly, the subjective improvement scores showed a good to very good response in 75% of GA patients and 65% of TCA patients. The difference between the two was not statistically significant. During the recovery periods, the GA patients were able to continue working whereas the TCA patients often had to take time off of work. At 6 months, two of the GA patients showed relapse. There is no mention as to which type of melasma (epidermal or mixed) did better for the TCA group. However, the GA acid group was evaluated for response with statistically significant reduction in MASI for the epidermal melasma patients (79% reduction) but not for the mixed-type melasma (27.8%).

Puri (2b) [5] compared 15% TCA peels ($n = 15$) versus 35% GA peels ($n = 15$) in 30 epidermal melasma patients. Patients were primed for 2 weeks prior to the peels with 2% Kojic acid or 0.25% tretinoin. There is no mention of SPF use. MASI scores were calculated at baseline and after each peel. Peels were performed at 3-week intervals for six sessions or once the melasma was clear (whichever occurred first). Subjectively, patients noted a good or very good response in 70% of the GA group and 64% of the TCA group. The difference between the two groups was not statistically significant. MASI scores showed a statistically significant improvement from baseline in both groups with the TCA group changing from 22.3 to 5.6 and the GA group changing from 23.6 to 4.25. The difference between the two groups' MASI scores was not statistically significant. Subjects found the GA peel easier to tolerate and that it required no time off from activities. The authors conclude that both peels were equally effective in the treatment of melasma. This study fails to mention the average number of peels needed per group, and there is no mention of the contact time that the GA peel was left on the skin. Furthermore, patient phototypes were not mentioned.

Safoury et al. (2c) [6] compared 15% TCA peels to a modified Jessner's Peel + 15% TCA peel in patients with phototypes III or IV. A modified Jessner's solution has salicylic acid, lactic acid, and citric acid (in place of resorcinol). Twenty patients with epidermal melasma were treated in a split-face, single-blinded manner. Prior to the peels, patients were primed for 2 weeks with a 10% zinc oxide sunblock daily and adapalene 0.1% gel nightly. The treating physician was not blinded. The left malar area was treated with the modified Jessner's solution until erythema appeared. Then a 15% TCA solution was in a uniform coat to the whole face

including the left malar "until frosting." Peels were repeated every 10 days until the melasma cleared or until a maximum of eight peels. MASI scores decreased from 4.46 to 2.04 on the TCA side (54.26%) and from 4.35 to 1.23 on the combination Jessner/TCA side (71.72%). Follow-up at 8 weeks showed a slight worsening of MASI scores to 2.27 (TCA) and 1.67 (Jessner/TCA), but these scores remained statistically significantly lower than the baseline. No comparison of scores were made between the two sides. No mention was made of the average number of peels performed. The authors conclude that the combination peel is superior to TCA alone.

Abdel-Meguid et al. (2b) [7] performed a single-blinded, split-face trial of 20–25% TCA peels versus Jessner + 20–25% TCA peels in 24 patients with phototypes IV–V. Patients were primed with 2% hydroquinone cream nightly and sunscreen daily for 2 weeks prior to the peels. Peels were performed six times at 2-week intervals. Patients were randomized to left or right cheek treatments with Jessner+TCA and TCA alone. The first three peels were with 20% TCA, and the last three peels were with 25% TCA. MASI scores were calculated at baseline and at the conclusion of the peels. Fourteen patients had epidermal melasma, and ten had mixed-type (epidermal and dermal) melasma. Four patients were dropped for non-compliance. Results showed a statistically significant decrease in MASI scores with either modality: Jessner + TCA (67.75% improvement) and TCA alone (48.60% improvement). Furthermore, the difference in improvements between the two modalities was statistically significant ($p < .05$). There is no mention of long-term follow up to evaluate relapse. Furthermore, there is no breakdown of response by melasma type. The authors conclude that both modalities are effective in improving melasma but that the Jessner + TCA combination is more efficacious.

Soliman et al. (2b) [8] evaluated 20% TCA peels versus 20% TCA peels + topical ascorbic acid cream in 30 patients with epidermal melasma with skin phototypes III or IV. Patients were randomized into two groups: group A 15% TCA peels and group B 15% TCA peels with home use of a topical ascorbic acid cream. All patients were primed with 2 weeks of 0.05% tretinoin gel daily and 4% hydroquinone daily and SPF > 15. In addition to these agents, group B received a 5% ascorbic acid cream to apply daily as well. MASI scores were calculated at the baseline, after peels were concluded, and at a 16-week follow-up. Peels were performed with 20% TCA weekly until melasma cleared or for a maximum of 6 sessions. Results for group A showed a MASI score reduction of 34.4% (15.31–10.107). This increased to an overall reduction of 20.06% by week 16. Results for group B showed a MASI score reduction of 61.75% (13.753–5.260). This increased by week 16 to reflect an overall reduction of 43.79% in group B. Comparing both groups showed a statistically significant reduction in MASI in group B over group A ($p < .001$). Patients rated themselves as good, marked, or moderate improvement in 13 of 15 patients (86.66%) in group B and 10 of 15 patients (66.66%) in group A. By week 16, group A showed that results maintained in 48%, worsened in 33%, and continued to improve in 19% of the cases. By week 16, group B showed results maintained in 60%, worsened in 13%, and continued to improve in 27% of the cases. All but two patients in group B required all six peel sessions.

Moubasher et al. (2b) [9] evaluated different concentrations of TCA peels versus 2 different Q-switched neodymium-doped yttrium-aluminum-garnet laser (Qs-Nd:YAG) laser treatments on 65 female patients, phototypes III to V. Patients were assigned to four groups. There was no special priming of the skin before or after treatments, only the use of topical sunscreen with an SPF > 50. MASI scores were calculated at baseline and after the treatments were completed. Group 1: 15 patients with epidermal melasma treated with 20% TCA. Group 2: 20 patients with epidermal, dermal, or mixed melasma were treated with 30% TCA. Group 3: 15 patients with dermal and mixed melasma were treated with 30% TCA. All peels were repeated at 2 week intervals up to eight sessions or until melasma clearance was achieved. Group 4: 15 patients were treated with Qs-Nd:YAG for epidermal melasma (7 patients treated with 532-nm) and dermal or mixed melasma (8 patients

treated with 1064-nm). All laser treatments were monthly for up to six sessions or until clearance was achieved. Patients were monitored for 3 months after treatment to evaluate for recurrence. Results showed the greatest reduction in MASI scores (64.7% improvement) in group 2 compared to group 1 (39.9%), group 3 (24.7%), and group 4. Group 4 showed worsening of MASI scores in the 532-nm group (−83.6%) and the 1064-nm group (−19.1%). Epidermal melasma (52% MASI reduction) improved more than the dermal type (12.1% MASI reduction) ($p = .0029$), whereas epidermal versus mixed-type melasma (49.5% MASI reduction) showed similar amounts of improvement ($p = .77$). Patients were "very satisfied" in group 2 (50%) followed by group 1 (40%), and then group 3 (6.7%). All patients (100%) in group 4 were "unsatisfied" followed by group 3 (46.7%), group 1 (6.7%), and group 2 (5%). By 3 months, there was a 32% recurrence rate. The authors conclude that 25% TCA peels were the most effective for melasma and that Qs-Nd:YAG should be avoided. However, it is noteworthy that the settings for the laser used in this study are much higher than those used in other melasma studies.

Conclusion on Peels for Melasma

The literature supports the use of low-concentration TCA peels (up to 25%) for the treatment of epidermal melasma and mixed-type melasma more so than dermal melasma. Phenol peels were not studied for melasma. Studies on dermal melasma are lacking. What is needed are more split-face studies to address melasma in the same patient using two different modalities including split-face peel and laser studies.

Effectiveness of Chemical Peels for Treating Lentigines and Actinic Keratosis

Many patients present for the treatment of lentigines and ephelides. These lesions can be seen across a wide range of ethnicities. Lasers and peels are commonly used modalities.

Li and Yang (2b) [10] evaluated a Qs-Nd:YAG laser versus 35% TCA for the treatment of lentigines in an Asian population. This was a split-lesion study of 20 patients with 37 lentigines in which the medial half of the lesion was treated with a Qs-Nd:YAG laser, 532-nm, 2.4–2.6 J/cm^2, 10 ns, 2 mm spot size and the lateral half was treated with 35% TCA until an even frost developed. Results were evaluated photographically by four investigators, and scored on a 5-point scale (1–5 with 5 being the best), comparing baseline photos to photos taken 6 months posttreatment. Results showed improvement with both modalities (4.16 for laser and 3.67 for TCA). However, 65% of lentigines responded better to Q-switched neodymium-doped yttrium-aluminum-garnet laser (Qs-Nd:YAG), 14% did better with TCA, and 21% were equal.

Raziee et al. (2b) [11] looked at cryotherapy versus 33% TCA in the treatment of lentigines on the dorsal surface of the hands in patients with phototypes II to IV. Thirty-three patients (2 men and 31 women) with at least 5 lentigines on each dorsal hand were treated with cryotherapy to lesions on one hand (cotton-tipped applicator for 3–5 s) versus 33% TCA to lentigines on the other hand (cotton-tipped applicator to a fine white frost). Patients were evaluated photographically at baseline and at 2 months. Eight patients did not complete the study. Results were judged by one attending dermatologist and two residents on a 4-point scale. No patient showed marked improvement (>75% change). Results of cryotherapy showed moderate (50–75%) improvement in phototype II (100%), phototype III (44%), and phototype IV (0). Results for the TCA group showed moderate (50–75%) improvement in phototype II (33%), phototype III (11%), and phototype IV (0). The main complication was post-inflammatory hyperpigmentation (PIH) seen in 40% of cryotherapy- and 44% of TCA-treated hands. The difference in PIH between the two groups was not statistically significant. Pain and length of healing was greater in the cryotherapy group with 84% of patients saying cryotherapy was more painful and 76% saying that TCA healed faster.

Holzer et al. (2c) [12] compared aminolevulinic acid + photodynamic therapy to 35% TCA in a split-face blinded study on patients with at least

five actinic keratosis (AKs) per treatment side. Patients were enrolled and randomized to left- and right-sided treatments on identical anatomic areas such as the forehead or midface or scalp. Twenty-eight patients were enrolled, but 23 completed the study. Aminolevulinic acid (ALA) + photodynamic therapy (PDT) was performed by applying 5% ALA to the anatomic area being treated, occluded for 4 h, and then activated by red light (Waldman PDT 1200), 600–740 nm, 75 J/cm^2 at an irradiance of 75 mW/cm^2. The TCA group had a topical anesthetic applied for 30 min, degreased with 95% alcohol followed by TCA 35% to an end point of an "even pink white frosting." Results showed a reduction in AKs with ALA+PDT (58%) compared to TCA (31.9%). At 12 months, the ALA+PDT group showed 73.7% complete clearance compared to the TCA group with 48.8% ($p = 0.011$). Pain was notably higher in the PDT group (7.5 on visual analog score) compared to TCA (5.1). However, non-permanent scarring was seen in the TCA group in 6 patients (21.4%).

Hantash BM et al. (2b) [13] performed a prospective study of three groups of patients with extensive sun damage or a history of non-melanoma skin cancer (NMSC). Patients were phototypes I to III, had extensive AKs, and no history of prior skin resurfacing within 5 years of the study. They were primed and post treated with tretinoin 0.05% cream and a sunscreen. Patients were randomized to a 5-fluorouracil (5-FU) group ($n = 9$), 30% TCA peel ($n = 10$), ablative carbon dioxide skin resurfacing ($n = 8$). The 5-FU group had to apply the 5-FU cream twice a day for 3 weeks, the TCA group had one peel at 30% TCA performed to the level of an even frost, and the ablative CO_2 laser group underwent two passes of fully ablative laser resurfacing. Patients were followed up every 3 months for 24 months. Actinic keratosis recurrence was measured and the development of any NMSC was noted. Of note, all but three patients in this study had a history of a face or scalp NMSC. Results showed that all three groups had a statistically significant reduction in AKs, 5-FU (83%), TCA (89%), and CO_2 (92%), with no adverse scarring or pigment alterations. While it was a small study size, the TCA group exhibited a greater reduction in NMSC risk (3.75–5.25-fold) compared to the other two groups ($p < .001$).

Conclusion on Peels for Photodamage and Actinic Keratosis

Comparing Qs-Nd:YAG to 35% TCA for lentigines showed almost equal results. For areas that did not resolve, retreating with TCA or laser is an acceptable option. However, the cost-effectiveness of the TCA exceeds that of the laser. Similarly, the cost of cryotherapy or TCA peels are both very low. The improvement seen in cryotherapy over TCA for lentigines may suggest that the TCA peel was not performed deep enough. However, it is a fine balance between eliminating the lentigo and risking permanent hypopigmentation with any modality.

The use of ALA+PDT for AKs warrants a large study to truly draw conclusions on outcome. Studies need to be done with the same concentration of TCA but applied to a slightly deeper level. The authors mention "descaling" AKs before applying the ALA but did not do the same prior to applying the TCA. Furthermore, a slightly deeper peel may have resulted in more impressive AK reduction.

Reduction in AKs was seen as being substantial in 3 groups using 5-FU, TCA, or CO_2 laser resurfacing. Large studies should be conducted to see if the reduced risk of NMSC with TCA peels carries forward. However, patients found the TCA recovery to be easier than 5-FU and CO_2. That makes TCA a very cost-effective tool.

Effectiveness of Chemical Peels for Treating Acne Scars

In 2002, Lee et al. (2b) [14] described the CROSS technique now widely utilized for the treatment of icepick scars in which high-concentration TCA is applied focally to isolated scars to create wounding and subsequent improvement. This is performed by using a sharpened wooden applicator stick or other similar tool to focally apply TCA to the scar including the deep track of scar tissue associated with icepick scars.

Dalpizzol et al. (2b) [15] looked at the treatment of icepick and boxcar scars in a split-face,

non-randomized, single-blinded study of 15 patients, phototypes IV or lighter, using the CROSS technique with TCA or phenol. The skin was primed with 0.3% adapalene gel nightly for 15 days prior to the start of the peels. The left hemiface was treated with 88% phenol and the right hemiface with 90% TCA using the standard CROSS technique. The peels were repeated every 21 days for 4 sessions. Patients were assessed photographically and were asked to rate healing time and pain for each side. Prior to treatment, both sides showed similar scar scores on an acne scar grading scale (ECCA). After the treatments, both sides showed statistically significant improvement in scars compared to baseline (ECCA) but again, there was no statistically significant difference between the TCA or the phenol sides in regard to the degree of improvement. Patients rated the phenol side as more painful during the procedure. There was no significant difference in healing time between the two acids. The DLQI (dermatological quality of life index) score improved from a score of 6.7 to 3.3 ($p < .05$) after the treatments. Four patients developed hyperpigmentation (two with TCA, two with phenol), two patients developed hypochromia (TCA group), and two developed widening of the scars (TCA group).

Ramadan et al. (2b) [16] evaluated 20 patients, phototypes III and IV, in a split-face trial of 100% TCA CROSS technique to subcision in patients with rolling scars. Acne scar severity was measured on a 4-point scale from 1 (macular), 2 (mild atrophy), 3 (moderate) to 4 (severe). Patients were treated with CROSS 100% TCA on the left side of the face and subcision on the right (needle gauge was not mentioned). Patients were treated 1–3 times at 1–4-month intervals. All scars improved with both techniques but improved more with subcision than TCA ($p = 0.001$). Of note, there was a large difference in baseline scar sizes between the right (0.416 cm^2) and left (0.182 cm^2) sides of subjects.

Leheta et al. (2b) [17] compared percutaneous collagen induction (PCI) microneedling (1.5 mm) with 100% TCA CROSS technique in acne scars (rolling, boxcar, icepick), in 30 patients (27 completed the study), phototypes II to IV. Patients were randomized to either the PCI (five passes in four directions) or the TCA groups, primed with a topical retinoid and 4% hydroquinone for 2 weeks prior to treatment, and received four treatments at 4-week intervals. Results showed an improvement in the severity of acne scars in both groups ($p < .001$ for each group) but no statistically significant difference in improvement between the two groups. However, when looking at scar morphology, rolling scars did better with PCI while boxcar and icepick scars did better in the TCA group.

Nofal et al. (2b) [18] compared three modalities in patients with rolling, boxcar, and icepick scars. Patients were divided into 3 groups of 15 patients: intradermal platelet-rich plasma (PRP), 100% TCA CROSS, and topical PRP + microneedling (PCI, 2 mm, 6 passes in 4 directions). Three sessions were performed at 2-week intervals. All patients had an improvement in their scars with no statistically significant difference between the groups as graded by the patients, a quartile grading system, and photographic assessment (blinded evaluation). The authors did not breakdown responses by scar morphology.

Agarwal et al. (2b) [19] looked at 70% TCA CROSS in rolling, icepick, and boxcar scars in 62 patients (53 completed the study). Patients received four sessions at 2-week intervals. Blinded reviewers evaluated photographs, and patients performed a self-assessment and patient satisfaction survey. Physician assessment showed that 66% of patients had >50% improvement (22.6% excellent and 43.4% good). Patients reported excellent improvement (11.3%) and good improvement (54.7%). No patient reported a poor response. Boxcar scars showed the most improvement as rated by physicians and patients.

Conclusion on Peels for Acne Scars

The CROSS technique, utilizing 88% phenol or 90% TCA, has been shown to be effective in the treatment of boxcar and icepick scars. The treatment of choice for rolling or valley scars remains subcision or PCI. Rolling scars tend to be wider and deep, requiring a treatment that promotes

collagen building while not altering surface color or texture.

The shortcoming of these studies is the lack of a standardized acne scar scale across studies to allow for better comparisons of outcomes. Furthermore, larger studies are needed to look at scar morphology and treatment outcomes to better decipher which scars do better with different treatments.

Preoperative Evaluation

Since skin resurfacing procedures create controlled wounds in the skin, there are precautions taken with regard to selecting the correct patient, preparing the skin, and minimizing complications by obtaining a good medical and social history. Preoperatively, patients should be screened for medications, allergies, smoking, infections, and a history of any psychological or behavioral issues that may make them have unreasonable expectations or may make them less prone to following postoperative care. Patients that are pickers, for example, may pick at the unhealed skin and create infections or scars. Many studies talk about performing the procedure, but there have not been studies that objectively evaluate preresurfacing skin care, postoperative skin care, or the best regimen for viral and bacterial prophylaxis. Therefore, each study's patient cohort is based on protocols selected by the investigators according to their personal experiences rather than being firmly grounded in science.

Most investigators suggest a pretreatment regimen of a topical retinoid (retinol, retinoic acid, retinaldehyde), a topical hydroquinone cream (2% or 4% applied daily or twice daily), and a sunblock. The pretreatment routine is usually started 2–6 weeks prior to the peel and resumed upon healing of the skin.

Antiviral Therapy

When the perioral area is being treated, physicians usually start an antiviral regimen starting the day before and continuing until fully healed, 7–14 days. The dosing of the antiviral regimen is physician dependent and may be adjusted if a patient has a strong history of herpes simplex virus (HSV) outbreaks. There is general agreement that antiviral therapy is mandatory for all patients undergoing perioral resurfacing since the risk of HSV becoming disseminated and causing scarring is catastrophic.

Antibacterial Therapy

There is no consensus on the use of antibiotics to prophylactically prevent infection. The infection rate with skin resurfacing is not high to begin with, but should an infection occur, the risk of scarring goes up. For this reason, care is taken to monitor these patients postoperatively in order to detect and treat infections early. No studies have been done to look at the rate of infection in patients treated or not treated with prophylactic antibiotics. The author has anecdotally found that mupirocin ointment applied to the opening of the nostrils three times a day starting 1 week prior to the peel and for 1 week afterwards results in a lower rate of postoperative bacterial infections.

Best Techniques and Performance

There is no consensus statement on properly performing this procedure. Most physicians will degrease the skin with acetone or 70% alcohol prior to the peel. The peel solution is applied with cotton-tipped applicator (CTA) sticks (TCA or phenol), a triangular makeup sponge (TCA), or two to three CTAs (phenol).

TCA Peels

Most physicians will degrease the skin with acetone or 70% alcohol prior to the peel. The peel solution is applied with cotton-tipped applicator (CTA) sticks (TCA or phenol) or a triangular shaped makeup sponge (TCA). About 2 min is allowed between applications to be able to see the full frost as it develops. If more depth of pen-

etration is needed, more TCA is applied, and then the frost is re-evaluated. Frost is evaluated as mentioned earlier based on a level 1 to level 3 frost. As TCA is first applied, a light non-organized frost begins to form. This is a level 1 frost and signifies an epidermal level peel. Further application results in the frost being solid but with a diffuse pink background to become a level 2 frost. This marks a peel just reaching the papillary dermis level. Continued TCA application results in more solid white frost with a loss of the pink background indicating coagulation of the papillary dermis vascular plexus (level 3 frost). This is the deepest suggested level of application of TCA peels. Beyond this level, risk of scarring and hypopigmentation increases greatly.

Phenol Peel

Depending on the solution used and the extent of the peel, cardiac monitoring and intravenous (IV) hydration may be required. In instances of a half-face or full-face peel, the peel is performed in quadrants with a 15-min waiting time between application and lots of IV hydration to allow the body to metabolize and excrete any absorbed phenol. Great caution is indicated when performing a phenol peel on patients with impaired cardiac, hepatic, or renal function.

The skin is degreased with acetone. The phenol mixture must be swirled before dipping the CTA into it as the oil and water components have a tendency to separate. The solution is applied with 1–3 CTA (held like a fan). The skin quickly frosts when the solution is applied. The end point of a phenol peel is an even white frost. The frost quickly begins to dissipate so the physician must pay close attention to the treated area to avoid reapplying the solution and exceeding the desired depth of penetration.

Safety

There are no randomized clinical trials or large case series publications on the complications of chemical peels. Most publications report complications as they relate to the peels described in their study. In general, most peel complications stem from the depth of the peel and not from the actual solution used. Minor complications include post-procedure irritant or contact dermatitis to a product used for wound healing, acne flare up, swelling, erythema, sterile pustules, and PIH. Major complications include infection (viral, bacterial, fungal/yeast), hypertrophic/keloidal scarring, prolonged erythema, texture change, ocular injury from the solution, ectropion, and hypopigmentation. Early recognition and intervention is key to mitigating these complications.

Any suspected infection warrants a bacterial culture and sensitivity (aerobic, anaerobic, possibly mycobacterial) to identify the organism and to tailor antibiotics to the organism. The use of preoperative antibiotics that cover gram-positive bacteria may allow the growth of gram-negative bacteria by eliminating the normal flora balance. Infections typically are staphylococcus, but atypical mycobacteria, *Enterobacter*, *Pseudomonas aeruginosa*, and *Escherichia coli* have been reported.

Viral infections can present as areas that were healing and then began to regress. The virus can be herpes simplex or varicella zoster virus. Either of these can spread quickly on denuded skin and cause deep erosions and possible scarring. These viruses can erupt anywhere during the healing process until the skin is fully re-epithelialized. Cultures or direct immunofluorescence characterization of the virus should be performed, and high-dose (zoster dosing) antiviral medications should be implemented for 10 days and adjusted to clinical response.

With the occlusive dressings and use of antibiotics, patients can sometimes develop pruritic papules that show budding yeast on KOH prep. These usually develop by postoperative days 4 or 5. Oral anti-yeast agents can be helpful in treating this.

Postoperative Care and Follow-Up

There is no consensus on postoperative management. The extent of postoperative follow-up usually relates to procedure depth. “Lunchtime” peels

may not require a follow-up necessarily. However, medium and deep peels should be followed up at day 3 or 4, again at day 7, and further out until the patient is fully re-epithelialized. Patients should be brought in at anytime if they call with any symptoms that portend scarring or infection.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Chemical peels remain a very important tool in treating dyschromia, photodamage, and certain types of scars	D
With appropriate knowledge and training, physicians may find that they are able to treat a wider diversity of patients with peels as compared to laser resurfacing	D
Until larger studies are performed to standardize preoperative skin preparation, procedure performance, patient selection, postoperative management of complications, and indications, it behooves the physician to start slowly and gradually work his/her way up to deep peels	D

PubMed Search: Chemical Peel Dyschromia, Chemical Peel Melasma, TCA Melasma, Phenol Melasma, TCA acne scars, CROSS TCA, CROSS peel, TCA peel

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Self-Assessment Questions

1. A 53-year-old female, Fitzpatrick type III, Glogau type III, undergoes combination 30% TCA peel resurfacing of her face to a level 2 frost. She is at increased risk for all of the following *except:*
   (a) Post-inflammatory hyperpigmentation
   (b) Bacterial infection
   (c) Acne flare up
   (d) Textural abnormalities
   (e) Melasma flare up
2. On day 4, post-resurfacing, the patient presents with purulent drainage from the wound, some thick, honey-colored crusting, and a low-grade fever. The most likely infectious etiology is:
   (a) *Staphylococcus aureus*
   (b) *Candida albicans*
   (c) *Pseudomonas aeruginosa*
   (d) Herpes simplex virus
   (e) Contact dermatitis
3. In an attempt to minimize or avoid post-inflammatory hyperpigmentation (PIH) after a resurfacing procedure, it is appropriate to:
   (a) Begin hydroquinone in the immediate postoperative period
   (b) Wait until re-epithelialization is complete to begin hydroquinone
   (c) Wait until evidence of PIH manifests itself
   (d) Begin hydroquinone therapy 5–6 weeks postoperatively
4. A 40-year-old male, Fitzpatrick type II, is seeking treatment of shallow, small atrophic acne scars. All of the following would be appropriate treatment modalities *except*:
   (a) TCA peel to the level of the reticular dermis
   (b) A 1 min 70% glycolic acid peel
   (c) CROSS TCA technique
   (d) Fractionated CO_2 laser resurfacing
5. When evaluating a patient for chemical skin resurfacing, many factors must be assessed. Which of the following is the *least* important:
   (a) the patient's expectations of improvement
   (b) medical history
   (c) family history
   (d) pre-existing skin disease
   (e) history of keloids

Correct Answers

1. d: A level 2 frost should not reach the reticular dermis thus the risk of scarring or textural change with a level 2 frost peel is low.
2. a: The most common bacterial infection is staphylococcus aureus. However, on the setting of an infection while a patient is on an antibiotic that covers gram-positive bacteria, a gram-negative infection should be suspected.
3. b: Once the skin heals, reinstituting hydroquinone may help reduce PIH rather than if one were to start HQ once PIH has set in.
4. b: A 1 min 70% glycolic acid will not reach the dermis to a degree that will build collagen in shallow, atrophic, boxcar scars.
5. c: While everything is important in medical, social, and family history, the family history would yield the least helpful information. It is better to understand the patient's state of mind, health history, tendency to scar, and the history of skin diseases that may worsen or affect wound healing.

Superficial Chemical Peels and Microdermabrasion

20

Rachel Miest

Abstract

Superficial skin resurfacing is a process causing controlled injury to the epidermis. Processes can be chemical or mechanical and classified as laser or nonlaser. Although our armamentarium for skin resurfacing ranges from topical medicaments to ablative lasers, superficial skin resurfacing with chemical peels and microdermabrasion (MDA) has maintained its popularity. These well-established therapies have proven safe and effective, offer minimal risk, low cost, and are well-tolerated by patients often with little to no post-procedure downtime. Potential benefits extend to all Fitzpatrick skin types and if done appropriately are highly unlikely to cause significant dyspigmentation or scarring. Indications for treatment are acne vulgaris, rosacea, post-inflammatory hyperpigmentation, melasma, and photodamage including lentigines, fine rhytides, and actinic keratoses. Superficial resurfacing with chemical peels or MDA can be used in combination with other therapies (e.g., laser) and may enhance the efficacy of other topical treatments. A superficial depth of penetration may be of significant benefit to the patient but does have limitations. It is important for patients to understand the likely need for a series of treatments, the importance of pre- and post-care regimens, and expected outcomes.

Keywords

Chemical peels · Alpha hydroxy acid peels · Salicylic acid peels · Jessner's solution (JS) · Microdermabrasion

Introduction

Superficial skin resurfacing is a process causing controlled injury to the epidermis. The processes can be chemical or mechanical and classified as laser or nonlaser. Although our armamentarium for skin resurfacing ranges from topical medicaments to ablative lasers, superficial skin resurfacing with chemical peels and microdermabrasion (MDA) has maintained its popularity. These well-established therapies have proven safe and effective, offer minimal risk, are low cost, and are well-tolerated by patients, often with little to no post-procedure downtime. Potential benefits extend to all Fitzpatrick skin types and if done appropriately are highly unlikely to cause significant dyspigmentation or scarring. Indications for treatment are acne vulgaris, rosacea, post-inflammatory hyperpigmentation, melasma, and photodamage including lentigines, fine rhytides, and actinic keratoses. Superficial resurfacing with chemical peels or

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MDA can be used in combination with other therapies (e.g., laser) and may enhance the efficacy of other topical treatments. A superficial depth of penetration may be of significant benefit to the patient but does have limitations. It is important for patients to understand the likely need for a series of treatments, the importance of pre- and post-care regimens, and expected outcomes.

Chemical Peels

Chemical peels are the application of a chemical peeling agent to the skin that causes controlled destruction of the epidermis and/or dermis. A number of factors determine the depth of injury induced by the peeling agent including the specific chemical(s) and concentrations used, the preparation of the skin, application technique, duration of contact, and skin characteristics. Superficial chemical peels primarily affect the epidermis and so are indicated in the management of acne and its post-inflammatory erythema/hyperpigmentation, mild photoaging including fine rhytides and lentigines, and melasma. Peels may increase penetration of topical therapies (e.g., transdermal drug delivery) and may be used as an adjunct to topical or systemic therapies [1, 2]. Commonly used superficial peeling agents are alpha hydroxy acids (AHAs), salicylic acid (SA), and Jessner's solution (JS). These superficial peeling agents produce their effects by decreasing corneocyte adhesion in the epidermis and inducing neocollagenesis in the dermis [3–6]. Superficial chemical peels generally require four to six applications at 2–4-week intervals for desired clinical response. They are typically associated with mild burning or stinging with application and limited post-procedure downtime. Pre- and post-treatment regimens are integral to successful outcomes. Pre-treatment with a retinoid or an AHA 2–4 weeks prior to the procedure prepares the skin for the peeling process ensuring more homogenous penetration and consistent results and can hasten post-treatment healing. Post-treatment care including diligent photoprotection, and particularly in darker Fitzpatrick skin types, hydroquinone preparations or other bleaching agents are also important to prevent post-treatment dyschromia [6–10]. Complications of superficial chemical peels are rare but may include prolonged erythema, pigmentary changes including hyper/hypopigmentation, infection, and scarring [11, 12]. Superficial chemical peels are a useful tool to treat many skin conditions and may work synergistically with other treatment modalities to achieve optimal results.

Alpha Hydroxy Acid Peels

Alpha hydroxy acids (AHAs) are nontoxic organic acids found in foods and may be naturally occurring or synthetically produced [13]. AHAs include glycolic acid, lactic acid, malic acid, mandelic acid, oxalic acid, citric acid, pyruvic acid, and tartaric acid [5, 14]. Glycolic acid (GA) is the lowest molecular weight AHA and penetrates the skin readily making it a commonly used agent for chemical peeling. GA peels are commercially available as free acids, partially neutralized, or buffered solutions ranging from concentrations of 20% to 70% [11, 15]. Low concentrations decrease the cohesion of corneocytes, while higher concentrations may lead to complete epidermolysis [2, 14, 16]. AHAs have been associated with increased epidermal thickness, decreased melanin deposits in the epidermis, and increased fibroblast proliferation and collagen production [17–19]. A study of the effects of multiple peeling agents on mini-pig skin found minimal inflammation and a disproportionate increase in collagen deposition with GA, suggesting a stimulatory mechanism rather than damage and subsequent repair [20]. And in a study by Usuki et al., GA was shown to suppress melanin formation by direct inhibition of tyrosinase [21]. In another study, GA was found to have moderate growth inhibitory and bactericidal effects of *P. acnes* [22]. With these properties, AHAs are therefore beneficial for many cutaneous conditions including photodamage, melasma, and acne [8]. Application is often painless although may be associated with mild burning or stinging. GA is hydrophilic and has a low pH. The pH varies depending on the concentration of the

acid, with higher concentrations resulting in lower pH and increased peeling capacity. GA peels typically require neutralization to avoid excess acidification and subsequent burning of the skin. As with other superficial peeling agents, multiple treatments are typically required to achieve desired results. Concentration of the acid used and application time may be increased with serial treatments as tolerated [6, 23].

Photodamage

Early studies demonstrated reduced corneocyte cohesion with subsequent epidermal thinning and significant therapeutic benefit with application of AHAs to the skin of patients with disorders of keratinization [16, 24]. Subsequent studies focused the effects of AHA peels on photodamaged skin (Table 20.1). Ditre et al. demonstrated that application of GA, lactic acid (LA), or citric acid (25% lotion) to photoaged skin of the forearm resulted in histologic evidence of increased epidermal thickness and dermal changes including increased synthesis of glycosaminoglycans and collagen [25] (2b). A study examining the effect of GA 50% chemical peeling on photoaged skin using Skh:HR-1 hairless mice demonstrated an increase in dermal collagen on biochemical analysis that was not statistically significant [26] (5). In a double-blind, vehicle-controlled study of weekly GA 50% peels, Newman et al. demonstrated clinical improvement of photoaged skin including a decrease in rough texture and fine rhytides, a reduction of actinic keratosis, and lightening of lentigines. Histopathology was consistent with previous studies showing a thinning of the stratum corneum but overall increase in epidermal thickness [27] (3b). A randomized controlled trial comparing low-intensity MDA and low-intensity GA peels (20%) showed that while GA peels were preferred by patients, no significant clinical improvement from baseline was noted with either treatment [28] (2b). This finding supports the hypothesis that maximum efficacy is best achieved by a series of peels at the highest tolerated concentrations.

Melasma

The efficacy of AHA peels in the treatment of melasma has also been studied (Table 20.2). In a single-blind, right/left comparison study of glycolic acid peels with GA 10% and hydroquinone 2% gel, there was subjective improvement of melasma and fine rhytides when both treatments were utilized compared to the hydroquinone gel alone. This improvement was not statistically significant [29] (3b). A split-face study from Lawrence et al. comparing GA 70% and JS demonstrated equal efficacy in the treatment of melasma and a more rapid response than topical therapies alone [30] (3b). Similarly, a randomized controlled study of Kligman's formula (hydroquinone 5%, tretinoin 0.05%, and hydrocortisone acetate 1%) alone or in combination with GA 30–40% demonstrated a greater overall response and more rapid results with combination therapy [31] (3b). In a study from Hurley et al. of GA 20–30% peels added to a topical regimen of hydroquinone 4%, the addition of GA did not sig-

Table 20.1 Alpha hydroxy acid chemical peels in the treatment of photodamage

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Ditre et al. [25]	Randomized controlled	17	Increased epidermal thickness and dermal changes including increased synthesis of glycosaminoglyans and collagen	2b
Butler et al. [26]	Animal	20 (mice)	Non-statistically significant increase in dermal collagen	5
Newman et al. [27]	Controlled cohort	41	Improved skin texture; decreased fine rhytides, actinic keratosis, and lentigines Thinning of stratum corneum but overall increased epidermal thickness	3b
Alam et al. [28]	Randomized controlled	10	No significant improvement from baseline	2b

Table 20.2 Alpha hydroxy acid chemical peels in the treatment of melasma

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Lim and Tham [29]	Controlled cohort; GA 20%	10	Subjective improvement but not statistically significant	3b
Lawrence et al. [30]	Controlled cohort; GA 70% vs. JS	11	Statistically significant decrease in MASI score for both treatment groups, no statistically significant difference between treatment groups	3b
Sarkar et al. [31]	Controlled cohort; GA 30–40%	40	Statistically significant decrease in MASI score; trend toward greater and more rapid improvement	3b
Hurley et al. [32]	Controlled cohort; GA 20–30%	18	No significant difference when GA 20–30% added to topical regimen	3b
Coleman and Brody [33]	Expert clinical opinion	n/a	Improvement with GA 50–70% peels without adjunct topical therapy	5
Erbil et al. [18]	Randomized controlled; GA 20–70%	28	Statistically significant decrease in MASI score	2b
Sharquie et al. [34]	Case series; LA 92%	12	Statistically significant decrease in MASI score	4
Sharquie et al. [35]	Comparative cohort; LA 92% vs. JS	24	Statistically significant decrease in MASI score for both treatment groups, no statistically significant difference between treatment groups	3b
Sarkar et al. [36]	Randomized comparative; GA 35% vs. SMA (SA 20%/MA 10%) vs phytic acid combination	72	Statistically significant decrease in MASI scores for GA and SMA treatment groups, no statistically significant difference between the two groups	2b

nificantly enhance the effects of hydroquinone monotherapy [32] (3b). Subsequently, Coleman and Brody highlighted the low-strength GA used by Hurley et al. and cited their own experience with improvement of melasma following monthly higher concentration GA 50–70% peels without adjunctive topical therapies [33] (5). A prospective, randomized controlled trial examining serial GA 20–70% peels in combination with azaleic acid 20% cream two times a day and adapalene 0.1% gel nightly showed statistically significant improvement with the addition of GA peels. The statistical significance in treatment response between the control group and chemical peel group was most pronounced at week 12 and persisted through the end of the study at week 20, corresponding with higher concentrations of glycolic acid (50% at weeks 8 and 10, 70% at weeks 12 and 14), supporting the opinion that higher concentrations of glycolic acid are required for optimal clinical outcomes. The authors suggest that glycolic acid 50% acid may be ideal for treatment of melasma, noting diminishing returns with higher concentrations and increased risk for complications such as post-inflammatory hyperpigmentation [18] (2b).

Although the literature for GA in the treatment of melasma is more robust, alternative AHAs and superficial peeling agents have demonstrated efficacy. Lactic acid (LA) demonstrated statistically significant reductions in Melasma Area and Severity Index (MASI) scores in a study by Sharquie et al. [34] (4) A subsequent study again showed significant response and found LA to be as effective as JS in the treatment of melasma [35] (3b). In a recent study, Sarkar et al. compared the efficacy and tolerability of GA 35%, salicylic mandelic acid (SMA; SA 20%/mandelic acid (MA) 10%), and phytic acid combination peels in the treatment of melasma. Patients were primed with hydroquinone 4% and tretinoin 0.05% 4 weeks prior to the initiation of treatment. Peels were performed every 2 weeks for a total of 12 weeks. A decrease in MASI score was seen in all three treatment groups, but was statistically significantly lower in patients receiving GA and SMA peels. Although there was no statistically significant difference noted between these two treatment groups,

SMA has a larger molecular weight than GA and is associated with less procedural discomfort and increased tolerance by patients [36] (2b). Overall, superficial chemical peels are safe and efficacious for the treatment of melasma and are often used in combination with topical therapies to optimize results and reduce potential side effects [9].

Acne

AHAs have proven efficacious in the treatment of acne (Table 20.3). GA has been the most studied for treatment of comedonal and inflammatory acne and its sequelae including post-inflammatory hyperpigmentation and scarring. A 1997 study of the effect of GA 35% and 50% peels in addition to GA home care products on the treatment of acne in Asian patients showed significant improvement of skin texture including pore refinement, "brighter and lighter" looking skin, and resolution of comedones, papules, and pustules. Subtle improvement of acne scars was also noted [37] (4). Another study evaluating GA 70% peels for treatment of acne found the most rapid response in comedonal acne, although noted improvement of papulopustular and nodulocystic acne with additional applications. And a significant improvement in acne scarring was noted in patients with nodulocystic acne, although an increased number of applications (eight to ten) were required. Peels were performed in conjunction with a home care regimen of a topical antibiotic and GA 15% which may have contributed to the efficacy demonstrated, particularly for inflammatory acneiform lesions [38] (4). Kim et al. compared the effectiveness of GA 70% peels and JS in the treatment of facial acne in a split-face randomized clinical trial and found both treatments effective but no significant difference was seen in treatment effects. JS was associated with increased post-procedure exfoliation which led to patient preference for GA peels [39] (2b). In a split-face, double-blind, randomized controlled study, GA 30% peels were compared to SA 30% peels in the treatment of mild to moderate facial acne. Both chemical peels demonstrated statistically significant effectiveness as measured by a reduction of acne lesions, although patients treated with SA did have sustained

Table 20.3 Alpha hydroxy acid chemical peels in the treatment of acne and its sequelae

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Wang et al. [37]	Case series; GA 35–50%	40	Improvement/resolution of comedones, papules, and pustules; pore refinement Subtle improvement of acne scarring	4
Atzori et al. [38]	Case series; GA 70%	80	Most rapid response in comedonal acne, although improvement noted in papulopustular and nodulocystic acne with additional applications	4
Kim et al. [39]	Randomized comparative; GA 70% vs. JS	26	Improvement in both treatment groups but no statistically significant difference. Increased exfoliation with JS	2b
Kessler et al. [40]	Randomized comparative; GA 30% vs. SA 30%	17	Significant reduction of acne lesions in both treatment groups; sustained benefit in SA treatment group	2b
Lee et al. [41]	Case series; GA 30% vs. JS	38	No significant change in sebum levels in either group	4
Kaminaka et al. [42]	Randomized controlled; GA 40%	26	Significant reduction of acne lesions when compared to placebo	1b
Burns et al. [43]	Randomized controlled; GA ≤68%	16	A trend toward greater and more rapid improvement Increased lightening of unaffected skin noted	2b
Garg et al. [44]	Comparative cohort; GA 35% vs. SMA 20%/10%	44	Significant improvement of acne, acne scarring, and post-inflammatory hyperpigmentation in both treatment groups; SMA showed statistically significant superiority in treatment of active acne and post-inflammatory hyperpigmentation	3b

benefit with fewer lesions 2 months after treatment. Of note, patients in the study remained on topical therapies (e.g., retinoids) and oral antibiotics if using at the time of enrollment [40] (2b). In a study on the effect of GA 30% and JS on sebum secretion in patients with mild to moderate facial acne, Lee et al. found no significant difference in the sebum secretion after two peels performed 2 weeks apart [41] (4). A randomized, double-blind, placebo-controlled, split-face study of GA 40% peels in patients with moderate to severe facial acne demonstrated a statistically significant reduction in acne lesions compared to placebo. This study examined glycolic acid peels without the use of concurrent therapies, requiring a 2-month washout period prior to initial treatment [42] (1b).

The sequelae of acne including post-inflammatory hyperpigmentation and scarring may also benefit from treatment with AHAs. Burns et al. compared GA peels to a topical regimen of hydroquinone 2%/GA 10% gel two times a day and tretinoin 0.05% cream nightly in the treatment of post-inflammatory hyperpigmentation in patients with Fitzpatrick types IV–VI skin. Patients treated with GA peels showed a trend toward more rapid and greater improvement of post-inflammatory hyperpigmention. An increased lightening of unaffected skin was also noted [43] (2b). Garg et al. found both GA 35% and SMA peels to be effective in the treatment of acne, acne scarring, and post-inflammatory hyperpigmentation, but SMA peels showed statistically significant superiority in the treatment of active acne and post-inflammatory hyperpigmentation. The role of MA versus SA in the outcomes of this study is unclear [44] (3b). While the utility of SA in the treatment of acne is well established (Table 20.4), further study is needed to better understand the potential therapeutic efficacy of other chemical peeling agents for acne.

Salicylic Acid Peels

Salicylic acid (SA) is a 2-hydroxybenzoic acid or ortho-hydrobenzoic acid. Previously classified as a beta hydroxy acid, its properties are most consistent with a phenolic aromatic acid [51, 52]. Similar to AHAs, SA comes from natural sources such as willow bark or may be synthetically produced. As an organic acid, SA extracts desmosomal proteins including desmo-

Table 20.4 Salicylic acid chemical peels in the treatment of acne

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Lee and Kim [61]	Case series; SA 30%	35	A decrease in inflammatory and noninflammatory lesions; no post-procedure differences in stratum corneum hydration, skin surface lipid, skin pH, or transepidermal water loss	4
Ahn and Kim [62]	Case series; SA 30%	24	Gradual skin whitening and significant improvement of redness	4
Dainichi et al. [63]	Case series; SA 30%	436 6 (mice)	Reduced development of comedones and inflammatory papules Histopathology (mice): Early changes of decreased epidermal thickness, near complete removal of cornified cells from hair follicles; late change (2 weeks) of new regularly arranged cells of the cornified layer	4
Hashimoto et al. [64]	Case series; SA 30%	16	Significant reduction (mean of 75%) in comedones	4
Bae et al. [65]	Comparative cohort; SA 30% vs. JS	13	Reduction of inflammatory lesions in both treatments; SA more effective for noninflammatory lesions	3b
Dayal et al. [66]	Randomized comparative; JS vs. SA 30%	40	Greater overall improvement of acne severity including significantly reduced comedone counts with SA	2b

gleins, leading to a loss of cohesion of epidermal cells and subsequent exfoliation [52–54]. In a study of the histologic changes in the skin of hairless mice following peeling with SA, Imayama et al. noted a loss of cornified cells with subsequent activation of epidermal basal cells and underlying fibroblasts without degenerative or inflammatory changes [53] (5). SA is lipid-soluble allowing for penetration of the pilosebaceous unit and a unique comedolytic property. As a lipophilic agent, it removes intercellular lipids covalently linked to the cornified envelope in the uppermost layer of the skin [55]. This property in addition to keratolytic and anti-inflammatory effects make SA well-suited to treat acne. Although less well studied, SA can also be used to treat melasma and photodamage. SA peels are commonly performed at a concentration of 20–30% although lower concentrations are available, particularly over-the-counter for home use [56, 57]. SA has been used in ethyl alcohol solutions and a newer formulation in polyethylene glycol [50, 52, 58]. Although the risk of salicylism is very low in the use of SA as a peeling agent, this new formulation is associated with minimal systemic absorption and is thought to further reduce this risk. Application of SA is associated with a mild to moderate stinging or burning sensation but is transient given an inherent anesthetic effect. Unlike AHAs, SA is a self-neutralizing acid [52].

More recently, beta-lipohydroxy acid (LHA), a lipophilic derivative of SA, has become another option for patients. With an additional fatty chain, LHA has greater lipophilicity and keratolytic effect than SA. It also has comedolytic, antimicrobial, and anti-inflammatory properties [7, 59]. LHA targets the corneosome/corneocyte interface leading to detachment of individual corneosomes and even exfoliation mirroring the natural turnover of skin cells. It is worth noting that this unique property differs from AHAs and SA which may cause only partial detachment and uneven exfoliation. LHA is used in 5% and 10% concentrations. It has a pH similar to normal skin and does not require neutralization [6, 7]. Although the literature on LHA is limited, its efficacy in the treatment of acne and photoaging has been demonstrated in small studies and often in concentrations and vehicles suited for frequent home use [4, 59, 60].

Photodamage and Disorders of Pigmentation

Salicylic acid (SA) may be used to treat a variety of dermatologic conditions including acne, post-inflammatory hyperpigmentation, photodamage, melasma, and fine rhytides (Table 20.5). A pilot study of the safety and efficacy of SA 20–30% peels in the treatment of acne, post-inflammatory hyperpigmentation, melasma, and textural changes in patients with Fitzpatrick type V and VI skin showed moderate (51–75% clearance) to significant (>75% clearance) improvement in 88% of patients. Patients applied hydroquinone 4% for 2 weeks prior to initiation of five salicylic acid peels [45] (4). A prospective, randomized, split-face controlled trial of SA 20–30% peels in the treatment of melasma failed to demonstrate a significant difference when SA was added to hydroquinone 4% [46] (1b). In a double blind, randomized interventional comparative study of JS with SA 30% peels for epidermal melasma, Ejaz et al. demonstrated a statistically significant decrease in MASI scores for both treatment groups, but no significant difference between the groups [47] (2b). And as shown by Joshi et al. in a prospective, randomized controlled, split-face study, SA 20–30% peels for treatment of post-inflammatory hyperpigmentation were rated as clinically effective by patients and approached but did not reach statistical significance according to blinded dermatologist evaluators [48] (1b). Kligman and Kligman described improved texture and a reduction of hyperpigmentation and fine rhytides following treatment with SA 30% peels [49] (4). Furthermore, a study evaluating the effects of SA 30% on tumor formation using hairless SKH/hr1 mice demonstrated a reduction of ultraviolet B-induced skin tumors [50] (5).

Acne

SA has anti-inflammatory, keratolytic, and comedolytic properties that make it a particularly useful treatment for acne. In a study of salicylic acid

30% peels for the treatment of acne in Fitzpatrick type III and IV skin, a decrease in both inflammatory and noninflammatory acne lesions was achieved. No post-procedure differences in stratum corneum hydration, skin surface lipid, skin pH, or transepidermal water loss were seen [61] (4). A subsequent study from the same institution showed a gradual but continual skin whitening effect and a statistically significant improvement in redness following the application of SA 30% peels to acne patients at 2-week intervals for 12 weeks [62] (4). Dainchi et al. demonstrated a reduction of comedones and inflammatory papules with SA 30% peels. Histopathology performed on mice showed early epidermal thinning and dissolution of cornified cells from hair follicles, while late change showed new, regularly arranged cells of the cornified layer [63] (4). As discussed above, Kessler et al. compared GA 30% and SA 30% peels for treatment of acne in a split-face, double-blind, randomized, controlled study and found the peels to be similarly effective [40]. SA peels were associated with a sustained reduction of acne lesions, hypothesized to be secondary to the lipophilicity of SA [40]. This lipophilicity is also responsible for the comedolytic property of SA, and in a study of SA in the treatment of comedonal acne, Hashimoto et al. demonstrated a significant reduction (mean 75%) in comedones [64] (4). This effect was further demonstrated by Bae et al. in a comparative study of SA 30% peels versus JS for acne. Both treatments reduced inflammatory acne lesions, but SA 30% peels were more effective for treating noninflammatory acne [65] (3b). And in a recent comparative study, SA 30% peels were more effective than JS in overall improvement of acne severity including significantly reduced comedone counts [66] (2b).

Jessner's Solution

Jessner's solution (JS) is composed of lactic acid 14%, salicylic acid 14%, and resorcinol 14% in ethyl alcohol. Despite keratolytic properties that have been recognized since the early twentieth century, there is a paucity of literature on its efficacy as a therapeutic agent. Thought to disrupt the epidermal barrier, it is often used to enhance the penetration of additional peeling agents such as trichloroacetic acid (TCA). When used as monotherapy, it has been shown to be effective for many hyperkeratotic skin conditions as well as for acne and melasma [39, 47, 67, 68]. As above, JS has shown equal efficacy to AHAs in the treatment of melasma [30, 47] and acne [39] (2b–3b). And when compared to SA, JS demon-

Table 20.5 Salicylic acid chemical peels in the treatment of photodamage and disorders of pigmentation

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Grimes et al. [45]	Case series; SA 20–30%	25	Moderate (51–75%) to significant (>75%) clearance in 88% of patients treated for acne, post-inflammatory hyperpigmentation, photodamage, melasma, and fine rhytides	4
Kodali et al. [46]	Randomized controlled; SA 20–30%	18	No significant difference when SA added to topical regimen for melasma	1b
Ejaz et al. [47]	Randomized comparative; SA 30% vs. JS	60	Statistically significant decrease in MASI score for both treatment groups, no statistically significant difference between treatment groups	2b
Joshi et al. [48]	Randomized controlled; SA 20–30%	10	Subjective improvement of post-inflammatory hyperpigmentation but not statistically significant when evaluated by blinded dermatologists	1b
Kligman and Kligman [49]	Case series; SA 30%	50	Improved skin texture and a reduction of hyperpigmentation and fine rhytides	4
Dainichi et al. [50]	Animal; SA 30%	10 (mice)	Reduction of UVB-induced skin tumors	5

strates similar effectiveness for treatment of inflammatory acne, but not noninflammatory acne [65, 66] (2b–3b).

Microdermabrasion

Developed in Italy in 1985, microdermabrasion (MDA) is an effective method of superficial skin resurfacing [69]. It is appealing to providers and patients given its safety and tolerability. No local anesthesia or preoperative medications are required, and post-procedure recovery is minimal. MDA has been classified by the US Food and Drug Administration as a Class 1 device (low risk) and is therefore subject to little regulatory control [70]. Many MDA units are closed-loop negative pressure systems that pass aluminum oxide microcrystals over the skin while simultaneously vacuuming used crystals and skin debris. Other microcrystals used include magnesium oxide, sodium bicarbonate, and sodium chloride. Some systems are crystal-free utilizing a handpiece with an abrasive diamond-studded tip [71, 72]. MDA has shown to be effective for treatment of photodamage, acne and post-procedure scars, striae distensae, and superficial rhytides [73]. The number of passes performed depends on desired effect and patient tolerability although typically a minimum of 2–3 passes is required [57, 73]. Mild to moderate erythema without significant abrasion, petechiae, or purpura is the desired post-procedure end point. As with superficial chemical peels, a series of treatments (usually four to eight) is recommended. Treatments may be performed weekly to every other week. Complications include petechiae or purpura and may be indicative of prolonged dwell time or excessive vacuum suction. This may also be seen in patients with severely photodamaged skin or on anti-coagulation. Treatment may induce or exacerbate erythema or telangiectasia, so it should be used with extreme caution or perhaps contraindicated in patients with rosacea [73].

Indications for treatment are varied and data on efficacy is limited for MDA but growing (Table 20.6). In an early study of microdermabrasion, Tsai et al. demonstrated good to excellent

Table 20.6 Microdermabrasion in the treatment of multiple cutaneous conditions

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Tsai et al. [74]	Case series	41	Good to excellent clinical improvement of scarring related to acne, surgery, burns, and varicella zoster infection	4
Shim et al. [73]	Case series	14	Statistically significant improvement in roughness/textural irregularities, mottled pigmentation, and complexion but not in rhytides, comedones, or milia Acute histopathology: Thinning of the stratum corneum with focal compaction and homogenization Chronic histopathology: Thickened epidermis, decreased melanization, increased elastin	4
Tan et. Al [75]	Case series	10	Mild improvement of photodamage Histopathology: Slight orthokeratosis and flattening of rete ridges; perivascular infiltrate, edema, and vascular ectasia	4
Lloyd et al. [76]	Case series	25	Good to excellent improvement of acne	4
Hernandez-Perez and Ibiett [77]	Case series	7	Improvement of skin, dilated pores, thick skin, and fine rhytides Histopathology: Increased epidermal thickness; decreased atrophy, horny plugs, and basal cell liquefaction; increased epidermal polarity Dermal changes included decreased elastosis, edema, telangiectasias, and inflammation	4
Coimbra et al. [78]	Case series	25	Improvement of hyperchromatic discoloration with subjective improvement of fine rhytides Histopathology: Increase in organized collagen and epidermal thickness	4

(continued)

Table 20.6 (continued)

Reference	Study design	N	Clinical/histopathologic outcomes	Evidence level
Bhalla and Thami [79]	Randomized comparative	30	Mild improvement in post-acne scarring, melasma, and facial rejuvenation	2b
El-Domyati et al. [80]	Case series	38	Majority of patients with mild to moderate clinical improvement in melasma, acne scars, and striae distensae; mild in photoaging Histopathology: Decreased melanization and regular distribution of melanosomes in the epidermis in the melasma treatment group; increased density of collagen fibers with more regular arrangement in collagen bundles in the melasma, acne scars, and striae distensae treatment groups	4
Abdel-Latif and Elbendary [81]	Controlled cohort	20	Good to excellent results (greater than 50% improvement of appearance) in 50% of the patients; more marked improvement was noted of striae rubra compared to striae alba Upregulation of type I procollagen mRNA expression was increased in treated skin	3b
Freedman et al. [82]	Case series	10	Histopathology: Epidermal and papillary dermal thickening, increased dermal inflammation, and increased collagen and elastic fibers	4
Hussein et al. [83]	Comparative cohort	45	Histopathology: Increases in epidermal thickness, fibroblast count, dermal vascular ectasia, patchy and perivascular inflammation, and densely arranged thick collagen fibers	3b
Karimipour et al. [84]	Case series	49	Elevation of transcription factors, primary cytokines, matrix metalloproteinases, type I procollagen mRNA and protein levels	4
Karimipour et al. [85]	Comparative cohort	10	Negative pressure: Increased gene expression of MMP-1 and MMP-3 Negative pressure + abrasion: Increased c-Jun component of activator protein-1, interleukin 1β, tumor necrosis factor-α, MMP-1, 3, 9	3b
Rajan and Grimes [86]	Comparative cohort	8	Aluminum oxide and sodium chloride MDA associated with a statistically significant initial increase in transepidermal water loss followed by return to less than baseline at day 7 Statistically significant increase in stratum corneum hydration observed at day 7 with sodium chloride MDA, similar trend with aluminum oxide MDA	3b

clinical improvement of scarring related to acne, surgery, burns, and varicella zoster infection. A pressure between 1 and 4 bar (76 mmHg) was used and multiple treatments (mean 9.1) were required for the 41 patients studied, highlighting the need for more aggressive MDA in the treatment of acne scars in particular (mean treatments 15.19) [74] (4). Further supporting the possible benefit of more aggressive treatment, Alam et al. compared low-intensity glycolic acid peels to low-intensity MDA for facial skin rejuvenation and found no significant clinical improvement from baseline with either treatment (Table 20.1) [28] (2b). A study looking at the clinical improvement of photoaging by patient assessment following MDA every 2 weeks for a total of six to seven treatments over 12–14 weeks showed statistically significant improvement in roughness/textural irregularities, mottled pigmentation, and complexion, but not in rhytides, comedones, or milia. And consistent with previous studies, acne scarring did occasionally improve but required deeper ablation [73] (4). Tan et al. also evaluated the effect of MDA on photodamaged skin. Of nine patients that completed at least five weekly treatments, five patients had mild (1–25%) improvement and one patient had moderate (26–75%) improvement as determined by physician review of post-treatment photographs. Skin thermography showed increased skin temperature, consistent with increased blood flow, while transient decreases in surface sebum post-procedure were also noted. Analysis of cheek skin demon-

strated a statistically significant decrease in skin stiffness and an increase in skin compliance [75] (4). A pilot study on the use of MDA for grade II-III acne in 24 patients demonstrated excellent results in 9 patients, good results in 8 patients, fair results in 4 patients, and poor results in 3 patients. Notably, 23 of 24 patients were happy with their results [76] (4). MDA has also been reported to improve oily skin, dilated pores, thick skin, and fine rhytides [77] (III/B). Using blinded observers (plastic surgeons and laypersons), Coimbra et al. demonstrated subjective improvement in hyperchromatic discoloration (both groups) and fine rhytides (laypersons only) after patients had received eight MDA treatments at 1-week intervals [78] (IV/B). A study of MDA in post-acne scarring, melasma, and facial rejuvenation demonstrated mild improvement that increased when used with a topical retinoid [79] (II/A). And in a recent study by El-Domyati et al., 38 patients with melasma, acne scars, striae distensae, or photoaging were treated with eight microdermabrasion treatments performed at 1-week intervals. A majority of patients had mild to moderate clinical improvement in melasma, acne scars, and striae distensae, while mild improvement was most common in photoaging. Histopathology demonstrated decreased melanization and regular distribution of melanosomes in the epidermis in the melasma treatment group and an increased density of collagen fibers with more regular arrangement in collagen bundles in the melasma, acne scars, and striae distensae treatment groups [80] (III/B). In a clinical and molecular study of MDA on striae distensae in 20 patients receiving five MDA treatments at weekly intervals to one side of the body with the other side of the body used as a matched control, good to excellent results (greater than 50% improvement of appearance) were achieved in 10 patients, with mild to moderate results (up to 50% improvement of appearance) in the remaining 10 patients. More marked improvement was noted of striae rubra compared to striae alba. Using real-time reverse transcriptional polymerase chain reaction for assay in patient biopsies, upregulation of type I procollagen mRNA expression was increased in treated skin [81] (III/B). The effectiveness of MDA in treating disorders of collagen appears to be proportional to the overall aggressiveness of the treatments including level of ablation and total number of treatments [73, 74]. The histopathologic changes in the skin following MDA have been studied in an effort to better understand the mechanism behind improvement of disorders of collagen. Shim et al. found that acute histopathologic change included thinning of the stratum corneum with focal compaction and homogenization. The chronic effects of MDA treatment included a thickened epidermis without a change in the stratum corneum from baseline, a more regular distribution of melanosomes and decreased melanization, and increased elastin. Papillary mucin and collagen content were not consistently elevated [73] (III/B). Hernandez-Perez et al. evaluated atrophy, horny plugs, loss of polarity, and basal cell liquefaction of the epidermis after five weekly MDA treatments and saw microscopic improvement in all parameters. The most marked change was in epidermal thickness with statistically significant post-treatment changes ranging from 0.01 mm to 0.1 mm. Dermal changes included decreased elastosis, edema, telangiectasias, and inflammation [77] (4). Another study found epidermal and papillary dermal thickening, increased dermal inflammation, and increased collagen and elastic fibers [82] (4). It has been noted that the inflammation seen after repetitive epidermal and dermal injury following a series of MDA treatments resembles a reparative process with increases in fibroblasts and collagen and is ultimately responsible for the clinical effects of MDA [77, 83]. Coimbra et al. also demonstrated an increase in organized collagen and epidermal thickness [78] (4). An immunohistological and ultrastructural study confirmed increases in epidermal thickness, fibroblast count, dermal vascular ectasia, patchy and perivascular inflammation, and densely arranged thick collagen fibers [83] (3b). Karimipour et al. examined the molecular effects of a single MDA treatment in 49 patients. Elevation of transcription factors, primary cytokines, matrix metalloproteinases, type I procollagen mRNA, and protein levels was noted.[84] (4). A subsequent study concluded that abrasion is required for stimulating the expression of genes involved in dermal remodeling [85] (3b). Rajan

and Grimes evaluated skin barrier changes following MDA in a split-face study of aluminum oxide and sodium chloride MDA. Both treatments were associated with a statistically significant initial increase in transepidermal water loss followed by return to less than baseline at day 7. A statistically significant increase in stratum corneum hydration was seen with sodium chloride MDA at day 7. The authors note that these findings suggest enhanced lipid barrier function and are likely responsible for improved clinical appearance following MDA [86] (3b). This barrier disruption also increases skin permeability and can serve to enhance transdermal drug delivery [87, 88].

The risks associated with MDA are limited. Mild abrasion and petechiae may occur. Scarring may be possible with aggressive treatment but has not been reported. Post-treatment pigmentary aberrations are rare, but MDA should be used cautiously in darker Fitzpatrick skin types. Ocular complications can be seen in crystal-based systems. Infections, including reactivation of herpes simplex virus can occur [79, 89].

Conclusion

Superficial chemical peels and microdermabrasion have proven to be safe and efficacious for many skin disorders. Often best performed in a series, they are an acceptable alternative to more aggressive procedures for patients seeking mild to moderate results, limited downtime, and with a willingness to undergo a series of treatments with diligent pre- and post-treatment regimens. These procedures have the added benefit of safety for patients with darker Fitzpatrick types. Serving to enhance the effects of other therapies, they play an important role in the armamentarium available to clinicians.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE
Commonly used nonlaser superficial resurfacing procedures include chemical peels (alpha hydroxy acids, salicylic acid, Jessner's solution) and microdermabrasion	N/A
Alpha hydroxy acids are effective in disorders of keratinization and photodamage	B
Alpha hydroxy acids are effective in the treatment of melasma, particularly as an adjunct to topical therapy	B
Alpha hydroxy acids are effective in the treatment of acne and its sequalae	B
Alpha hydroxy acids induce histopathologic changes including thinning of the stratum corneum and thickening of the epidermis	B
Salicylic acid is effective in the treatment of acne	B
Salicylic acid is effective in the treatment of photodamage and pigmentary changes	B
Salicylic acid has been shown to induce the following histopathologic changes: loss of cornified cells and cornified material within hair follicles, activation of epidermal basal cells and underlying fibroblasts without degenerative or inflammatory changes	D
Microdermabrasion has shown efficacy in the treatment of photodamage, acne, acne scarring, melasma, and striae distensae	B
Microdermabrasion has been shown to induce the following histopathologic changes of the epidermis: increased epidermal thickness, a more regular distribution of melanosomes and decreased melanization, decreased basal cell liquefaction, normalization of epidermal polarity	C
Microdermabrasion has been shown to induce the following histopathologic changes of the dermis: papillary dermal thickening, increased collagen and elastic fibers, decreased elastosis	C
Microdermabrasion has been shown to activate a dermal remodeling cascade including cytokines, transcription factors, and matrix metalloproteinases.	C
Microdermabrasion has been shown to decrease transepidermal water loss and increase stratum corneum hydration	C

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Self-Assessment Questions

1. Which of the following is NOT a superficial resurfacing technique?
   (a) Jessner's solution
   (b) Jessner's-trichloroacetic acid peel
   (c) Salicylic acid peel
   (d) Glycolic acid peel
   (e) Microdermabrasion
2. Alpha hydroxy acids are effective in the treatment of which of the following?
   (a) Disorders of keratinization
   (b) Acne
   (c) Melasma
   (d) Photodamage
   (e) All of the above
3. Salicylic acid is a particularly effective treatment for acne due to which properties?
   (a) Anti-inflammatory
   (b) Keratolytic
   (c) Lipophilic/comedolytic
   (d) b and c
   (e) All of the above
4. Jessner's solution contains all of the following EXCEPT:
   (a) Glycolic acid
   (b) Resorcinol
   (c) Ethanol
   (d) Salicylic acid
   (e) Lactic acid
5. Which of the following is TRUE regarding microdermabrasion?
   (a) Microcrystals passed over the skin include aluminum oxide, magnesium oxide, sodium bicarbonate, and sodium chloride
   (b) Classified by the US Food and Drug Administration as a Class 1 device (low risk) and is therefore subject to little regulatory control
   (c) Induces epidermal and papillary dermal thickening on histopathology
   (d) Has shown efficacy in the treatment of photodamage, acne, acne scarring, melasma, and striae distensae
   (e) All of the above

Correct Answers

1. b: Jessner's-trichloroacetic acid peel. The Jessner's + trichloroacetic acid (35%) peel is a medium-depth peel (destruction of the epidermis and a portion of or the entire papillary dermis) used for treatment of photodamage, rhytides, and actinic keratoses. Superficial chemical peels primarily affect the epidermis and include alpha hydroxy acids (AHAs), salicylic acid (SA), and Jessner's solution.
2. e: All of the above. Alpha hydroxy acid chemical peels may be an effective treatment for disorders of keratinization, acne, melisma, and photodamage.
3. e: All of the above. Salicylic acid has anti-inflammatory, keratolytic, and comedolytic properties that make it a particularly useful treatment for acne.
4. a: Glycolic acid. Jessner's solution (JS) is composed of lactic acid 14%, salicylic acid 14%, and resorcinol 14% in ethyl alcohol.
5. e: All of the above. All statements are true. Microdermabrasion is an effective method of superficial skin resurfacing and has shown to be effective for treatment of photodamage, acne and post-procedure scars, striae distensae, and superficial rhytides.

Dermabrasion

21

Ramona Behshad

Abstract

Dermabrasion (DA) has been in the dermatology armamentarium since the early 1900s with both aesthetic and therapeutic indications. DA physically removes the superficial skin layers in a stepwise fashion and allows healing to occur with a more cosmetically acceptable result. There are a variety of abrasive instruments available to perform DA. Mechanical DA uses a rotating diamond fraise or wire brush attached to a motorized hand piece to abrade the epidermis and papillary and/or reticular dermis. The wire brush has numerous small caliber, stainless steel wires that project circumferentially from the curved side of a cylindrical hub, while the diamond fraise consists of a stainless steel cylinder to which industrial-grade diamonds are bonded to create the abrasive surface. Selection of an appropriate end piece for use in the handheld rotary motor is up to the preference of the surgeon, but there has been a slow movement toward the diamond fraise because it is less aggressive and more forgiving than the wire brush (Alt, J Dermatol Surg Oncol 13:618–624, 1987). An alternative to mechanical DA is manual DA, which is performed in an analogous fashion by hand with a variety of coarse surfaces such as sandpaper, drywall screen, electrocautery tip cleaners, the diamond fraise unattached to the electric motor, abrasive pads, tangential planning or scalpel sculpting with a standard #15 surgical blade or razor blade, as well as the standard curette. Regardless of motorized or manual DA selected, depth of injury is controlled by the amount of pressure holding the instrument tip against the skin, the speed of rotation/abrasion, the coarseness of the tip chosen, and the patient's skin type and texture (Orentreich and Orentreich, Dermatol Clin 13:313–327, 1995). The operator has excellent control of the anatomic depth of tissue removed, since the depth of tissue can be visualized sequentially from epidermis and the papillary, superficial, and deep reticular dermis.

Keywords

Dermabrasion · Scar revision · Rhytids · Mechanical resurfacing · Wrinkles · Acne scars

Introduction

Dermabrasion (DA) has been in the dermatology armamentarium since the early 1900s with both aesthetic and therapeutic indications. DA physically removes the superficial skin layers in a

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stepwise fashion and allows healing to occur with a more cosmetically acceptable result. There are a variety of abrasive instruments available to perform DA. Mechanical DA uses a rotating diamond fraise or wire brush attached to a motorized hand piece to abrade the epidermis and papillary and/or reticular dermis. The wire brush has numerous small caliber, stainless steel wires that project circumferentially from the curved side of a cylindrical hub, while the diamond fraise consists of a stainless steel cylinder to which industrial-grade diamonds are bonded to create the abrasive surface. Selection of an appropriate end piece for use in the handheld rotary motor is up to the preference of the surgeon, but there has been a slow movement toward the diamond fraise because it is less aggressive and more forgiving than the wire brush [1]. An alternative to mechanical DA is manual DA, which is performed in an analogous fashion by hand with a variety of coarse surfaces such as sandpaper, drywall screen, electrocautery tip cleaners, the diamond fraise unattached to the electric motor, abrasive pads, tangential planning or scalpel sculpting with a standard #15 surgical blade or razor blade, as well as the standard curette. Regardless of motorized or manual DA selected, depth of injury is controlled by the amount of pressure holding the instrument tip against the skin, the speed of rotation/abrasion, the coarseness of the tip chosen, and the patient's skin type and texture [2]. The operator has excellent control of the anatomic depth of tissue removed, since the depth of tissue can be visualized sequentially from epidermis and the papillary, superficial, and deep reticular dermis.

Molecular Mechanisms

The ultrastructural and molecular alterations that accompany the clinically visible changes apparent in dermabraded skin have been investigated. Harmon et al. performed an ultrastructural evaluation of scars resulting from a primary closure and those who underwent primary closure with diamond fraise DA 6–8 weeks later [3]. Serial punch biopsies showed organized, unidirectional collagen fiber orientation parallel to the epidermal surface in the DA specimens, whereas the control specimens were found to have sparser and less well-organized collagen fiber orientation. They also observed that DA alters cell–cell and cell–matrix interactions between the epidermis and the dermis by up-regulation of tenascin (an extracellular matrix glycoprotein) expression throughout the papillary dermis, which may promote both epithelial cell migration and fibroblast movement, and of α6 β4 integrin subunit (a transmembrane adhesion receptor) on the keratinocytes throughout the stratum spinosum, which may coincide with an increase in cell migration and may promote re-epithelialization across the scar. Yarborough proposed that DA created a reorientation of collagen fibers parallel to the lines of wound tension, which may account for some of the scar contour smoothing effects noted after the procedure [4]. Similar changes have been seen in photoaging and rhytids. Nelson et al. looked at patients with photoaging who underwent motorized DA before and after treatment [5]. At 12 weeks, when compared to baseline, they showed significant increases in collagen and a sixfold increase in procollagen I mRNA in papillary dermal fibroblasts.

There is a great deal of literature regarding the utility of DA in dermatology, but the bulk of the literature consists of personal experiences, case studies, cohort studies, and randomized controlled trials of varying quality. The fact remains that variable results will always occur when a technically demanding procedure is performed by operators with various levels of skill. This chapter will present the published literature on DA and when available, the level and method of DA is included. To determine whether the evidence is applicable to a specific patient requires physician expertise, an understanding of the patient's preferences, and consideration of the availability, risks, and benefits of the intervention.

Indications for Dermabrasion

DA is most commonly used to improve the appearance of acne scars, but many physicians have successfully used DA to treat skin diseases which previously had no known treatment or as an adjunct in the treatment of dermatologic disorders. Case reports document response to hypertrophic and traumatic scars, actinically damaged and wrinkled skin, pigmentary abnormalities, tattoo removal, adnexal tumors, and Darier's disease, among others. A list of these case studies has been summarized in Table 21.1. A review of these cases, in addition to the literature presented in this chapter, demonstrates that DA has been successfully used in all patient

Table 21.1 Case studies on dermabrasion

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Agrawal et al. 1995 [6]	Vitiligo	21 patients (10–33 years) with 32 stable vitiligo patches (neck, abdomen, chest, lower limb, upper limb, face)	1–6 years, with 3 patients lost to follow-up	Dermabrasion with thin STSG (0.025–0.03 mm thick) from the posterior arm, posterior thighs, and gluteal region; 100% repigmentation was seen in 27 patches and 90–95% in 10 patches. Time to satisfactory color match was 4–9 months (average 6.3 months)	5 cases of donor site pain, 6 cases of milia at the recipient site, 3 cases of overhanging margin due to the thicker graft, and 2 cases of irregularity over the surface of the graft
Agrawal et al. 1992 [7]	Xeroderma pigmentosum	3 patients (10–22 years, 2 females and 1 male) with xeroderma pigmentosum	18–24 months	Dermabraded areas tumor-free at follow-up	None
Bergfeld et al. 1970 [8]	Granuloma faciale	1 patient (31-year-old African American lady)	6 months	Lesions on malar cheek with sustained flattening, lesions on nose with poor response	None
Clabaugh et al. 1975 [9]	Tattoos	250 patients	Up to 5 years	85% good-to-excellent results, 10% fair results, and 5% poor results	Hyperpigmentation, atrophy, hypopigmentation, hypertrophic scarring in 4 cases
Coleman et al. 1996 [10]	Actinic keratoses	23 patients (33–76 years)	At least from 2 years up to 10 years	96% of patients remained free of new actinic keratoses for 1 year, 83% remained free for 2 years, 70% remained free for 3 years, 64% remained free for 4 years, and 54% remained free for 5 years	None
Diven et al. 1990 [11]	Exogenous ochronosis	53-year-old African American lady	Not mentioned	Improved color and surface contour	None
Drake et al. 1992 [12]	Facial angiofibromas	24-year-old woman	6 months	Cosmetic improvement; no hemorrhage	None

(continued)

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Dufresne et al. 2008 [13]	Actinic cheilitis	4 patients after Mohs for SCC of the lower lip with intraoperative DA	6 months	No recurrence of SCC or actinic cheilitis	One patient had a small vertical scar
Earhart et al. 1976 [14]	Adenoma sebaceum	15-year-old white girl and 15 –year-old white male	2–4 years	Excellent cosmetic improvement with flattening of lesions and obliteration of telangiectasias	None
Emsen et al. 2007 [15]	Acne scars and burn scars	15 patients with mature acne (8 men and 1 women; average 20.5 years) and acute burn scars (5 men and 1 women; average age 25.5 years) on the head and neck	Not stated	Physician and patients retrospectively rated outcomes after a single treatment as good, very good, and excellent	None
Emsen et al. 2008 [16]	Scars, tattoo	40 patients for burn scars (15 patients), depressed scars (6), acne scars (2), hypertrophic scars (3), trap door scars (9), cellulite (2), periorbital wrinkles (2), and a tattoo (1)	10 months to 6 years	Improvement was seen in 80% of patients at 10-month follow-up (95% CI 60–100%). Ten patients felt that the untreated side looked better	4 patients developed infections that were controlled with antibiotics
English et al. 1971 [17]	Favre-Racouchot syndrome	51-year-old white man	1 month	Dermabrasion with extraction of some cysts during procedure; excellent cosmetic result	None
Epstein et al. 1956 [18]	Actinic keratoses	57-year-old women, 44-year-old white man, 38-year-old white man	N/A	Removal of actinic keratoses in 1 patient on hand, unsuccessful in 1 patient on nose, improvement in number of keratoses posttreatment on lower lip of 1 patient	None

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Epstein et al. 1966 [19]	Actinic keratosis, leukoplakia, radiodermatitis	10 patients	10 years	4 patients with no recurrences (3 actinic keratoses patients and one leukoplakia patient), 4 cases with recurrences but benefit (one radiodermatitis patient, 2 leukoplakia patients, 1 actinic keratoses patient); 2 patients with fairly early recurrence and/or the development of malignant neoplasia (1 radiodermatitis patient, 1 actinic keratosis patient)	None
Fischer et al. 2001 [20]	Facial angiofibromas	37-year-old African American man	6 months	Shave excision followed by two DA treatments to papillary dermis; smoothing of skin with good cosmetic outcome	No hypopigmentation; no regrowth at follow-up
Fowler et al. 1985 [21]	Non-X histiocytosis on face	22–year-old male	18 months	Excellent cosmetic results with resolution of histiocytic infiltrate on biopsy	None
Fulton et al. 1987 [22]	Osteoma cutis secondary to acne	3 patients (23–48-year white females)	2 months	Dermabrasion followed by punch excision; marked cosmetic improvement	1 keloid that resolved with flurandrenolide tape
Gold et al. 1987 [23]	Hypertrophic psoriasis	65-year-old white male	8 weeks+	8-week clearance possibly due to a temporary reverse Koebner phenomenon; disease recurred shortly thereafter	None
Hamm et al. et al. 1994 [24]	Hailey-Hailey disease	10 patients (36–57 years)	3–79 months (median 42 months)	Treated areas were disease-free, except for major recurrences in 4 sites and minor recurrences in 4 sites; areas were retreated without relapse; punch biopsies up to 59 months later showed no histologic abnormalities beyond scarring	Hypertrophic scarring in 6 patients; 2 patients with hypopigmentation
Hanke et al. 1987 [25]	Multiple facial neurofibromas	3 patients (33–46-year-old women)	5–6 years (one patient lost to follow-up)	Considerable smoothing of the skin for all patients; one patient with moderate recurrence of neurofibromas at 5 years although still more improved than baseline	One patient had postoperative erythema that resolved after 4 months

(continued)

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Iverson et al. 1947 [26]	Traumatic tattoos	5 photographic cases	5 weeks	Avoidance of disfigurement and surgical repair	Scarring, including hypertrophic scarring; 8–10 weeks of erythema
Kahn et al. 1995 [27]	Vitiligo	1 patient (35 years old Caucasian man)	14 weeks	Dermabrasion prior to epithelial sheet grafting from thighs; 95% of the operative areas had regained pigmentation	None
Kaufman et al. 1987 [28]	Scleromyxedema	1 patient	4 months	Smoother skin noted	None
Kishi et al. 2007 [29]	Congenital melanocytic nevi	23 patients (from 1 month to 19 years)	At least 3 years	Curettage followed by dermabrasion; 2 patients had recurrence after 1 month thought to be due to extension of nevoid cells around and within hair follicles, sebaceous glands and eccrine apparatus	None
Konrad et al. 2001 [30]	Hailey-Hailey disease	62-year-old lady	12 months	Area pretreated with botulinum toxin A before dermabrasion; remission of disease	None
Lapins 1983 [31]	Telangiectasia on nose	46-year-old white lady	6 months	Good ablation of vessels	None
Lien et al. 1997 [32]	Nodular amyloidosis	1 patient (45-year-old male)	26 months	No recurrence	None
Manchada et al. 1967 [33]	Small pox scar	60 patients (11–40 years)	4 months–4 years	Superficial and discrete scars became fairly imperceptible, moderate scars improved 30–40%, deep scars demonstrated temporary benefit	Hyperpigmentation in 6 patients
Menon 1982 [34]	Facial angiofibromas	17-year-old girl	2 weeks	Considerable flattening and cosmetic improvement	None
Niechajev et al. 1992 [35]	Perioral wrinkles	54 patients (27–73-year-old women)	1–5 years	A long-standing improvement in superficial and deep wrinkles was obtained, and there was only a slight improvement to the nasolabial fold	Permanent hypopigmentation was seen in 67% of patients that was easily coverable with makeup; milia
Notaro 1983 [36]	Traumatic tattoo	1 patient (21-year-old white male)	2 weeks	Acceptable cosmetic results	Mild residual erythema at 2 weeks
O'Neill et al. 2011 [37]	Large congenital melanocytic nevus on the face	4-week-only infant	5 months	Mechanical dermabrasion combined with autologous cell suspension (ReCell®); improved skin texture and normalization of skin color	None

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Olson 1960 [38]	Psoriasis	17 patients	10 weeks	Patients pleased	2 patients discontinued treatment due to oozing
Olsson et al. 1995 [39]	Vitiligo	100 patients (60 women and 40 men) aged 12–68	5–8 months	90–100% repigmentation were seen in 40 patients, 65–94% in 32 patients, 20–64% in 22 patients, and 0–19% in 6 patients. At 1-year f/u in 50 patients and 2 years in 10 patients, all the repigmented areas seen at the 6-month examination remained pigment	Hypopigmentation around the periphery of the graft
Pepper E et al. 1985 [40]	Giant seborrheic keratosis	71-year-old white male	2 weeks	No recurrence	Mild hypertrophic scarring
Roenigk et al. 1977 [41]	Nevus angiomatosus	1 patient (28 years)	Not provided	Good result	None
	Trichoepithelioma	2 patients (28–42 years)	From 1 month to 3 years	Partial recurrence at 3 years; no recurrence in 1 patient at 1 month	Hypopigmentation that resolved after 3–4 months in a black patient
	Syringoma	1 patient (25-year-old black lady)	6 months	Partial recurrence at 6 months	None
	Adenoma sebaceum	3 patients	3 years	Good cosmetic outcome	None
	Recurrent BCC	1 patient (42-year-old lady)	1 year	No recurrence	None
	Decorative tattoo	1 patient	N/A	Good clearance	None
	Traumatic tattoo	1 patient (28-year-old male)	N/A	Complete clearance	None
	Keloid scar	21-year-old lady	N/A	Significant improvement	None
	Discoid lupus erythematosus	N/A	N/A	Improvement in scarring but not in pigment	Flare of disease
	Darier's disease	N/A	N/A	Good improvement in dermabraded areas	None
	Epidermal nevus	3 patients (8–21 years)	From 6 months to 1 year follow-up	No recurrence in 2 patients; 1 partial recurrence at 6 months	Temporary hyperpigmentation that resolved after 3 months in an Indian patient

(continued)

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Rompel et al. 1997 [42]	Congenital nevocellular nevi	215 patients	Median 24 months	Good reduction in pigment in 33.8% and satisfactory removal in 29.7%; improvement showed a significant dependence of the size of the congenital nevus ($p < 0.0001$) and the age at the time of DA ($p < 0.001$) with best results in large nevi treated during newborn age	Hypertrophic scarring in 14.6%, fever without infection in 10.5%, hemoglobin decreased in 2.7%, wound infection in 5.9%, postoperative bleeding in 0.5%
Spencer et al. 1992 [43]	Porokeratosis of Mibelli	79-year-old Pilipino lady	15 months	No evidence of recurrence	Hypertrophic scar that resolved with 20 mg/ml triamcinolone injection
van Lynden-van Nes 2005 [44]	Milia en plaque	60-year-old white lady	9 months	Complete resolution with additional improvement in telangiectasias	None
Vukas 1974 [45]	Small pox scars	3 patients et al. 19–56 (2 women, 1 man)	N/A	Improvement in 2 patients; no change in 1 patient	None
Wee et al. et al. 1990 [46]	Hypertrophic flap (nasalis myocutaneous island flap)	19 patients (11 women, 8 men; 30–76 years)	1 month to 2.5 years	Selected patients, including those younger than 40 years, had scars greatly improved by early dermabrasion 6–8 weeks following surgery	None
Wong et al. et al. 1982 [47]	Lichen amyloidosus	7 patients (7 men, 48–61 years)	5–7 years	Itching disappeared in all cases with satisfactory clinical results with resolution of hyperkeratosis; 3 patients had follow-up biopsies at 3 years with one showing no amyloid and two showing markedly reduced amyloid	Mild hyperpigmentation; infection in one patient that healed with hypertrophic scarring

Table 21.1 (continued)

Reference	Condition treated	Patient(s) characteristics	Follow-up	Outcomes/comments	Side effects
Zachariae et al. et al. 1993 [48]	Vitiligo	3 female patients (12–60 years)	1–3 years	Dermabrasion with epithelial suction blister grafts (3 patients) and autologous cultured melanocytes (1 patient, who had both procedures separately); 1 patient with repigmentation after sheet grafting who later underwent cultured melanocyte transfer with treated areas stable for 1–3 years; 2 patients with incomplete and uneven pigmentation with epidermal grafting alone	Donor sites with slight hyperpigmentation

demographics. Those with dark complexions, however, may experience pigment issues post-treatment that require additional counseling. Yarborough has shown that all skin types can be dermabraded with reasonably predictable pigmentary response with procedure-related dyschromia resolving within 3–4 weeks [49]. Orentreich, in a description of his own experience with DA, reiterates that black patients fare extremely well with DA but Asiatic skin is extremely reactive [2]. Aggressive therapy is associated with a higher complication rate such as hypopigmentation and scarring, and it is best to advise multiple DAs or ancillary techniques such as punch grafting or excisional techniques in patients with darker Fitzpatrick skin types (III–VI). Although a favorable test spot result does not guarantee a positive outcome following DA, an unfavorable test spot result is useful in identifying patients at risk for such complications [50].

Effectiveness of Dermabrasion

The indications for DA include those lesions or skin defects of the epidermis, papillary dermis, and upper reticular dermis that can be partially or completely removed by resurfacing to the level of the reticular dermis. Acne scars, surgical scars, striae, actinic keratosis, and photodamage have all been investigated.

Acne Scars

DA has been particularly successful in treating superficial atrophic acne scars, such as rolling or

boxcar scars [51] (IIB). In a study of 25 patients aged 20–42 years (23 were Fitzpatrick skin types I–III, 2 were Fitzpatrick skin type IV; 18 females and 7 males) treated with diamond fraise DA evaluated with flash photography, case impressions with computer analysis of surface irregularities, and scar counting, there was a statistically significant reduction in the number of superficial scars, but not deep scars, after 1 year ($p < 0.05$). The results were rated by two independent clinicians. This suggests that deeper, ice pick scars are too deep to be effectively treated by DA. Computer analysis showed smoothing in approximately 50% of patients. On the patient satisfaction survey, 21 were satisfied or content, while 4 were unsatisfied. These results are lower than other published studies and may underestimate the true improvement seen with DA given the dry wound care allowing eschars to form, which is contrary to the moist wound care practices of today.

Surgical Scars

DA has been shown to improve the appearance of elevated full-thickness skin grafts [52] (IIB). Two hundred consecutive Mohs surgery patients repaired with a full-thickness skin graft on the nose (105 patients), periorbital skin (57), lips (5), and chin (3) were included in the study. All patients were followed up for 2 years, and eight patients were subsequently excluded because their graft size was too small (lip and chin grafts). The remaining 192 patients were followed up at 6–8 months and sequentially assigned to DA (diamond fraise, endpoint papillary dermis) or to sun protection over a 3-year period. The method of group assignment was not clear. Photographs were taken up to 24 months after grafting, and clinical assessment was made in a blinded fashion. The control group experienced most improvement by 6 months, although 27% continued to improve between 6 and 18 months. The authors suggested cautious waiting for at least 6 months before correcting a graft, given the spontaneous improvement without treatment during this time. Grafts that were depressed at 6 months remained depressed regardless of treatment, suggesting DA is not the treatment for these grafts. The greatest objective improvement is obtained by DA when the grafted skin border is elevated above the surrounding skin. Similar grafts in age-matched control subjects did not spontaneously flatten to the same extent. When taking all grafts in all locations, there was no statistical difference in clinical assessment between the control group and treated group (50% vs. 60%, $p > 0.2$). A patient questionnaire after 18 months that showed fewer patients in the DA group believed they were greatly improved when compared to the control group (40% vs. 12%, $p < 0.001$), possibly due to unmet expectations from treatment.

Manual DA has also been evaluated in improving surgical scars. In a prospective, randomized, split-scar model, facial surgical scars were evaluated in 15 patients after manual DA using sterile 200 grit sandpaper (endpoint pinpoint bleeding) [53] (IIB). Patients who had undergone a surgical procedure on the face within 8 weeks prior to enrollment were enrolled in this prospective study. Follow-up visits were scheduled at 1 month, 3 months, and at least 6 months after treatment when two blinded reviewers evaluated the appearance of the halves. There was 100% follow-up at 6 months, with improvement in the treated half of the scar seen in 12 of 15 (80%) scars (95% CI, 60–100%). Three scars were graded to have a better clinical appearance on the untreated side, which the authors attributed to baseline asymmetries in the scars. A patient questionnaire was distributed and showed that 73% of patients indicated that they would have the procedure again, with the treated side having a better overall appearance.

Striae

Striae rubra may respond to superficial DA based on limited evidence. A randomized, open-label, single-center study of 32 young women (11–24 years) with narrow, early striae rubra (≤6 months old) on the trunk and thighs compared the efficacy of 16 weekly sessions of superficial DA (endpoint no bleeding or pain) to daily application of topical tretinoin 0.05% cream for

16 weeks [54] (IIB). Treatment groups were well matched. Striae length and width were measured and compared between groups for up to 16 weeks with photographs and assessment for side effects. The Global Aesthetic Improvement Scale scores and patient satisfaction scores were also assessed. Three DA patients (one lost to follow-up, one withdrawal of consent, one due to weight gain) and seven tretinoin patients did not complete the study (three due to irritant dermatitis, three withdrawal of consent, and one loss to follow-up). Both treatments demonstrated significant improvement of early striae rubra from baseline, and there was no significant difference in efficacy between the two treatment groups in striae measures (length and width), the Global Aesthetic Improvement Scale, or in subject satisfaction. Adverse events included pruritus, erythema, burning sensation, scaling, crusts, pain and swelling, and papules, although there were no statistically significant differences ($p > 0.05$) between the two treatment groups. All patients were either satisfied or indifferent. Nine patients agreed to biopsy, with eight from the DA group and one from the tretinoin group. No histologic changes were seen in the only tretinoin patient, while the superficial DA group had a reduction in elastolysis, collagen fragmentation, and epidermal atrophy and with collagen formation after treatment.

Actinic Keratoses/Photodamage

Another frequent indications for DA besides acne scarring has been the treatment of actinic keratosis and photodamage. Many of these studies were carried out by the pioneers of DA, and much of the original work is retrospective, nonrandomized, and suffers from selection bias.

Burks et al. completed hemifacial DA (wire brush) on 22 patients (39–77 years) with diffuse photodamage. Only 15 patients were available for review given the high mortality rate in the study population and the patient's request for DA of the untreated side, which disqualified them from the study [55] (IV). He found decreased cancerous and precancerous lesions in two thirds of patients on the treated side that persisted for up to 5 years. Ninety-two percent of observers agreed that the treated side appeared therapeutically improved. Although not the primary objective, cosmetic improvement was also noted by 85% of raters. These subjective changes were supported histologically, with easily identifiable changes between the treated and untreated sides, including the replacement of elastotic material with newly formed collagen. This improvement seems to be achieved when abrasion is carried deep enough to remove and regenerate the epidermal papillary dermal unit even if residual elastotic collagen is left below.

Benedetto et al. prospectively followed up 12 patients with photoaging after full-face wire brush DA with biopsy specimens and clinical exam for various time intervals from 6 months up to 8 years after DA [56] (IIB). All patients had actinic keratoses that were treated regularly prior to DA, and five patients had nonmelanoma skin cancer that was treated prior to DA. Posttreatment, only two patients had one treatment session for actinic keratoses that occurred approximately 4 years later, with no further occurrences for at least 7.5 years. Of the 12 patients in the study, 10 patients had pre-procedure biopsy tissue available for comparison. There was normalization of epidermal morphology demonstrated by lack of dyskeratotic cells and return of rete ridges. In the dermis, there was a widening of the papillary dermal grenz zone with increased collagen bundles and collagen bundle thickness that were more parallel to the skin surface. All patients had repigmentation of their skin to its pre-DA color or only slightly lighter when compared with the adjacent untreated skin.

Spira et al. compared chemical peeling with Baker Gordon peel, DA, and 1% 5-fluorouracil cream twice daily for 3–6 weeks in treating actinic keratosis [57] (IV). Seven patients received phenol solution occluded for 48 h on the entire face or on half the face while the other half was dermabraded, 7 patients received DA (serrated steel wheel to reticular dermis), 1 patient received split-face DA and chemical peeling, and 20 patients received 1% 5-fluorouracil cream twice daily for up to 6 weeks. Pre- and post-photographs and biopsies were taken in most

cases with a follow-up of 4 months to 3 years. Reduction in rhytids and hyperpigmentation was only seen with DA and chemical peeling. Chemical peeling resulted in recurrences as soon as 1 month after treatment, while DA had recurrences at 6 months. The patient who had a split-face application of chemical peeling and DA experienced recurrence on the chemical peel side first. The authors concluded that 5-fluorouracil is far superior to chemical peeling and DA given the longer time to recurrence and the development of fewer new lesions. The results from 5-fluorouracil group were not presented by the authors, however, making their conclusion difficult to accept. Histologic review from all three groups was similar with a thin epidermal layer, a reduced number of rete pegs, and a replacement of a portion of the actinically degenerated basophilic collagen in the papillary layer of the dermis by new collagen.

Winton [58] (IV) retrospectively looked at five patients who received DA (diamond fraise; endpoint papillary dermis) to the bald scalp for actinic keratoses. All patients were white elderly men with skin type II, ranging in age from 61 to 71 years. Two patients who treated themselves with 5-fluorouracil twice daily for 6 weeks were used as a comparison, although their results were never revealed in the study. Using a 6-point scale from 0 (none) to 6+, keratoses improved from 3.2 to 0, dyspigmentation improved from 4.6 to 0.6, and telangiectasias improved from 4.2 to 1.4. Scarring did not occur. Although 5-fluorouracil eradicated actinic keratoses (data not shown) similar to Spira's study [57], it did not improve solar dyspigmentation or telangiectasias.

New Directions

DA as a technique for epidermal skin sampling has been well described. A 2009 study used a modified dermabrader as an epidermal harvesting tool, and the authors were able to obtain representative samples of the epidermis for biomolecular analysis without creating a scar or inducing more than mild pain [59].

Preoperative Evaluation

Patient Expectations

Patient selection is key to obtaining excellent results with any elective procedure, and a thorough history and targeted physical exam is performed at the initial consultation. Patients must have realistic expectations with proper informed consent that discusses common risks such as scarring, infection, redness, and dyspigmentation [60]. Patients with body dysmorphic disorder most frequently seek dermatologic and surgical treatments, including DA [61]. In a retrospective study describing the frequency, types, and outcomes of treatments sought and received by 200 individuals with body dysmorphic disorder, approximately 2% of the dermatologic procedures were DA. Such treatment rarely improved body dysmorphic disorder, with 96% seeing no change in or worsening of their complaint. Care should be taken to identify these patients prior to treatment.

Viral Transmission

Another preoperative consideration is human immunodeficiency virus (HIV) and hepatitis. Since DA results in a great deal of blood accumulating in the field, proper history regarding hepatitis and HIV should be obtained. Wentzell indicated that aerosolized particles produced during DA were of sufficient size to allow access to, and retention by, mucosal and pulmonary surfaces [62]. While no cases of viral transmission have occurred during DA, the studies suggest that commonly used personal protection devices do not prevent inhalation of these particles and that infection can theoretically occur. The room should have proper ventilation, and all persons present in the room need to wear protective gear including 0.1 um filtration face masks, face shields, surgical gowns, and gloves, although there still remains a degree of risk since the seal on masks is rarely perfect. A contained breathing apparatus to isolate the surgeon and his or her assistants from the patient's tissue and body flu-

ids in advisable [63], and a shielded dermabrader with an attached hydration suction apparatus has been described to reduce this risk [64]. Alternatively, manual DA can be used since no aerosol is produced. Similar precautions are recommended when dealing with hepatitis patients.

Isotretinoin

Physicians should obtain medication lists to ensure that patients are not taking drugs that may lead to complications or compromise wound healing. Patients seeking DA for acne scars often have a history of severe acne and may have received isotretinoin therapy.

Clinical Studies

Early reports suggested that DA patients were unaffected by previous treatment with isotretinoin. Roenigk reported nine patients with severe nodulocystic acne who were treated with oral 13-cis-isotretinoin and subsequently received full-face DA without sequelae [65] (IV). Later reports documented patients who were dermabraded after isotretinoin and developed atypical scarring. Rubenstein first reported the occurrence of keloids on the cheeks, chin, and face of six patients (27–48 years) undergoing mechanical DA during (three cases) or within 6 months of treatment (three cases) with isotretinoin [66] (IV). Zachariae reported delayed healing and keloid formation in three patients (25–70 years) treated with DA (two cases) and argon laser treatment (one case) during isotretinoin treatment for acne or rosacea [67] (IV). Katz reported atypical facial scarring after the use of oral isotretinoin in a 30-year-old patient who had just undergone DA for severe cystic acne scarring [68] (IV).

More recent data is once again conflicting, as other surgeons have compiled patients that have been treated with isotretinoin and dermabraded without difficulty [69] (IIB). Picosse et al. prospectively evaluated healing from chemabrasion with 35% trichloroacetic acid (TCA) and manual DA (endpoint pinpoint bleeding) of depressed scars in ten patients who had isotretinoin 1–3 months prior to treatment. Follow-up at 6 months revealed normal healing with neither hypertrophic nor keloid scars, although all patients applied a topical steroid following the procedure. Bagatin performed manual DA on seven patients with atrophic acne scars on the face and neck, all actively taking oral isotretinoin. No topical steroids or oral steroids were given, and there was no abnormal scarring or keloid formation in this study population at 6-month follow-up [70] (IIB). The treatment area, however, was only 1 cm^2 and may not have been large enough to evaluate healing. This conflicting data is difficult to apply in clinical practice because adequate control studies have never been done. Therefore, many advocate for DA to be performed a minimum of 6 months after isotretinoin intake [66]. Guidelines of care for DA have also been published and suggest warning patients of the potential for atypical scarring as well [71] (V).

Herpes Simplex Virus Prophylaxis

Prophylaxis with an antiviral agent prior to DA is prudent in patients known to have a history of herpes simplex virus (HSV); however, significant consideration should also be given to prophylaxis in patients with a negative history of HSV. A retrospective evaluation of 181 consecutive patients undergoing perioral chemical peel or DA from 1983 to 1990 suggests that all patients are at risk for infection regardless of history [72] (IV). Patients with a history of oral HSV were pretreated with oral acyclovir and those without a history were not treated with acyclovir. A subset of 12 patients whose procedures predated acyclovir's commercial availability received no prophylactic treatment despite a positive history, which allowed for a comparison group. This group of patients developed herpetic infections 50% of the time. Interestingly, 6.6% of patients without an HSV history also developed infection within 5–12 days after the procedure. From this, they concluded that all patients should be treated preoperatively with acyclovir regardless of past history, and that treatment should continue for 2 weeks. The treated group with standard doses had an 8.3% infection rate (600 mg/day). No

patient developed herpetic infections if high-dose acyclovir was given (2400 mg/day). Fortunately, although these outbreaks are quite uncomfortable and appear to be severe, the incidences of scarring and long-term poor cosmetic outcomes in this study were low.

Beeson et al. looked at length of treatment and randomized 120 patients to either a 10-day or 14-day course of valacyclovir 500 mg BID starting on the day prior to the procedure [73] (IB). No patient in either group developed an HSV infection. The authors also performed serology and Tzank preparations to determine past exposure to HSV and the presence of virus. Reported histories of herpetic infection were given by 40–60% of patients, but over 80% had serologic evidence of previous infection. This study also found that 70% of patients with negative history did in fact have positive immunoglobulin G antibodies to HSV type 1. This further suggests that prophylaxis based on patient recollection is not reliable.

Opinions vary regarding when to start prophylactic treatment. One study randomly divided 84 resurfacing patients [CO_2 or Er:YAG laser (30 patients), chemical peeling (46), and DA (8)] to start valacyclovir 500 mg BID either the morning before or the morning of the procedure and to continue for 14 days [74] (IB). Patients were followed up for 21 days postoperatively. They found that valacyclovir is 100% effective for preventing herpetic lesions in in both groups with no adverse events reported.

Tretinoin

Prior to the procedure, patients can be pretreated with tretinoin cream to accelerate postoperative healing. In a porcine model, pretreatment with 0.05% tretinoin cream daily for 10 days prior to wounding significantly accelerated wound healing as compared with vehicle ($p = 0.015$) [75] (V). Clinically, Mandy used full-face or half-face DA (wire brush, diamond fraise to depth of scarring) for acne scarring in 123 patients, 88 of whom received pretreatment with 0.05% tretinoin acid cream [76] (IIIB). In the treated group, re-epithelialization occurred in 7 days compared to 11 days in the untreated group. One patient had a split-face treatment, and the pretreated side re-epithelialized in 7 days compared to 9 days for the untreated side. If the tretinoin was restarted 1 week after DA, no milia or post-inflammatory hyperpigmentation was seen, compared to 28% and 20%, respectively in the control group. Based on these findings, many dermatologists prescribed topical retinoids before and after resurfacing to expedite healing and reduce side effects.

Best Techniques and Performance

Describe what is known about optimal methods for this procedure. The standard methodology can be described in just a paragraph or two, but the focus should be on technique elements for which data exists, and these should be discussed in depth (e.g., predetermined number of passes in ablative laser resurfacing due to lack of tissue effect) and the evidence for and against weighed carefully.

Include pertinent negatives. For instance, if there are important elements of technique for which the evidence is lacking or insufficient (e.g., does eversion lead to narrower scars), this should be stated and discussed briefly.

DA is commonly performed in office-based procedure rooms under local anesthesia, although intravenous sedation or general anesthesia is used by some. Regional blocks are effective and additional anesthetic sprays may be used to freeze the skin. Freon-based refrigerants such as Frigiderm (Delasco, Council Bluffs, IA), Fluoro Ethyl (Gebauer Company, Cleveland, OH), and Fluori-Methane (Gebauer Company, Cleveland, OH) were widely used but have limited availability in many countries, including the United States, due to concerns of ozone destruction. Ethyl chloride (Gebauer Company, Cleveland, OH) is flammable but ozone safe, and Instant Cold Spray (HL Moore, New Britain, CT) is ozone safe [77]. Tumescent anesthesia can also be used to stiffen and anesthetize the skin. Goodman reported the 14 patients (average age 31 years) dermabraded with tumescent anes-

thesia and topical anesthesia (EMLA; Astra Pharmaceuticals) using a diamond fraise (endpoint pinpoint bleeding) [78] (IV). Seven patients had full-face DA, four had regional DA, and one had subregional DA. The procedure was found to be effective in producing anesthesia, eliminating the need to freeze the skin, and limiting the necessity for sedatives, narcotics, and other anesthesia. There was also less spatter and therefore less risk for the surgeon. Side effects were limited to one case of transient hyperpigmentation, one case of milia, and one case of irritant dermatitis. Of the 12 patients who completed the patient questionnaire, 8 stated they would go through a subsequent tumescent DA, 11 felt they had an improvement with the technique, and only 1 patient found it painful. All four patients who had DA previously felt that healing was faster with tumescence, and three of four patients felt that the results were better.

When treating scars, the question of timing is important. Katz et al. designed a split-scar study looking at surgical scars in 48 patients aged 25–86 years [79] (IB). Scars were located on the face (19 scars), trunk (20), and extremities (1). The scars were randomly assigned to DA (diamond fraise; pinpoint bleeding) 4, 6, and 8 weeks after surgery. The treated half was not randomized and always assigned to the left half of the scar. Ratings were performed by the physicians, laypersons, and the patients themselves. Photographs and scar measurements were taken at 1 month, 3 months, and 6 months after treatment. There was a statistically significant improvement in the DA portion of the scar compared to no treatment at 8 weeks ($p < 0.05$), but not at 4 weeks and 6 weeks after treatment. Trunk and face and extremities showed comparable improvement. While only 25% of patients responded to the questionnaire, all thought the treated side looked better. They reported mild post-inflammatory hypopigmentation that spontaneously resolved. Four patients agreed to histologic evaluation of each side of the scar at 6 months. Histologically, there were no significant differences between the two groups at 6 months and only scar tissue was seen.

Yarborough similarly showed that post-traumatic scars or scars as a result of excisional surgery could result in a much more acceptable result if DA (wire brush) occurred 6–8 weeks after the skin injury [4] (IIIB). He looked at 97 facial scars (35 surgical and 62 traumatic) on 37 patients between the ages of 15 and 78 who had their scars abraded 4–8 weeks following injury. The comparison group consisted of 64 mature scars from 3 months to 13 years on 24 patients. Evaluations were made for up to 6 months, with 89% of the early group showing no visible scarring at 6 months. In four patients, scars improved but were still visible. Of the 64 mature scars, all were still apparent, essentially unchanged, or modestly improved.

The selection of a dermabrasive device is often determined by surgeon preference. Nelson et al. compared DA with the wire brush and diamond fraise in photoaged skin [80] (IB). Eight photoaged patients (49–80 years) underwent facial dermabrasion to the level of the papillary dermis. Two blinded observers rated photographs at baseline and 12 weeks using a 5-point scale (0 = none, 5 = severe). Side effects were also noted. Biopsies were taken from both halves of the scar and assessed by routine histologic and immunohistologic examinations, Western blot analysis, and radioimmunoassay. Both methods of DA resulted in significant resolution of actinic keratoses, lentigines, and wrinkles at both 3 and 12 weeks postoperatively, although there were no statistically significant differences between the two techniques ($p < 0.01$). Significantly fewer milia occurred with diamond fraise than with wire brush ($p = 0.02$), but no statistically significant differences were found between the two techniques with erythema or hypopigmentation. At 12 weeks, immunohistologic evaluation demonstrated a significant increase in papillary dermal fibroblast staining for type 1 pN-collagen with wire brush and diamond fraise ($p = 0.002$ and 0.008, respectively) and for type 3 pN-collagen with wire brush and diamond fraise ($p = 0.05$ and 0.04, respectively) compared to baseline. A telephone survey 2 years after treatment reached seven patients who were satisfied. Three patients

preferred the diamond fraise, but they did not make any distinction between the two sides in terms of healing.

Gillard et al. compared manual spot DA with diamond fraise DA in patients who had undergone facial skin cancer surgery [81] (IB). Twenty-one patients (34–86 years) with facial scars, including 14 patients with sutured wounds and 7 patients with wounds left to heal by secondary intention, were examined. Scars were divided in half, and each side was randomly assigned to treatment by diamond fraise DA or by manual DA with a medium-grade drywall plaster sanding screen. A blinded observer judged each scar and found no differences between the two methods in quality of contour correction, time for re-epithelialization, camouflage of the scar, hypertrophic scarring, infection, or hyperpigmentation during the 6 months of follow-up ($p > 0.16$). Interestingly, no patient exhibited any perceived difference in correction of contour at any time point between the two treated halves. The authors conclude from this study that manual DA and motorized DA are equally effective in the treatment of facial scars.

Safety

DA remains much more dependent on operative techniques than lasers or chemical peels and is thus more vulnerable to operator error. Scarring, although rare, can occur for many reasons. Cryogenic sprays, which are used to provide a firm base against which to abrade, produce thermal damage that can lead to scarring over boney prominences. Newer freons used to rapidly harden the skin prior to DA can produce their own complications and accelerate the incidence of keloid formation [82–84]. When the skin refrigerants are used for short bursts, little if any dermal damage or impaired healing is seen. Strauss and Kligman found that freezing human cheek skin for up to 6 min with dichlorotetrafluoroethane (Freon 114) resulted in no scarring or clinically significant pigmentary changes [85]. In some subjects, the skin was retreated three times without scarring. Despite this, dermal damage can be seen histologically with prolonged freezing or refreezing [86] and newer refrigerants that can achieve lower temperatures that increase chances of freeze injury [82, 83, 87, 88]. Hanke et al. [84] (IV) reported three patients who were dermabraded with a new potent skin refrigerant mixture. Two patients developed hypertrophic scarring over the mandible (one patient's course was complicated by an infection), and the third had prolonged erythema of the cheeks that was still present (although improved) after 1 year. All three patients received Cryosthesia −30 °C and/or −60 °C (Chemtrex Inc., Hauppauge, NY), which produces a more rapid freeze than Fluoro Ethyl (max cooling temp −42.8 °C) or Frigiderm (−40.6 °C). This was supported by a later study where guinea pig skin was used to compare these three refrigerants. In this study, Cryosthesia both −30 °C (max cooling temp −52 °C) and −60 °C (max cooling temp −66 °C) could cause necrosis and inflammation without subsequent DA, while Frigiderm and Fluro Ethyl produced very little effect on the skin [82].

Infection is uncommon after DA, occurring in less than 4–8% of patients [89]. The most common microorganisms include *Staphylococcus aureus*, HSV, and *Candida* species [90]. Prophylactic antibiotics have been associated with selection for pathogenic organisms and a tendency toward higher infection rates [91]. *Candida* infections are promoted by topical and/or oral antibiotics, and they can manifest up to 2 weeks after the procedure [92] (IV). Nevertheless, many surgeons still prescribe a cephalosporin. Siegle et al. reported three cases (two women and one man, aged 19–38) of facial candidiasis complicating DA. With topical antifungals (two patients) and oral antifungals (one patient), all healed without sequelae. Two patients were on prednisone postoperatively and prophylactic oral antibiotics, and all patients were using topical Polysporin for wound care. The postdermabrasion state was thus strongly conducive to developing a secondary candidosis due to oral and topical antibiotics, which should be used judiciously in DA.

Pigmentary changes are the most common complications after DA and usually take from

weeks to months to resolve [89, 93]. As with any resurfacing method, darker-skinned people are at greater risk of pigmentary changes, but good postoperative skin care and the rigorous use of sunscreen can prevent many of these patients from suffering this complication. Ship et al. looked retrospectively at 63 DA patients (17–63 years; 22 males and 41 females) consisting of 11 Caucasians, 6 Hispanics, 4 blacks, and 1 Oriental [94] (IV). Diamond fraise was used for 21 full-face procedures and 42 spot treatments without refrigerant. Over the follow-up period from 6 months to 15 years, only eight patients had pigmentation changes that resolved (one patient lost to follow-up). Sixty-seven percent (42) of patients reported some pigmentation that resolved before the 6 months. Three patients developed hypopigmentation that also resolved at 1 year plus (two blacks, one Caucasian), and three Caucasian patients developed redness, which was present up to 4 years later in one naturally ruddy patient. As a result, the authors concluded that adverse pigmentation frequently self-resolves.

Fakhouri and Harmon reported subarachnoid hemorrhage during DA in a 69-year-old patient on dabigatran for atrial fibrillation [95] (IV). She complained of gastrointestinal upset prior to the visit and developing chest and shoulder discomfort, diaphoresis, and pallor after the procedure. The authors highlighted the importance of considering all potential complications of a patient's medical history and medication list. It is prudent to have an action plan in place to manage emergent complications of anticoagulant therapy since most patients are maintained on medically necessary anticoagulation during surgery.

Alternative Procedures and Modifications

The preoperative consultation is extremely important. The surgeon should list alternative and adjunctive procedures such as chemical peels, lasers, and surgery.

CO_2 Laser Versus Dermabrasion

Perioral Rhytids

Holmkvist and Rogers compared a pulsed, scanning CO_2 laser with DA in the treatment of perioral rhytides in a split-face manner [96] (IB). Fifteen patients were randomly assigned to DA (eight patients with diamond fraise and seven to manual DA; endpoint pinpoint bleeding) to half the face and a pulsed scanning carbon dioxide laser [LX-20SP Novapulse [(Luxar Corp, Bothell, Wash), 4.24 J/cm^2 with 5–6 W/pass for 2–3 passes)] to the other half of the face. Only skin types 1–3 were included, and all patients were pretreated with 0.025% tretinoin and 4% hydroquinone for 2 weeks. Standardized photographs and clinical exam were assessed by blinded observers for up to 4 months, and all patients were interviewed subjectively throughout the study. Using a 5-point rhytid scale, both treatments resulted in improvement ($p = 0.001$ for DA and $p = 0.002$ for CO_2), and there was no statistically significant difference between the two sides ($p = 0.35$). Subjective opinions regarding superior cosmetic outcomes were similar for patients and blinded observers, with 50% of both groups seeing no difference. Postoperative pain was not significantly different, although crusting was greater with laser ($p = 0.002$) and healing was faster with DA (60% with DA vs. 7% with CO_2 at 6–7 days) with significantly less postoperative erythema at 1 month ($p = 0.003$) but not at 4 months ($p = 0.15$).

Gin et al. used a similar approach to evaluate and compare the scanning CO_2 laser with diamond fraise DA in the treatment of 20 patients (48–76 years, Fitzpatrick skin types I–III) with perioral rhytides [97] (IB). One half of the perioral area was randomly assigned to CO_2 laser (CW 18 W using a 6 mm scan size with a 950 μsec dwell time, three passes) and the remaining half assigned to DA (endpoint pinpoint bleeding or dermal collagen over wrinkles). Rhytides were evaluated by an independent, blinded investigator on a graded scale at baseline and up to 26 weeks after the procedure. Of the 19 patients who completed the study, the mean rhytid score for the laser treated and dermabraded side improved significantly ($p < 0.001$ for both modalities), the

difference between the two techniques being nonsignificant ($p = 0.216$). No major differences were observed in erythema between DA and CO_2 laser, which lasted an average of 2.5 months (range 1–6 months). The authors concluded that DA and CO_2 laser are equally effective in the treatment of perioral rhytides. Side effects were limited. Three patients developed herpes infection that healed without consequence. One patient developed a hypertrophic scar within the dermabraded side, two patients developed dermatitis, and three patients developed milia.

Combined treatments have been shown to decrease downtime and improve efficacy of treatment [98] (IV). Fezza et al. compared the combination of CO_2 laser (details not provided) and manual DA (Silicone carbide 220 grit sandpaper, endpoint pinpoint bleeding) to a historical control of CO_2 laser alone. Ninety patients with perioral wrinkles (Glogau IV wrinkles) underwent treatment and were assessed clinically by the surgeon and staff for wrinkle reduction, healing, and complications. Photographs were also taken at baseline and at 3 months. The combination reduced 95% of heavy perioral wrinkles compared to a historical rate of 75% with laser alone. Healing time for the combination treatment was shorter (9 days) instead of laser alone (12 days). No complications were seen. A subset of 26 patients were followed for a year, and all maintained good results with no additional hypopigmentation.

In 2000, Kitzmiller and colleagues recruited 20 females with moderate-to-severe upper-lip wrinkles to assess the CO_2 laser and DA [99] (IIB). They randomly assigned half the perioral area to DA and half the perioral area to UltraPulse CO_2 laser (2–4 passes, 300 mJ, density 5–6). Photographs at 1 week, 1 month, and 6 months following the procedure were compared by ten blinded plastic surgeons. The laser had higher erythema score at 1 month ($p < 0.001$) but a small, significantly greater improvement in wrinkle score at 6 months ($p = 0.016$). Both treatments reduced facial rhytides by approximately 50%. The participant's overall impression, assessed by a 6-month questionnaire, was that the laser gave a better result tempered with more intraoperative pain and postoperative drainage. Patients reported that they would recommend both procedures equally to a friend. The authors concluded that the pulsed CO_2 laser is slightly more effective at improving perioral rhytides than DA, although they acknowledged that his change may not have been observed if they were more aggressive with their DA technique. As a result, they recommended incorporating operator experience into determining which modality would be optimal for a specific patient.

Surgical Scars

Nehal et al. prospectively compared the clinical effects of DA and high-energy pulsed CO_2 resurfacing (18 W, 6 mm spot, SilkTouch; Sharplan Lasers Inc., Allentown PA) in the revision of surgical scars [100] (IV). They employed a split-scar model in four patients with one half of the scar being dermabraded using a diamond fraise (endpoint reticular dermis) and the other half being resurfaced with the high-energy pulsed CO_2 laser. Three independent investigators compared photos at baseline at 4, 8, and 12 weeks using a four-point scale. Both treatment sites re-epithelialized in 7–10 days with a comparable degree of erythema in both treatment halves at 4–8 weeks. No other complications were observed. Clinical assessments were performed in a non-blinded fashion with photographs, and comparable clinical improvement was seen in all four scars. No statistical analysis was performed given the small sample size. Silicone rubber casts and optical profilometry objectively demonstrated improvement in scar texture following both modalities as well. While both treatment modalities achieved similar clinical improvements, the CO_2 half remained bloodless during treatment, which, the authors commented, allowed greater visibility during the procedure and lowered risk of transmission of blood-borne pathogens to the staff.

For postsurgical scar resurfacing, Christophel et al. compared the safety of fractionated CO_2 laser with DA [101] (IB). A randomized, blinded, split-scar model was used to compare a single treatment of fractionated CO_2 [Fraxel Re:Pair (Solta Medical Inc., Hayward CA), 40 mj, treatment level eight, two passes] with diamond fraise

DA (endpoint punctate bleeding) on postsurgical scars of the face. Six patients (45–64 years, three men and three women) completed the study and were assessed for up to 1 month. They used a four-point scale for safety measures and a visual quartile scale for assessing scar improvement. Secondary endpoint was efficacy at 3 months as measured by blinded evaluation of standardized photographs. Both treatments yielded equivalent scar improvements ($p = 0.77$) at 3 months, although there was less bleeding ($p = 0.001$) and erythema ($p = 0.01$) with fractionated CO_2 laser at day zero and less erythema ($p = 0.01$) and edema ($p = 0.046$) at 1 week; there were no statistically significant differences in safety measures at 1 month.

Chemabrasion (Chemical Peeling Combined with Dermabrasion)

Rhytids

Chemabrasion was first described in 1982 and is the combination of chemical peels and DA. Harris advocated the addition of manual DA to augment a 25% TCA peel and reported his experience with the technique on over 300 patients over 7 years aged 28–66 [102] (V). In his hands, expected results include 70–90% of improvement in wrinkles with less dyschromia. He reported only two cases of hypopigmentation, four cases of hypertrophic scarring along the mandible, and erythema that takes from weeks to months to resolve.

Actinic Keratoses

Cooley et al. looked at 40 patients with actinic damage who were treated split face with manual resurfacing (vigorous pinpoint bleeding) plus 25% TCA on one side and either DA alone or 35%TCA/Jessner's alone on the other side [103] (IV). Four patients underwent sequential biopsies within 1 week and again within 90 days to evaluate the depth of wounding using these techniques. In the chemical peeling group, significant improvements in the epidermis were seen with little change in the elastotic band in the papillary dermis. The DA alone group produced a depth of injury similar to the Jessner's 35% TCA. The combination group revealed a deeper injury histologically, with nearly complete obliteration of the elastotic band, which was replaced with an approximately 0.4 mm wider band of new collagen. Clinically, the combination consistently produced excellent cosmetic results and nearly complete removal of actinic keratoses. The combination treatment resulted in longer healing time by several days and duration of erythema that persisted until day 30 in one patient, as well as occasional pigmentary changes. No scarring was seen. The authors concluded that manual resurfacing combined with TCA is an excellent technique for patients with widespread actinic keratosis and extensive photodamage, although longer healing times can be expected.

Chemical Peeling Versus Dermabrasion

El-Domyati compared microscopic and ultrastructural changes that occur in photoaged facial skin Fitzpatricks type IV and V after treatment with either superficial TCA peeling or DA [104] (IIB). Patients with mild-to-moderate photodamage were treated weekly to biweekly with increasing percentages of TCA (10%, 20%, and 30% TCA), and those with advanced-to-severe photodamage were treated with DA using the diamond fraise until pinpoint bleeding was visible. Punch biopsies were taken at baseline 3 months after treatment for the DA group and within 3 months after the TCA peeling at the sign of clinical improvement, usually after three to five sessions. Both TCA peeling and DA had beneficial effects in improving photoaged facial skin and in revitalization of the skin at histologic and ultrastructural levels, mainly by increasing the amounts of collagen I and collagen III and improving the morphologic appearance of collagen and elastic fibers. While it is difficult to compare the two groups given the baseline differences in photodamage and the variable time of biopsy in the TCA group compared to the standard 3 months in the DA group, the tissue response was more prominent in the patients treated with DA.

Surgical Scar Revision and Dermabrasion

Surgical scar revision prior to DA is an important adjunctive procedure that can improve the ultimate cosmetic outcome. Scar excision, punch elevation, and punch grafting can be used to improve deep scars that are beyond the reach of DA. Whang et al. devised a three-step treatment that combines (1) focal chemical peeling with 50% TCA for 1–3 monthly treatments; (2) excision, punch grafting/elevation, and/or CO_2 laser according to the type of remaining scars; and (3) DA performed 6–8 weeks later for resurfacing the remaining areas [105] (IV). This treatment plan was derived from their published clinical experience, which included 32 patients with acne scars (average age of 26.8 years) who received focal chemical peeling with 50% TCA to their depressed scar for 1–3 treatments. They added CO_2 (3–6 W, 0.05 s/pulse) in six patients, excision in two patients, punch graft/elevation in three patients, and DA in five patients simultaneously or sequentially after chemical peeling. Results were obtained 6–18 months after treatment and were rated from poor to excellent. Seventy-five percent of patients were excellent or good for chemical peeling alone, 70–80% from good to excellent for chemical peeling combined with another modality (CO_2 or DA), and 100% from good to excellent for the patients who underwent all three stages of treatment. Complications arose in six patients and consisted of hyperpigmentation that lasted longer than 3 months in two patients, erythema that persisted longer than 3 months in three patients, and hypertrophic scarring in one patient.

Dermabrasion with Melanocyte Transfer

Vitiligo

DA is also useful for deepithelializing vitiliginous skin recipient sites for epidermal or melanocyte grafts, as part of repigmentation procedures [6, 27, 39, 106]. Although beyond the scope of this chapter, plastic surgeons have combined DA with skin grafts and acellular tissue substitutes as a technique for restoring skin pigmentation after burn injuries in the adult and pediatric populations [107–110].

Vazquez Martinez et al. looked at patients with stable vitiligo over 3 years and compared DA with melanocyte keratinocyte cell suspension transplantation with DA alone on separate achromic macules of the same patient. Lesions were on the trunk (64%), limbs (29%), and face (9%). Blinded dermatologists measured the area of repigmentation in the area treated 3 and 12 months after implantation. At 12 months, the percentage of the treated area that had undergone repigmentation with DA + MKT was not statistically greater than that of the skin treated with DA alone ($p = 0.733$) [111] (IV).

Future Directions

Bacterial Colonization

DA is also used in burn victims as a method for collecting cutaneous samples from the wounds to assess bacterial colonization [112] (IIB). DA of the upper layers of the wound was performed in 12 burn patients using a diamond fraise with the tissue analyzed for bacterial growth in different culture media and compared with biopsy and swab. The abrasion method yielded more bacteria than the swab method and the biopsy method ($p < 0.05$).

Postoperative Care and Follow-Up

Appropriate wound care is vital to success. A moist environment is necessary to promote wound healing, and most practitioners rely on an open technique of treatment with frequent application of ointments. Multiple petroleum-based products are available to maintain a moist environment and prevent crusting. The closed technique involves application of a biosynthetic dressing material and has evidence to support its use after DA. The use of semipermeable dressings reduces the time for re-epithelialization by up to 40% compared to open techniques of

wound care, and this effect is attributed to the ability of these dressings to maintain a critical plane of humidity for epithelial cell migration [113, 114]. These dressings can be left in place for 24–48 h and then changed by the patient every 2–3 days. Following this, ointment dressings can be started. In addition to moist wound care, whether closed or open, patients should minimize sun exposure and/or wear appropriate sunblock for 6–12 months following the procedure to avoid hyperpigmentation. As previously discussed, topical retinoids can be applied 1 week after DA to help prevent hyperpigmentation and milia formation. Residual erythema and edema should be expected to last 1–2 months, and if appropriate, nonallergenic makeup is worn during this time. In the studies reviewed, most patients only required one DA to achieve results, although repeated treatments can also be safely prescribed.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Dermabrasion is indicated for the treatment of superficial and moderate depth wrinkles in the perioral area	B
All patients should receive appropriate antiviral therapy to prevent and treat possible herpetic outbreaks prior to skin resurfacing	B
Dermabrasion is effective in postsurgical scar treatment	B
Dermabrasion is effective in treating actinic keratoses	B
A short preoperative course of tretinoin cream has the benefit of reducing the time required for re-epithelialization after dermabrasion	C
Patients who have completed isotretinoin therapy within the last 6 months should be counseled on the possibility for atypical scarring	C

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Self-Assessment Questions

1. When considering dermabrasion for a full-thickness skin graft, which grafts respond the best?
   (a) Depressed grafts
   (b) Elevated/hypertrophic grafts
   (c) Periocular grafts
   (d) All grafts within the first month of bolster removal
2. A 55-year-old Hispanic lady comes for a 4-week follow-up visit. She had perioral dermabrasion for fine lines and wrinkling. She complains of skin darkening in the treated area. Which of the following statements is true?
   (a) This side effect is usually self-limited and resolves within weeks to months
   (b) Restarting her topical tretinoin 1 week after the procedure caused this side effect
   (c) A laser would not have caused this side effect
   (d) Perioperative acyclovir would have prevented this side effect
3. Which of the following cryoanesthetics is commercially available and ozone safe?
   (a) Frigiderm (Delasco, Council Bluffs, IA)
   (b) Fluoro Ethyl (Gebauer Company, Cleveland, OH)
   (c) Instant Cold Spray (HL Moore, New Britain, CT)
   (d) Fluori-Methane (Gebauer Company, Cleveland, OH)
4. A 35-year-old male comes to the office requesting improvement in a bilobed flap on his nasal supratip that has not responded to corticosteroid injections. He has HIV that is poorly controlled. How do you proceed?
   (a) Tell him that you will not perform HIV status
   (b) Proceed with mechanical dermabrasion and wear protective gear including 0.1 um filtration face masks, face shields, surgical gowns, and gloves
   (c) Proceed with manual dermabrasion and wear protective gear including 0.1 um filtration face masks, face shields, surgical gowns, and gloves
   (d) Proceed with dermabrasion per routine if his CD4 count is above 200
5. A 40-year-old gentleman comes in for a 10-day follow-up. He had dermabrasion to bilateral cheeks for acne scarring. He is a very compliant patient and was prescribed a 10-day course of cephalosporin and acyclovir, was instructed to apply petrolatum ointment to the treated skin postoperatively, and was counseled on strict photoprotection. He complains of new-onset redness and mild itching confined to the cheeks for 1 day. There is no pain, crusting, or drainage. What is the next step in evaluating the cause of his symptoms?
   (a) Prescribe a fluoroquinolone antibiotic for broader bacterial coverage
   (b) Take culture (bacterial, viral, and fungal) culture and add a topical antifungal therapy while awaiting the results of culture
   (c) Prescribe a 2-week course of prednisone for allergic contact dermatitis
   (d) Reassure him that redness and itching is normal after dermabrasion

Correct Answers

1. b: Robinson et al. performed a controlled study looking at the effect of dermabrasion on the appearance of full-thickness skin grafts on the face [52]. When compared to matched controls, the greatest objective improvement was seen in elevated grafts. Depressed grafts and periocular grafts did not improve with dermabrasion. She found that grafts spontaneously improved over the first 6 months, suggesting that patience can prevent an unnecessary procedure.
2. b: This lady has developed post-inflammatory hyperpigmentation, which usually presents several weeks after the procedure. With photoprotection, this condition resolves over weeks to months. The use of post-procedure topical tretinoin does not predispose to post-inflammatory hyperpigmentation. It may, in fact, help prevent it. Any trauma to the skin can predispose to pigment changes, including lasers or chemical peels. Post-inflammatory hyperpigmentation is not prevented by acyclovir.
3. c: Instant Cold Spray (HL Moore, New Britain, CT) is commercially available and ozone safe.
4. c: Unlike mechanical dermabrasion, manual dermabrasion does not create blood spatter and thus reduces the chance of inhaling and/or ingesting aerosolized viral particles. Despite this, proper personal protective gear should still be worn during the procedure. Discriminating against patients based on their HIV status is illegal. A high CD4 count, while good for the patient, will not prevent viral transmission.
5. b: Infection must be ruled out. Since he is already taking an antibiotic and antiviral, bacterial and viral infection are possible but less likely. There have been published reports of candidiasis up to 2 weeks after dermabrasion [92], and antibiotic use is a risk factor. Studies suggest that a 10-day course of an antiviral is adequate length of therapy for HSV prophylaxis [73]. Therefore, taking cultures and prescribing a topical antifungal cream is the best option. Since he is only applying petrolatum, an allergic contact dermatitis is unlikely and a 2-week course of prednisone is a risky treatment for tolerable itching. Without a positive culture to suggest otherwise, adding a fluoroquinolone is not indicated and contrary to antibiotic stewardship. While redness and itching can be a normal part of healing, the new-onset nature warrants investigation.

Subcision (Including Energy and Device-Mediated)

22

Daniel E. Edmondson and Douglas Fife

Abstract

Subcision, short for "subcutaneous incisionless" surgery (Orentreich and Orentreich, Dermatol Surg 21(6):543–549, 1995), is a minor surgical intervention that is useful in the treatment of several types of scars and other contour defects. The procedure involves the insertion of a beveled needle into the skin adjacent to a scar which is advanced forward, backward, and side-to-side to create a pocket underneath the scar, ultimately allowing the skin surface to float up to a more normal level. This procedure is indicated in the treatment of rolling acne scars, depressed scars and contours (due to many causes including skin grafts, surgical wounds, and malar grooves), and wrinkles. While it has also been proposed for treating cellulite dimples, striae, and axillary osmohydrosis, the evidence for improvement in these conditions with subcision is scarce (2b) (Balighi et al., J Eur Acad Dermatol Venereol 22(6):707–711, 2008). Refer to Table 22.1 for a summary of indications.

Keywords

Subcutaneous incisionless surgery · Subcision · Scars · Contour defects

Indications for Subcision

Subcision, short for "subcutaneous incisionless" surgery [1], is a minor surgical intervention that is useful in the treatment of several types of scars and other contour defects. The procedure involves the insertion of a beveled needle into the skin adjacent to a scar which is advanced forward, backward, and side-to-side to create a pocket underneath the scar, ultimately allowing the skin surface to float up to a more normal level. This procedure is indicated in the treatment of rolling acne scars, depressed scars and contours (due to many causes including skin grafts, surgical wounds, and malar grooves), and wrinkles. While it has also been proposed for treating cellulite dimples, striae, and axillary osmohydrosis, the evidence for improvement in these conditions with subcision is scarce (2b) [2]. Refer to Table 22.1 for a summary of indications.

It is generally agreed that subcision is ineffective for certain other forms of scarring, such as boxcar and ice pick acne scars; however, this has not been rigorously studied. It has been suggested that subcision is notably more effective at treating scars with bases that have normal skin quality

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Table 22.1 Indications for subcision

Indications for subcision	Level of evidence
Rolling acne scars	2b
Depressed scars and contours	5
Traumatic	5
Surgical	5
Varicella	5
Anetoderma	5
Malar groove	5
Skin grafts	5
Wrinkles	5
Cellulite dimples	5
Axillary osmohydrosis	5

as opposed to those which are hypopigmented or sclerotic (5) [3].

Demographics and Body Areas Appropriate for Subcision

Subcision is used on patients of all ages and skin types and can be performed on any area of the body. While this has not been studied specifically, some authors warn that certain areas of the body, particularly those with increased skin tension, have a greater likelihood of undergoing hyperplasia following subcision. These locations include the periorbital, glabellar, labial commissure, and upper lip areas (4) [1]. In contrast, others have proposed that subcision can be done anywhere on the face (4) [4].

Efficacy of Subcision

Since Orentreich first described subcision in 1995, many studies have been performed to evaluate its effectiveness for acne scars. This has led to an accumulation of data that allows the modern clinician to counsel patients concerning the likelihood of positive outcomes following subcision. While some variability in treatment success has arisen from the utilization of procedural adaptations, studies report percent improvement to be between 25% and 80% (Table 22.2). Several factors may influence the effectiveness of subcision, including the type of needle used, number of treatment sessions performed, the type of postoperative care, the amount of time allowed for follow-up, and the age of the patient. These variables and the evidence supporting them are discussed.

Evidence suggests that multiple subcision sessions on the same scar are more effective than only one session. A case series of 15 patients found that after one session, patients had only 15–30% improvement, while those who completed 3 sessions had improvement of 40–80% (4) [5].

There is lack of uniformity in the follow-up period between studies, and it is likely that subcised scars change over time as post-procedure scar maturation and remodeling occurs. For example, Vaishani et al. found that a 5–10% improvement was seen between the 2- and 6-month follow-up visits. The authors attributed this to the fact that scar remodeling is a continuous process, noting that it takes at least 2 years to reach steady state [5]. Overall, there is mixed evidence on whether longer-term follow-up leads to greater or lesser measured scar improvement (Table 22.3).

The postoperative care may also affect the overall outcome of subcision. A study by Harandi et al. demonstrated the benefit of daily suction after subcision. Even though they had a higher amount of post-subcision bruising and swelling, patients who underwent daily suction with a microdermabrasion device on the skin overlying each scar in the immediate postoperative period had a significantly better overall result (2b) [6].

Another observation regarding subcision that could have clinical implications was made by Ramadan et al. when they found that increasing patient age correlated with a greater degree of scar improvement (2b) [7]. However, since this finding has not been replicated, further investigation is warranted.

Preoperative Evaluation

While studies have not addressed the preoperative evaluation of the patient prior to subcision, it is generally accepted that soft, distensible,

Table 22.2 Studies assessing efficacy of subcision for acne scars

Study	Year	Number of subjects (N)	Study type	Level of evidence	Investigator imp (range) mean	Pt reported (range) mean
Sage et al. [17]	2011	10	Prosp, split face	2b	61%	80%
Harandi et al. [6]	2011	12 (infreq suction)	Prosp, split face	2b	30–60% (44%)	49%
		46 (freq suction)	Prosp, split face		60–90% (72%)	75%
Ramadan et al. [7]	2011	20	Prosp, split face	2b	82%	81%
Vaishnani et al. [5]	2008	15	Case series	4	40–80%	40–80%
Balighi et al. [2]	2008	20	Prosp, split face	2b	25–75%	53, 51%
Alam et al. [4]	2005	40	Case series	4	30–90% (50–60%)	51%

Table 22.3 Variability in measured improvement at different points in follow-up timeline

Author, date	Follow-up time	Improvement	Other observations
Alam, 2005 [4]	1 and 6 months	50–60% improvement of appearance	Depth of scar improvement = 52% Visibility of scar improvement = 54% 90% of patients reported that subcision improved their scar appearance
Vaishani, 2008 [5]	2 and 6 months	The visual analog scale improvement ranged from 40% to 80% About 15–30% correction in first sitting	Slightly larger improvement in type-2 rolling scars than in type 1
Ramadan, 2011 [7]	10 months	Mean decrease in size for subcised scars was $0.386 \pm 0.391\ cm^2$	The older the patient, the greater the scar depth improved
Balighi, 2008 [2]	1 and 6 months	Patient assessment was 59.5 +/− 1.57% at 1 month and 53 +/− 1.57% at 6 months	12 cases (60%) had mild improvement 8 cases (40%) showed moderate improvement

rolling acne scars (those which have a gentle, sloped border) are the optimal scars for subcision. It is also important that the quality of skin overlying the depressed scar be normal, without hypopigmentation or fibrosis. Scars which have a sharply angled border such as ice pick and boxcar scars do not improve as much. Notably, subcision appears to be safe in all skin types (5) [3, 8].

While subcision is only minimally invasive and has relatively low risk of causing serious adverse events, there are several contraindications with which the clinician must be familiar (Table 22.4). As with all procedures that disrupt epidermal integrity, it is important that the patient be screened for active infection at or near the site of treatment. Other contraindications include bleeding diathesis, a history of keloid scarring in the area of subcision, and active inflammatory or cystic acne (2b, 4, 5) [6, 8, 9].

Table 22.4 Contraindications to subcision

Contraindications
Absolute
Active infective–at or immediately adjacent to the site to be treated
Deep, ice pick scar–ineffective
Relative
Active acne, especially cystic acne
Bleeding diathesis
History of keloid scarring after trauma or surgery

Overall, the level of evidence supporting the exact indications and contraindications for subcision is poor and consists primarily of clinical experience and expert opinion.

Treatment Technique

Most authors describe a similar technique for performing subcision. Local anesthetic is infiltrated into the treatment area after a sterile surgical preparation of the skin. A needle is then inserted lateral to the scar, which passes forward and backward underneath the scar and is then swept back and forth like a windshield wiper. The back-and-forth and side-to-side movements of the needle sever fibers in the dermis or superficial subcutaneous fat, allowing a space or "pocket" to form. The skin over this space is allowed to float upward to a level that is more consistent with the surrounding skin. In the immediate postoperative period, the pocket created underneath the scar is thought to be filled with serous fluid, a fibrin clot, or a hematoma; however, this has not been studied. The exact mechanism of the long-lasting scar improvement has also not been investigated; however, it is thought to be due to either the production of new collagen or scar tissue underneath the scar or the organization of a hematoma with subsequent fibrosis [3].

The literature does not contain high-quality evidence elucidating an optimal method of subcision. The variables in the subcision technique include the type of needle used, the intensity of sweeping of the needle, and the size of the pocket created under the scar. Some authors recommend small hollow-bore injection needles which are unlikely to create a significant open pocket under the skin, while others recommend more aggressive subdermal undermining with larger needles with large blades, such as the Nokor needle or the cataract blade.

The type of needle that will be utilized is an important decision to be made when preparing to perform subcision. When Orentreich first described subcision, he noted that a number of different needle gauges and lengths could be useful [1]. The paper stated that for larger, more bound-down scars, such as cellulite and surgical scars, 16-gauge needles could be used. Conversely, for smaller, more superficial scars and wrinkles, 25- to 30-gauge needles could be useful. Since that time, numerous studies have been published which have reported successfully using different needle types for subcision (Table 22.5). What it ultimately comes down to is that the needle of choice depends on the scar being treated, and this will require clinical evaluation. The opinion that larger bore needles are useful for larger or bound-down scars and that thinner needles are more useful for smaller, superficial scars is shared by other authors [4–6, 8]. Ayeni described the use of a 20-gauge cataract blade, which is a very sharp, tri-beveled blade that very efficiently creates a pocket underneath the scar (5) [9]. It should be noted however that comparative, prospective studies have not been done to evaluate one needle type against another.

Comparative studies have also not been performed to evaluate differences in treatment techniques such as the number of passes underneath each scar, the size of the pocket created, the optimal depth of injury, or the total number of sessions. However, a number of authors have given recommendations, or treatment pearls, intended to optimize outcomes based on their personal clinical experience. Some of these recommendations address the challenge of maintaining the orientation of the needle once it is inserted into the skin so that the flat, cutting portion is kept parallel to the skin surface. Khunger advised to bend the needle as a way of controlling needle tip orientation and also as a way to maintain a horizontal orientation of the entire needle (5) [10]. Al Ghamdi advised clamping the needle with a needle driver as a way of maintaining orientation (5) [11]. These procedural adaptations may be particularly pertinent, considering the warning made by Alam and colleagues that clinicians take care to keep the needle parallel to the skin surface to avoid injuring deeper structures or potentially even branches of the facial nerve that could be in the treatment area [4]. A few authors recommend multiple sessions over an extended period of time, ranging from three to six sessions [1, 9]; however, the exact number of sessions necessary for optimal improvement has not been studied.

Table 22.5 Types of needles that can be used for subcision

Needle type	Author	Level of evidence	Advantages	Disadvantages
1-inch, 22-G, hypodermic B-D needle [4]	Orentreich	4	Readily available Inexpensive	Small tip not as efficient at cutting dermal/subcutaneous attachments as Nokor or cataract blade
20-G microvitreoretinal (MVR) cataract blade [9]	Ayeni	5	Its diamond shape with a triangular point facilitates lateral sweeping motion Extremely sharp Longer cutting distance because it is sharp along the length of its bevel Has a handle	Significantly more expensive than other needles
18-G 1.5-inch Nokor admix needle [9]	Facts discussed by Ayeni	5	Blade is more efficient at cutting and releasing dermal attachments than standard syringe needles	Not very sharp Can cause significant injury at insertion site No handle, making it difficult to use
24-G needle [5]	Vaishnani	4	Less painful and traumatic, so that unnecessary trauma to normal dermal tissue can be avoided. Smaller hematoma, so chances of post-subcision fibrous nodule are diminished	Small tip not as efficient at cutting dermal/subcutaneous attachments as Nokor or cataract blade
23-G needle [6]	Harandi	4	Accessible for all Does not traumatize the skin at the insertion site	Small tip not as efficient at cutting dermal/subcutaneous attachments than Nokor or cataract blade

Combining Subcision with Other Treatments

Incomplete improvement is a possible outcome of subcision, and investigators have sought ways of making the improvement of scars more substantial or longer lasting by implanting material into the subcision pocket. Materials suggested include the patient's own dermis which is harvested from another site, absorbable plain catgut, and injectable filler substances [2]. No benefit was found in any of the studies evaluating subdermally implanted material over subcision alone, and some cases resulted in long-lasting nodules [2, 3]. Harandi and colleagues evaluated suction onto the skin using a microdermabrasion device in the postoperative period. Patients who received daily or every-other-day suction at subcision sites had a greater degree of improvement than those who had it less frequently; however, suction caused more nodules and bruising [6]. The results of this study have not been replicated. Investigators have also sought to combine subcision with other treatments either on the same day or in the immediate postoperative period. A study of one patient found that a nonablative 1320-nm Nd:YAG laser on scars treated with subcision produced greater improvement than subcision performed alone (4) [12]. It is possible that other treatments could be combined with subcision, such as carbon-dioxide laser, microneedling, and fractional radiofrequency; however, these have not been studied in combination with subcision.

Safety

Overall, subcision appears to be a relatively safe procedure with low risk of major sequelae. Common self-limited complications include pain, swelling, and bruising in the first 1–2 weeks after the procedure (4) [4, 13]. Rare adverse events are infection and hypertrophic scarring [4, 6, 13]. A fairly common, longer-term sequela of subcision is the formation of small to large firm elevations at the treatment site. The composition of the firm subcutaneous elevations has not been described in the literature by histopathology but is thought to be either early fibrosis or organization of a hematoma underneath the scar [13]. These subcutaneous nodules are thought to be responsible for the improvement of the depressed scars and usually resolve by 3 months after the procedure [4]. Goodman describes intralesional corticosteroids as a treatment for those nodules lasting longer than 3 months, which he reports as happening 5–10% of the time. Suction over the lesion in the postoperative period not only increases the amount and duration of bruising, but it also increases the height and the duration of subcutaneous indurations [6]. A final complication described is the formation of acneiform cysts that can result from the disruption of the pilosebaceous unit or subcutaneous sinus tracts (4, 5) [13, 14].

Alternative or Complementary Procedures

The most similar alternative procedure to subcision is the injection of soft tissue augmentation filler material underneath scar tissue. Like subcision, the goal of filler injection is to lift the base of rolling acne scars upward to minimize scar depth and ultimately improve the contour of the skin. The products which have been described include temporary fillers such as naturally sourced porcine collagen and hyaluronic acid, as well as permanent or long-lasting products such as micro-droplet silicone and polymethyl methacrylate microspheres in a bovine collagen matrix (1b, 3b) [15, 16]. The proposed advantages of filler injection include immediate results, minimal to no bruising or swelling, fairly predictable results, and the ability to make corrections at follow-up visits or completely reverse the procedure with hyaluronidase (2b) [3, 8, 17]. Disadvantages of filler injections include the temporary nature of products such as hyaluronic acid and collagen. While other products are longer lasting, they carry the risk of long-term nodules if the scar is overcorrected. These products include PMMA-collagen, calcium hydroxyapatite, poly-L-lactic acid, and autologous fat.

Only one study compared subcision to filler material head-to-head. This was a prospective, randomized, split-face, evaluator-blinded study of 10 patients. The subjects were randomly assigned to undergo subcision one side of the face and to receive injections of a naturally sourced porcine collagen filler on the other. Patients reported a superior result of subcision at 3 months compared to filler ($p = 0.03$); however, at 6 months, subcision was only slightly better ($p = 0.12$). Blinded evaluators scored subcision slightly better at 3 months ($p = 0.12$) and found no difference between the treatments at 6 months ($p = 0.69$) [17].

Some data exists that supports the suggestion that longer-acting or permanent fillers can effectively treat acne scars. A double-blind, randomized, multicenter, split-face, placebo-controlled trial compared saline injections to injections of polymethylmethacrylate microspheres suspended in collagen (PMMA-collagen) for atrophic acne scars in 147 subjects. Subjects received two different sessions of the injections and were evaluated over 6 months with a validated rating scale for each scar. A statistically significant improvement of the PMMA-collagen over saline at 6 months ($p = 0.0005$) was observed. The safety profile was excellent with mild, reversible side effects and no difference noted in different ages, gender, or skin type [15]. Another desirable quality of the PMMA-collagen is its purported permanent or long-lasting effect compared to hyaluronic acid fillers; however, this was not evaluated in this study. Another long-lasting filler is liquid silicone. While it has not been evaluated in a prospective, controlled trial, it has been

reported as being effective and long-lasting for the improvement of acne scars [16].

Finally, surgical and laser procedures are other potential alternatives to treatment. Punch elevation is the surgical procedure that best addresses the same types of scars which are optimal for subcision—rolling acne scars which have good quality skin at the base of the scar (Goodman). The procedure involves performing a punch around the scar and then lifting the scar upwards with either sutures or Steri-Strips. Other surgical procedures such as punch grafts, punch excision, and larger excisions are more appropriate for ice pick, boxcar, or sclerotic scars according to expert opinion article by Jacobs et al. (5) [8, 18]. Resurfacing procedures such as ablative and nonablative fractional lasers also do not address the same types of scars and have not been studied in head-to-head comparative studies with subcision. There is no strong evidence supporting these resurfacing procedures as alternatives to or adjuvants of subcision.

Overall, the evidence is lacking to recommend subcision over any other treatment for rolling, atrophic acne scars. This absence of evidence regarding subcision is consistent with the absence of high-quality evidence in the field of acne scar treatment generally. A Cochrane review made this comment after evaluating 24 randomized controlled studies of various acne scar therapies: "There is lack of high-quality evidence about the effects of different interventions for treating acne scars because of poor methodology, underpowered studies, lack of standardized improvement assessments, and different baseline variables." (1a) [19].

Postoperative Management and Follow-Up

Little has been discovered about the appropriate postoperative management of subcision. Balighi advised that little is required for postoperative care [2]. Alam and colleagues recommended that pressure dressings be placed and removed at 24 h [4]. If suction is to be performed, then daily or every-other-day follow-up visits would be required [6]. Goodman recommended that sun exposure should be minimized for 4 weeks after surgery, especially in olive-skinned patients to minimize the possibility of post-inflammatory hyperpigmentation [13]. Visible elevations and firm nodules can occur in the weeks and months following subcision; however, these resolve on their own. The rare nodule that persists can be treated with intralesional corticosteroid injections [13].

The duration of time required for the skin to achieve its steady state after subcision is also unclear. Vaishani suggested that 2 years is required for scar remodeling to be completed after subcision [5]. Orentreich advised follow-up treatments at 6–12 months for new or recurrent depressions after subcision [1].

Recommendations

- Subcision is effective for treating rolling acne scars on the face (B).
- Subcision is a safe procedure for all skin types, with low risk of serious or long-term complications (B).
- Contraindications for subcision include active infection, history of keloid scars in the area of treatment, bleeding diathesis, and current isotretinoin use (B).
- Various needle types can be used for subcision, depending on the size and depth of the scar to be treated. The needles range from 22- to 30-gauge standard hypodermic needles to Nokor needles or tri-beveled 20-gauge cataract blades (B–C).
- Studies have not demonstrated subcision to be superior or inferior to alternative therapies which treat the same type of scars, such as punch elevation and filler injection (B).

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Self-Assessment Questions

1. Subcision is optimal for which types of scars:
   (a) Rolling or atrophic acne scars
   (b) Varicella scars
   (c) Ice-pick acne scars
   (d) Hypertrophic scars
   (e) Subcutaneous sinus tracts
2. What is the level of evidence supporting subcision as an effective treatment for acne scars?
   (a) Primarily level 1A (Systematic review with homogeneity of randomized, controlled trials)
   (b) Primarily level 2A (Systematic reviews with homogeneity of cohort studies)
   (c) Primarily level 3A (Systematic reviews with homogeneity of case-control studies)
   (d) Primarily level 4 and 5 (Case series and expert opinion)
   (e) None of the above
3. What are common postoperative events associated with subcision?
   (a) Bruising
   (b) Swelling
   (c) Self-limited subcutaneous nodules
   (d) Bacterial infection
   (e) All of the above
   (f) a, b, and c
4. Which of the following statements is true?
   (a) Silicone injections have been shown in a randomized, controlled study to be effective for atrophic acne scars.
   (b) Subcision was shown to be superior to polymethacrylate microspheres in collagen (PMMA-collagen) for acne scarring in prospective controlled trial.
   (c) PMMA-collagen was superior to saline injections for atrophic acne scars at 6 months in a prospective, randomized trial.
   (d) CO_2 laser resurfacing was shown to be more effective at treating atrophic acne scars compared to placebo.
5. Comparative studies have determined that the optimal needle to use for subcision is the:
   (a) 18-gauge 1.5-inch Nokor needle.
   (b) 20-G microvitreoretinal (MVR) cataract blade.
   (c) 22–25 gauge hypodermic needle.
   (d) Comparative studies have not been performed to determine the optimal needle to use for subcision.

Correct Answers

1. a: Rolling acne scars with quality skin at the base are considered the optimal scars for subcision. Varicella scars or ice pick scars, which have either sharp borders or poor-quality, scarred skin at the base do not respond as well to subcision. Hypertrophic scars and subcutaneous sinus tracts are not treated by subcision. Subcutaneous sinus tracts can actually be disrupted by subcision.
2. d: The majority of publications supporting subcision are either expert opinion or case series.
3. f: Bruising and swelling are common and expected immediate, self-limited sequelae of subcision. Subcutaneous thickening or nodules are also common, but they resolve over time. Infection is not a common postoperative event.
4. c: A prospective, randomized, placebo-controlled, split-face study demonstrated improvement of atrophic acne scars with PMMA-collagen. Prospective, controlled studies have not been performed comparing injected silicone to placebo, subcision to PMMA-collagen, or CO_2 laser to placebo.
5. d: While specific authors recommend certain blades as being the most effective, comparative studies have not been performed.

Liposuction

23

Ashley Decker and Naomi Lawrence

Abstract

Liposuction is a safe and effective method of subcutaneous fat removal involving aspiration of subcutaneous adipose tissue via cannulas introduced through small skin incisions. In tumescent liposuction, the surgeon utilizes subcutaneous infiltration of dilute lidocaine and epinephrine to provide local anesthesia and hemostasis prior to aspiration of the adipose tissue. In addition to its aesthetic indications, tumescent liposuction is also a safe and effective treatment modality for breast reduction, gynecomastia, lipomas, lipoedema, and hyperhidrosis. Despite the development of newer, noninvasive body-contouring modalities, liposuction remains the gold standard.

Keywords

Liposuction · Tumescent liposuction · Body contouring · Tumescent anesthesia · Noninvasive body contouring

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Indications for Liposuction

Liposuction is the surgical removal of subcutaneous adipose tissue using aspiration cannulas introduced through small skin incisions. In tumescent liposuction, the surgeon utilizes subcutaneous infiltration of dilute lidocaine and epinephrine to provide local anesthesia and hemostasis prior to aspiration of the adipose tissue. This technique was refined and popularized in the United States by Klein in 1987 [1]. Today, tumescent liposuction is the accepted standard of care for liposuction surgery performed for both aesthetic and non-aesthetic purposes. A key advantage of this approach is the ability to perform the procedure in the outpatient setting, leading to increased patient convenience, decreased risk of nosocomial infection, and lower costs [2].

Adipose tissue is a loose connective tissue that is the site of storage of energy in lipid form, insulation and heat production, and production of several hormones including leptin and estrogen and is divided into two main types based on location: visceral and subcutaneous. Visceral adipose tissue represents approximately 18% of the total body fat and has historically been linked to metabolic disease; however, the role that each type plays in the development of metabolic syndrome is not fully elucidated (5, 5) [3, 4]. Although it has been hypothesized that changing the proportion of visceral to subcutaneous fat through liposuction may unfavorably alter metabolic disease

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risk (5) [5], most studies show no post-procedure change in the parameters associated with metabolic syndrome (4, 4, 2b, 2b) [3, 6–9].

The primary aesthetic indication for tumescent liposuction is the correction or removal of disproportionate, localized deposits of adipose tissue (5) [10]. This therapy has successfully treated undesired adiposity in nearly all body sites. Tumescent liposuction is also an effective procedure for non-cosmetic treatment of adipose collections in cases such as breast reduction, lipomas, gynecomastia, lipoedema, and hyperhidrosis. For hyperhidrosis/bromhidrosis specifically, tumescent liposuction is indicated after failure of conventional medical therapies and can be used alone or in combination with curettage. In order to assess treatment efficacy for this indication, pre- and postoperative gravimetry studies should be considered.

Effectiveness of Liposuction

The majority of data indicates that tumescent liposuction results in the effective, durable removal of localized adiposity when used for both cosmetic and non-cosmetic indications. An assessment of changes in body contour after liposuction is largely based on qualitative comparisons using pre-/postoperative photography and circumference measurements. Using more robust 3D digital photoimaging and standardized measuring techniques, Cohen et al. found a 30% decrease in mean abdominal volume after tumescent liposuction (4) [11]. The available literature suggests that most patients are satisfied with the results of liposuction performed for body contouring. Broughton et al. reported that 80% of patients who underwent liposuction at the University of Texas Southwestern Medical Center between 1999 and 2003 were satisfied with the outcome of their procedure (5) [12].

Treatment of lipomas with tumescent liposuction can reduce scarring compared to standard surgical excision. In addition, the use of tumescent anesthesia with epinephrine creates a near-bloodless field and may aid in the disruption fibrous septae leading to easier extraction during surgery or liposuction. A prospective review by Choi et al. described the use of liposuction for the treatment of 31 lipomas located on the head or neck, trunk, abdomen, or extremities in 21 patients (4) [13]. In total, 23 lipomas were removed without complications. The remaining cases were complicated by incomplete fat removal, bruising, hematoma, and dimpling [13]. In the cases of large fibrous lipomas, laser lipolysis followed by liposuction can be necessary (4) [14].

Tumescent liposuction for hyperhidrosis/bromhidrosis can lead to significant improvement in sweating, with patient satisfaction ranging from 80% to 98% (4, 4) [15, 16]. Patients with high sweat rates respond better to liposuction-curettage than those with normal to slightly elevated sweat rates. Posttreatment recurrence rates reported in the literature range from 4.6% to 30% (4, 4, 4) [17–19]. This large variation is due to residual apocrine glands present after treatment opposed to apocrine gland regeneration. Treatment success largely depends on the technique utilized. When compared to open excision, liposuction with curettage results in higher patient satisfaction rates and less severe scarring. However, symptom recurrence is more common among patients treated with liposuction-curettage (3b) [20]. There are a number of papers comparing these two modalities, and although symptom recurrence is more common with liposuction-curettage, most studies show that patients prefer it because it is a procedure with significantly less morbidity. A recently randomized controlled clinical trial comparing liposuction-curettage to neurotoxin for axillary hyperhidrosis showed a statistically significant decrease in heavy sweating with neurotoxin compared to liposuction (2b) [21]. However, neurotoxins have the disadvantages of repeated treatments and are not usually covered by insurance.

Breast liposuction is indicated in male and female patients with enlarged breasts. First introduced in 1991, it is a safe and effective procedure to decrease breast volume and improve breast ptosis (4, 4, 4, 4) [22–25]. In addition, patients report improvement in symptoms associated with large breasts including intertrigo, postural issues,

and neck, back, and shoulder pain. Studies show no significant changes in mammography occur after breast liposuction (4) [24, 26].

Preoperative Evaluation

Proper patient selection is imperative. The ideal patient has localized deposits of adipose tissue recalcitrant to diet and exercise, is otherwise healthy, and has realistic expectations about the procedure. Patients may incorrectly seek tumescent liposuction consultation as a method of weight loss. Tumescent liposuction is not used for weight loss/weight control but rather to improve body contour; any weight loss from the procedure is incidental (5) [27]. Current recommendations suggest that patients should be within 30% of their ideal body weight (5) [28]. Removal of a maximum of 4–5 L of adipose tissue is considered safe during tumescent liposuction (4) [29]. Removal of greater amounts predisposes to higher risk as the risk of complications is proportional to the volume of fat removed.

During the pre-procedure consultation, complete a thorough history of medical conditions and previous surgeries, allergies, and medications, including over-the-counter medications, vitamins, and supplements. Liposuction is contraindicated in patients with severe cardiovascular disease, allergy to lidocaine, and severe coagulation disorders including thrombophilia and during pregnancy. Patients with a history of bleeding diathesis, emboli, thrombophlebitis, infectious diseases, poor wound healing, or diabetes mellitus should receive medical clearance. Ask about history of prior abdominal surgeries or problems during previous surgical procedures. Stop all nonessential medications prior to surgery to minimize the risk of bleeding complications. Discontinue aspirin (ASA) 2 weeks prior to surgery and other nonsteroidal anti-inflammatory medications 5 days prior to surgery. If the patient is on anticoagulation, discuss with the prescribing provider whether perioperative discontinuation is safe. If the patient cannot stop anticoagulants for an appropriate amount of time, they are not a candidate for liposuction. The procedure results in a dead space and a risk of delayed bleeding that creates a greater challenge than conventional surgery. Discontinue any medication that may interfere with lidocaine metabolism 2 weeks prior to the procedure (Table 23.1). If not possible to discontinue a medication that may interfere with lidocaine metabolism, use of a lower total amount of lidocaine or general anesthesia should be considered.

Completion of a psychosocial history is imperative when assessing a patient for liposuction. Ask about dietary habits and exercise, history of weight loss/gain, familial body shape, and patient's emotional ability to endure the procedure. Assess the patient's expectations following the procedure. A history of weight cycling prior to the procedure is often a poor prognostic indicator of the outcome.

After completion of the medical and psychosocial history, perform a complete physical exam with emphasis on the body sites under consideration. Distinguish between subdermal and vis-

Table 23.1 Drug interactions with lidocaine

Alprazolam	Clarithromycin	Erythromycin	Lovastatin	Paroxetine	Tacrine
Amiodarone	Clomipramine	Felodipine	Mexiletine	Phenytoin	Tamoxifen
Amiodarone	Cyclosporine	Fluconazole	Miconazole	Propofol	Triazolam
Amitriptyline	Danazol	Fluoxetine	Midazolam	Propranolol	Valproic acid
Atazanavir	Diazepam	Flurazepam	Nefazodone	Quinidine	Verapamil
Atorvastatin	Diethyldithiocarbamate	Fluvoxamine	Nelfinavir	Quinupristin	Zileuton
Carbamazepine	Diltiazem	Grapefruit	Nevirapine	Ritonavir	
Cerivastatin	Disopyramide	Indinavir	Nicardipine	Saquinavir	
Cimetidine	Divalproex	Itraconazole	Nifedipine	Sertraline	
Ciprofloxacin	Enoxacin	Ketoconazole	Norfloxacin	Simvastatin	

Adapted from Heuther and Brodland [30] and http://www.Liposuction.com

ceral fat on the abdomen. Assess skin quality and texture in the affected areas and evaluate for any scars or keloids indicating prior procedures [10]. Check for complete blood count, platelet count, prothrombin times, partial thromboplastin time, and complete metabolic panel and conduct a pregnancy test in women of childbearing age prior to the procedure. A preoperative mammogram is necessary to screen for malignant and benign tumors in women undergoing liposuction for breast reduction. Take high-quality photographs in three dimensions during consultation and preoperatively on the day of surgery.

Best Techniques and Performance

Mark the patient in a standing position paying attention to the areas of interest. Make note of any asymmetries and adjust predicted volume removal accordingly. View each area from the anterior, posterior, and oblique positions to best appreciate the three-dimensional nature of adiposity. After the markings are complete, review with the patient to ensure all areas of concern are addressed. Choose access points that can treat multiple different areas or the same area in multiple different directions. The incisions should be 3–4 mm in length and placed in well-concealed areas (5) [31]. Ultrasound-assisted liposuction requires larger incisions (5–6 mm) because of the placement of skin protectors that minimize heat transfer to the skin [31]. Cannulas with a tapered tip or an increased number of holes near the tip are for more aggressive suctioning. Blunt-tipped cannulas, or those with the holes located further away from the tip, are less aggressive. Most areas can be suctioned with relatively thin cannulas. In large or fibrous areas, it is helpful to start with "aggressive" tips to break up the adipose and fibrous tissue and then switch to a larger gauge blunt-tipped cannula. Small-diameter, blunt-tipped cannulas are used to minimize perforation risk and decrease contour irregularities. Patient positioning depends on the area being treated (see Table 23.2).

Anatomically, fat is separated into layers by Scarpa's fascia, but for the purposes of liposuc-

Table 23.2 Anatomic considerations

Neck
Forward placed hyoid bone may limit ability to fully contour the anterior neck
Enlarged thyroid or submandibular glands may contribute to neck fullness
Micrognathia contributes to chin deformity and skin redundancy
Have patient contract platysma in a grimace to define the preplatysmal fat pad
Two layers of fat: subcutaneous and deep to the muscle. It is important to temper patient expectations in the setting of significant submuscular fat
Abdomen
Lateral hip-flexed (diver's) position helps delineate superficial fat from the muscle and omental fat
Check for abdominal hernia or defects in the rectus
Place the patient in a comfortable supine position
Discuss differences between subcutaneous fat and visceral fat. Temper expectations of the procedure in patients with significant visceral fat
Outer thigh
Determine the extent to which the buttocks' weight contributes to the outer thigh deformity
Flexion of gluteal musculature defines the contribution of adipose in the buttocks to the protuberance of the outer thigh—if the outer thigh decreased on gluteal contraction, the weight of the buttocks is significant
Abduct the thigh using a wedge-shaped pillow to eliminate the "pseudobulge" which is seen over the trochanteric process. This decreases the risk of iatrogenic depression caused by excessive liposuction [32]
Inner thigh
Loose skin and adipose tissue
Place the patient in a modified lateral decubitus position with the uppermost hip flexed in a high-step position and ipsilateral leg resting on surgical positioning pillow. This allows for easy accessibility of the posterior medial fat pad, which is not adequately accessed in a supine position [32]
Back
Dense fibrous fat

Table 23.2 (continued)

Upper arms Distinguish lax muscle and redundant skin from adipose tissue Extensor fat pad overlies the triceps and biceps. Place patient in lateral decubitus position and rest the arm on patient's uppermost side [32] For the volar or axillary portion of arm fat, place the patient in a lateral decubitus position. Raise the arm above the head, with hand resting over or behind the head [32]
Breast Palpate the breast to evaluate for fibrocystic disease and to distinguish between glandular and adipose tissue
Knees Majority of adipose tissue is located on the medial aspect of the knee, but there is suprapatellar and subpatellar extension Place the patient in a modified lateral decubitus position with the uppermost hip flexed in a high-step position and ipsilateral leg resting on surgical positioning pillow [32]
Hips Adipose tissue extends toward the back Place the patient in a lateral decubitus position

tion, it is divided into three layers: superficial, intermediate, and deep. Intermediate and deep layers are suctioned; the superficial layer should remain undisturbed. Liposuction of the superficial layer may lead to dimples and skin irregularities that are cosmetically unacceptable (5) [33]. Anatomic "zones of adherence" are present in both men and women and need to be avoided because of high risk of contour deformities. They are composed of dense fascial extensions extending from the superficial fat to the underlying musculature and help define the natural shape and musculature of the body [4, 28]. Men have more fibrous adipose tissue than women, except in specific situations and locations such as fibrocystic breast disease and on the back. The outer and inner thighs are comprised of soft fat.

Several liposuction treatment modalities exist including suction-assisted ("traditional liposuction"), power-assisted, laser-assisted, ultrasound-assisted, and radiofrequency-assisted liposuction. Deciding on what type of modality to use depends largely on the surgeon's preference. The authors prefer traditional suction-assisted lipectomy with tumescent anesthesia as none of the new modalities have improved patient outcomes or experience. Some of the technology-assisted modalities are preferred by liposuction surgeons, who feel that it decreases the work of the procedure for the physician.

Suction-assisted liposuction is the most common form of liposuction. It involves the use of various sized cannulas attached to the suction to facilitate removal of aspirate. Power-assisted liposuction involves a variable speed motor that provides a reciprocating motion to the cannula facilitating removal of adipose tissue (4) [31, 34]. Some consider the use of power-assisted liposuction in fibrous areas, such as areas of revision, or for large-volume liposuction.

Laser-assisted liposuction involves the use of laser energy to facilitate fat breakdown prior to aspiration. There are several FDA-approved laser lipolysis devices available in the market (5) [35]. The most commonly used wavelengths are 924/975 nm, 1064 nm, and 1319/1320 nm [31, 35]. The procedure is carried out in four stages: infiltration, application of energy to subcutaneous tissues, evacuation, and subdermal skin stimulation. These devices are marketed for the additional benefit of skin tightening. Prado et al. conducted a prospective, randomized, double-blind controlled trial comparing 1064 nm Nd:Yag-assisted lipolysis to suction-assisted liposuction in 25 patients (2b) [36]. Each patient served as their own control with one side treated with laser-assisted lipolysis and the contralateral side with suction-assisted liposuction [36]. No clinical difference was seen between the treatment modalities [36]. Higher concentrations of free fatty acids were seen after laser-assisted lipolysis [36]. One proposed additional benefit of laser-assisted lipolysis is skin tightening from subdermal heating; however, this has never been

substantiated. Traditional liposuction leads to some skin tightening because of retraction. Longer-wavelength lasers have a higher risk of burns because of increased dermal absorption and localized heating [35].

Ultrasound-assisted liposuction uses ultrasound energy to break down fat allowing for easier removal. It may decrease surgeon fatigue and is useful in areas with increased fibrosis. Its primary mechanism is mechanical but cavitation and thermal damage can occur [31]. Vibration amplification of sound energy at resonance (VASER)-assisted lipoplasty is a third-generation ultrasound system that was introduced after mixed results from hollow probe ultrasonic liposuction. A prospective study by Nagy et al. compared the blood loss and skin retraction-associated VASER-assisted lipoplasty versus suction-assisted liposuction in 20 patients. Patients served as their own controls. The VASER-associated lipoplasty resulted in a statistically significant improvement in both skin retraction and blood loss compared to standard suction-associated liposuction (2b) [37]. This small study has not been validated by other studies. The technique is also really slow.

Radiofrequency-assisted liposuction applies electromagnetic energy in a bipolar manner to both the subcutaneous adipose tissue and the subdermal skin surface (4, 4) [38, 39]. A study by Paul et al. demonstrated radiofrequency-associated liposuction leads to rapid preaspiration liquefaction of adipose tissue, coagulation of subcutaneous blood vessels, and uniformed sustained heating of the tissue [38]. Some recent literature has purported radiofrequency-assisted liposuction is faster, reduces tissue trauma, and has potential for skin retraction; however, these studies are small and underpowered (4, 4) [40, 41].

Safety

Tumescent liposuction is a safe procedure with a low complication rate. Several large surveys report of a systemic complication rate of less than 1% (5, 5, 5) [42–44]. Data over a 7-year time period from the Florida Agency for Health Care Administration found eight deaths associated with in-office liposuction, all of which were performed under general anesthesia ($n = 7$) or IV sedation ($n = 1$) (5, 5) [45, 46]. No adverse events were reported with tumescent liposuction [45, 46].

Tumescent anesthesia is a low-risk procedure; proper patient selection coupled with a well-trained physician mitigates these risks even further.

Safety of Tumescent Anesthesia

The use of tumescent anesthesia confers a risk of lidocaine toxicity. The half-life of lidocaine is 120 min, and tumescent anesthesia can lead to levels that cause symptoms of lidocaine toxicity. Most cases of lidocaine toxicity are due to incorrect mixing or dosing of the lidocaine solution. As serum lidocaine levels approach 3 μg/mL, subjective symptoms such as feeling lightheaded, dizzy, and/or drowsy may occur (4) [47]. Muscular fasciculation, tinnitus, and paresthesia occur with serum lidocaine levels >5 μg/ml [47]. Concentrations >9 μg/ml are associated with coma, seizures, respiratory arrest, and cardiac arrest [47].

Klein first showed that 35 mg/kg of tumescent lidocaine was safe, with peak plasma levels reaching at 12 h post infusion (V) [48]. Subsequent studies showed lidocaine doses up to 50–55 mg/kg are safe in tumescent anesthesia (4) [49]. Accordingly, the current guidelines in the dermatology literature recommend a maximum dose of lidocaine in tumescent anesthesia of 50–55 mg/kg (5) [1, 2, 50]. However, the rate of systemic absorption is location dependent with peak serum lidocaine levels reached more quickly when tumescent anesthesia is administered above the clavicles (3b) [51]. The risk of toxicity remains low overall because of the low volume of tumescent anesthesia used in those areas. In contrast, the presence of dilute epinephrine leads to vasoconstriction and slows the systemic absorption of the lidocaine. Finally, the surgical procedure performed following tumescent anesthesia

should influence the total lidocaine dose. A significant amount of lidocaine is removed during liposuction, and this may play a role in peak absorption levels. A recent prospective study by Klein et al. suggested that the maximum tumescent lidocaine dose be limited to 28 mg/kg in patients where tumescent anesthesia was not followed by liposuction. Their data indicate that a significant amount of lidocaine is likely removed by the liposuction procedure and does not reach the systemic circulation (3b) [52]. Data supporting maximum lidocaine dose of 55 mg/kg in tumescent liposuction should not be extrapolated to estimate the maximum dose of tumescent anesthesia for other procedures.

Local and Systemic Complications

Local adverse effects include erythema, ecchymoses, edema, and seromas. Tumescent liposuction can result in significant fluid shift and intravascular volume changes leading to a vasovagal reaction. The most frequent potentially lethal complications associated with liposuction are infection, pulmonary embolism, fat embolism, sepsis, necrotizing fasciitis, and perforation of abdominal viscera [28]. Both Group A strep (GAS) and *Mycobacterium* species have been identified in post-liposuction infections. An investigation into an outbreak of GAS infection following liposuction at a single outpatient cosmetic surgery facility determined that GAS infection was caused by transmission from colonized health workers during the procedure (4) [30]. Although the risk of significant systemic complications from tumescent liposuction is low compared to general anesthesia, when present, they still confer significant morbidity and mortality.

Deaths associated with tumescent liposuction are more common in the plastic surgery literature. A study by Lehnhardt et al. sent out 3500 questionnaires to departments of pathology, intensive care units, insurance companies, and district attorney offices. Two thousand and seventy-five (65%) surveys were returned with 72 cases of reported severe systemic complications. Forty-one of the 72 severe complications were with tumescent anesthesia, four of which resulted in death (4) [53]. The major risk factors for complications were insufficient hygiene standards, increased amounts of tumescent anesthesia, poor patient selection, permissive discharge, and inexperience of the provider [53].

In summary, tumescent liposuction is a safe and efficacious procedure. Increased mortality is seen with aggressive liposuction, large-volume procedures, general anesthesia, or IV sedation. Liposuction under general anesthesia has a higher-than-acceptable complication rate and should be abandoned in practice.

Postoperative Care and Follow-Up

After completion of the procedure, appropriate compression garments should be placed to minimize the risk of bruising, hematomas, seromas, and pain. Application of heavy compression in the first 24 h helps to facilitate drainage followed by mild compression for the next 2–4 days (5) [54]. Prolonged compression may lead to skin creases, pain, swelling, and hyperpigmentation [28]. Educate the patient that swelling and bruising are normal after the procedure. Drainage from the puncture sites may occur in the first 24–48 h after surgery. Encourage the patient to ambulate the night of surgery. The initial postoperative visit is 1 week after surgery. Patients can resume activities immediately but will be sore. Most patients prefer to wait a week. Swelling can persist for 3–4 weeks; final results are expected in 3–4 months [31]. In patients with elastic skin, contour improves after swelling is resolved. In patients with poor elasticity and lax skin, full retraction can take 6–12 months.

Alternative Procedures and Modifications

Although liposuction remains the most popular body-contouring procedure, the need for post-procedure downtime and the desire for noninvasive procedures led to the development of noninvasive procedures for fat reduction such as

high-intensity focused ultrasound (HIFU), radiofrequency, laser-assisted lipolysis, and infrared light (4) [55]. At the forefront of noninvasive fat reduction treatment is cryolipolysis. This treatment is based on the observation that fat cells, relative to those of other tissues, are more sensitive to the cold (4, 4) [56, 57]. A preclinical study by Zelickson et al. showed that a controlled, cold application to the skin leads to selective damage of adipose tissue without adverse effects to the epidermis or dermis [55]. Cold exposure induces crystallization within the adipocytes leading to panniculitis and subsequent necrosis. The procedure is well tolerated. A study by Garibyan et al. showed an average of about 40 cc fat reduction in the treated flank 2 months after a single treatment (3b) [58]. Another study by Dierickx et al. demonstrated a 23% reduction in fat layer thickness at 3 months (3b) [59]. The back, flank, and abdomen were most responsive to treatment [59].

Side effects of treatment are localized pain, erythema, transient changes in sensation, and nodular or diffuse infiltration at the treatment site. All of these side effects are transient and resolve within weeks.

Radiofrequency without associated liposuction is another method of noninvasive body contouring and fat reduction. This procedure utilizes electromagnetic energy to generate heat within targeted tissues (5, 4) [60, 61]. Adipose tissue has high resistance but a low heat transfer coefficient. This enables significant heat generation resulting in adipolysis when radiofrequency passes through the tissue but minimal heat transfer or injury to surrounding structures (4) [62]. Some studies suggest radiofrequency also improves dermal collagen, elastin, and ground substance leading to skin tightening (5,5) [62, 63]. Monopolar, unipolar, bipolar, and multipolar mechanisms of radiofrequency delivery are available. Notably, this procedure works regardless of skin type or chromophore and is not dependent on selective photothermolysis [60]. Adverse effects include erythema, edema, heating sensation, and bruising (4, 4) [64, 65].

High-intensity focused ultrasound (HIFU) uses high-frequency acoustic energy to ablate focal areas of subcutaneous adipose tissue. It rapidly heats the adipose tissue to 55 °C, causing cellular membrane disruption/lysis and coagulative necrosis (5) [66]. It spares damage to the surrounding connective tissue, blood vessels, nerves, and overlying skin. HIFU devices are currently approved by the FDA for noninvasive waist circumference reduction. They target subcutaneous abdominal fat at a focal depth of 1.3 cm [66]. A randomized sham-controlled trial by Jewell et al. showed significantly greater waist reductions in patients in both treatment arms (141 J/cm [2] or 159 J/cm [2]) compared to the sham treatment group (2b) [67]. Mean waist circumference reduction was 2.51 cm ($p < 0.001$) in both treatment arms. Other studies showed similar reductions in mean waist circumference after a single treatment (4, 4, 2b) [68–70]. Unfortunately, circumference is known to be an unreliable measure. Adverse events include ecchymosis, tenderness, focal induration, and edema [66].

The use of infrared lasers and low-light laser therapy (LLLT) for subcutaneous adipose tissue reduction is based on the concept of selective photothermolysis. An in vitro study by Anderson et al. identified the absorption spectra of adipose tissue (1210 and 1720 nm) and suggested selective photothermal targeting of subcutaneous adipose tissue is achievable using infrared lasers that target these spectra (4) [71]. A study by Wanner et al. treated the abdomen of 24 adult patients with 1210 nm laser at 70, 80, and 90 J/cm [2] (10 mm spot size, 5 s pre-cooling, 3 s exposure) [72]. Exposure and control sites were biopsied at 1–3 days and 4–7 weeks (3b) [72]. Histologic evaluation showed laser-induced lipomembranous damage to the fat [72]. The laser treatments were painful and required local anesthesia [72]. Additional prospective studies are needed to elucidate if there is a role for infrared lasers in the treatment of subcutaneous adipose tissue.

LLLT is a noninvasive, nonthermal light source treatment (635 nm) that generates a single wavelength and acts by generating cellular nonthermal or photochemical reactions (2b) [73]. It is hypothesized to work by creating transient pores in adipocytes, allowing lipids to leak out (5) [74]. Used for years in a myriad of conditions across multiple specialties, recently its role in

noninvasive body contouring, in cellulite reduction, and as an adjunct to liposuction has been of some interest [74].

LLLT's role in fat reduction is controversial. A study by Brown et el. did not show any change in the structure or function of cultured human preadipocytes treated with up to 60 min of LLLT (3b) [75]. In this same study by Brown et al., no difference in adipocyte structure was noted in the adipocytes extracted through liposuction (with or without tumescence) following similar transcutaneous exposure times to LLLT in the human or porcine model [75]. A study by Kolari et al. questions the ability of LLLT to penetrate past the dermis into the subcutaneous adipose tissue and can explain the absence of structural/functional change in adipocytes treated with LLLT (4) [76]. However, clinical studies have shown a decrease in abdominal, hip, thigh, and waist circumference (2b, 4) [73, 77, 78]. These studies are limited by lack of clinical controls and short duration of follow-up.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Effectiveness	
Tumescent liposuction is effective in the removal of localized adipose tissue for cosmetic and non-cosmetic reasons	A
It is a safe and effective alternative for lipoma removal. Advantages include reduced scarring, near-bloodless field created by tumescent anesthesia, and disruption of fibrous septae leading to easier removal	B
Tumescent liposuction with curettage is an effective treatment for patients with brom-/hyperhidrosis	B
Breast liposuction can reduce the volume and improve ptosis in both men and women	B
Preoperative evaluation	
Appropriate patient selection is imperative to maximize treatment outcome and patient satisfaction	A
Complete a comprehensive history to identify any medical or psychosocial issues prior to the procedure	A
The physical exam should focus on the areas of adiposity, amount of visceral vs subdermal fat, and skin quality/texture	A
Best techniques and performance	
Cannulas with tapered tips are more aggressive; blunt-tipped cannulas are less aggressive	A
Pure tumescent anesthesia without sedation is the safest method	A
Some physicians use additional technology including:	
Power assisted: revisions or large volumes	B
Laser assisted and ultrasound assisted: assists in fat breakdown. Skin tightening has not been substantiated	C
All of these technologies are more expensive and have not been shown to be better tolerated by the patient, show superior results, prove better skin retraction consistently, are more comfortable for the patient, and show no decrease in postoperative adverse events	B
Safety	
Tumescent liposuction is a low-risk procedure	A
The maximum dose of tumescent lidocaine is 45–55 mg/kg	A
Increased mortality is seen with aggressive liposuction, large-volume procedures, general anesthesia, or IV sedation	A
Liposuction with general anesthesia is associated with a higher mortality rate	A

Findings	GRADE score: quality of evidence
Postoperative care and follow-up	
Place compression garments after the surgery to minimize bruising, swelling, hematomas/seromas, and pain	D
Improvement in body contour is immediate but full skin retraction can take 6–12 months to occur	D
Alternative procedures and modifications	
Liposuction remains the gold standard	A
Cryolipolysis can improve localized areas of adiposity. Side effects of treatment are transient and resolve in weeks	B
The evidence for the role of radiofrequency, high-intensity focused ultrasound, and low-light laser therapy remains controversial	C

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Self-Assessment Questions

1. What key aspects of the medical and surgical history should be documented during preoperative evaluation?
   (a) Previous surgeries with special attention to surgeries performed in the area to be suctioned
   (b) Psychosocial history including history of body dysmorphic disorder
   (c) Recent fluctuations in weight
   (d) Chronic medical conditions (i.e., cardiovascular disease, diabetes)
   (e) All of the above
2. What is the recommended maximum volume that should be aspirated during a single liposuction session?
   (a) 1–2 L
   (b) 2–3 L
   (c) 4–5 L
   (d) 5–6 L
   (e) 7–8 L
3. What is the half-life of lidocaine?
   (a) 30 min
   (b) 60 min
   (c) 90 min
   (d) 120 min
   (e) 180 min
4. What layer(s) of fat are targeted in tumescent liposuction?
   (a) Superficial
   (b) Superficial and intermediate
   (c) Deep
   (d) Intermediate and deep
   (e) Superficial, intermediate, and deep
5. What are the recommended qualifications of a physician performing liposuction?
   (a) Advance Cardiac Life Support certification
   (b) Board certification in a specialty that emphasizes training in cutaneous surgery
   (c) Evidence of liposuction surgery training in residency or documented liposuction-specific training postresidency
   (d) All of the above

Correct Answers

1. e: All of the above. A history of previous surgeries in the area can lead to scarring/fibrosis complicating the procedure. Patients with a history of psychosocial disorders, especially body dysmorphic disorder, can have unrealistic expectations of the outcome making them poor candidates for the procedure. Recent fluctuation in weight is a poor prognostic indicator of surgical outcome. Certain chronic medical conditions may be a contraindication for tumescent liposuction.
2. c: 4–5 L. The maximum amount of adipose tissue that can safely be removed during a single session of tumescent liposuction is 4–5 L. Additional volume can increase the risk of complications. All of the other answers are incorrect.
3. d: 120 min. The half-life of lidocaine is 120 min. All of the other answers are incorrect.
4. d: Intermediate and deep. In tumescent liposuction, intermediate and deep layers are suctioned. The superficial layer should remain undisturbed. Liposuction of the superficial layer may lead to dimples and skin irregularities that are cosmetically unacceptable.
5. d: All of the above. A physician performing tumescent liposuction should be certified in Advanced Cardiac Life Support, board certified in a specialty that emphasizes cutaneous surgery and evidence of postresidency training in liposuction.

Hair Transplant

24

Robert L. Finney and Marc R. Avram

Abstract

Both men and women are candidates for hair transplant surgery. There are a variety of causes that produce hair loss in patients, including genetic male and female pattern hair loss, primary inflammatory and infectious scalp dermatoses, and traumatic hair loss.

Keywords

Hair transplant · Techniques · Preoperative evaluation · Postoperative care · Safety

Indications for Hair Transplant

Both men and women are candidates for hair transplant surgery. There are a variety of causes that produce hair loss in patients, including genetic male and female pattern hair loss, primary inflammatory and infectious scalp dermatoses, and traumatic hair loss.

Hair transplantation is indicated for patients who would like to restore hair in regions of their scalp where they have suffered loss and there is little chance that medical therapy alone will restore their loss.

Ever since the 1990s, transplanting individual follicular units, each consisting of one to three hairs, has emerged as the standard of care (5) [1]. This method consistently produces results where both men and women can expect natural-appearing hair. Currently, two methods are used: follicular unit transplantation (FUT) and follicular unit extraction (FUE) . In FUT, a strip of hair is obtained from the donor area and then individual follicular units are created from the harvested tissue. This method leaves behind a thin linear scar and is not ideal for patients who wish to wear their hair short in the future. Alternatively, in FUE, individual follicular units are harvested directly from the donor area manually or with the help of a robotic system. The resultant pinpoint scars are not visible in patients who wear their hair short. Both methods share equivalent efficacy; however, depending on variable factors, one can be favored over the other (5) [2]. During the consult, the risk-benefit of FUE vs donor elliptical harvesting (FUT) is discussed, and the appropriate technique for each patient is chosen.

With either technique, the amount of donor hair available is critical to candidate selection. A patient with poor or depleted donor density will have little cosmetic impact from hair transplantation. Patients with high donor density are able to transplant a larger number of hair follicles and have greater cosmetic impact from a procedure.

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Patients must understand that a hair transplant will not change the natural rate of hair loss from their underlying male or female pattern alopecia and that full correction to their baseline appearance prior to balding is not possible. This procedure is not indicated in patients who do not understand the limited nature of donor hair available and the progressive nature of untreated pattern hair loss.

Effectiveness of Hair Transplants

Hair transplantation surgery is a very effective procedure; grafts that are harvested from the "safe" donor area in the mid-occipital scalp are not susceptible to the effects of androgens and thus survive long term. For a procedure to be considered "effective," it also has to meet the subjective quality assessment of the patient. A significant portion of the discussion in the consultation prior to a hair transplant should be spent assessing the patient's expectations and then conveying the benefits and limitations of hair surgery. It is important that a patient knows prior to receiving a transplant that although a natural cosmetic outcome is likely, full restoration is not possible. The patient will not return to having the hairline and density prior to the onset of their alopecia. Many variables can affect the perceived effectiveness of a surgery, including density and caliber of hair in the donor area, pattern of alopecia and surface area of exposed scalp, width of the scalp, hair color, and whether or not the hair is curly or straight. It is also important to stress that without any concurrent medical therapy, their pattern alopecia will continue as it was genetically programmed to do and that this will affect their hair density moving forward. A patient who is motivated to begin or maintain medical therapy is much more likely to have a better outcome.

From a technical aspect, several variables can affect the success of a surgery, including transection rate, amount of time the grafts are ex vivo, storage solution used, and trauma to the follicular units during the procedure. The reported transection rate for FUT with strip harvesting completed by experienced practitioners is approxiamtely 1.59% (4) [3]. FUE on the other hand can be done manually or robotically with reported transection rates that vary widely from one another. Reports range from a few percent to as much as 30% in some cases. In a study done by Avram et al., 20 patients underwent robotic hair transplantation with an average transection rate of 6.6% (4) [4]. Once successfully harvested, graft survival inversely correlates with how long it sits out prior to transplantation, with rates of survival quoted at 95% at 2 hours and 86% at 6 hours (4) [5]. The holding solution the grafts are placed into can also affect the survival of transplanted hair, with anecdotal studies showing those stored in solutions such as HypoThermosol® or HypoThermosol® + ATP outsurvive those stored in normal saline or lactated ringers (4) [6]. Lastly, graft survival is dependent upon amount of trauma it is subject to, which is why having experienced technicians who minimize trauma to the follicular units are irreplaceable members of the surgical team.

Preoperative Evaluation

The surgical consult is an important aspect of hair surgery. As discussed above, assessing the patient's expectations is an important step. Next, their history with regard to their alopecia onset and rate of progression should be assessed.

The primary reason for hair loss should be confirmed via physical exam. If there is any doubt regarding the etiology of a patient's hair loss, a biopsy should be performed. A complete medical history should be obtained for each patient. If any pertinent positives are present on review of systems, the practitioner should consider ordering bloodwork (i.e., iron studies, thyroid labs, hormone levels) or referring the patient to their primary physician for a medical work-up.

As mentioned in the prior section, once a diagnosis of pattern alopecia is made, the preoperative consult should include a discussion of the current medical therapies available to treat this condition. A hair transplant will have the biggest impact if a patient is able to halt further hair loss, something that is possible for a majority of patients with today's medical treatments. Whether male or

female, minoxidil should be discussed. Multiple clinical trials have proven the efficacy of topical minoxidil (1a). A recent trial showed that 5% minoxidil was effective in not only increasing hair counts but also stabilizing hair density over both the frontotemporal and vertex regions during a 2-year follow-up period [7–12]. Side effects are minimal, with the most common being irritation. Unwanted hair growth is a rare but reversible side effect that can occur, mainly on the face of women [8]. This may only require decreasing the frequency or strength of application in order to reverse the unwanted hair growth. Finasteride which blocks the formation of dihydrotestosterone (DHT), a hormone that promotes the miniaturization and loss of susceptible hair follicles, is also another option that has been proven to halt and potentially thicken hair in roughly 80% of patients (1a) [13–15]. This is only FDA approved for males, however it has been used off-label in postmenopausal females with mixed results (4) [16–18]. Finasteride should not be used by women in child-bearing years. The biggest deterrent in compliance with this medicine tends to be a result of the sexual side effects that can occur in up to 2–4% of patients [13]. There are also rare reports of post-finasteride syndrome, but no true causal link has been reported to date (5) [19]. Low-level laser light therapy is also another treatment offered to patients. Although the data is not as strong, enough studies have shown promising effects in 40–50% of patients and thus warrant discussion (1a) [20–22]. Lastly, platelet-rich plasma (PRP) injections should be discussed with patients. Although true, well-designed placebo-controlled blinded randomized control trials are somewhat lacking, data published to date has been positive enough to warrant this as a first or second line treatment option in both men and women suffering from hair loss. Since a patient's own plasma is being injected, it tends to be tolerated very well (4) [23–24]. It is thought that many of these treatments can be synergistic and a combination approach can be used. It is also likely that medical therapy has a better chance of efficacy, the earlier the stage of alopecia. Patients with advanced stage likely have irreversible follicular dropout that medical therapy may fail to ameliorate.

With respect to age, there are no specific restrictions to surgery. Younger patients have a more unpredictable course of future hair loss and often desire a full restoration, so surgery in this cohort should be planned conservatively and carried out with caution. Given that they may also decide to shave their head in the future, the reduced risk of apparent scarring with FUE makes this the obvious harvesting method of choice in this cohort. A patient should be in good health. If there are any active medical problems, they should get clearance from their physician. If a patient is on a blood-thinning medication that the prescribing physician believes should not be stopped, then the procedure should not be performed.

Best Techniques and Performance

With an experienced surgical team, both FUT and FUE are effective means of harvesting grafts for hair transplantation (Table 24.1). The donor

Table 24.1 Comparison of FUT and FUE

FUT (donor elliptical harvesting)	FUE
Pros	Pros
Average time for a clinician to harvest a strip is only 15 minutes Does not require a patient to trim their whole donor area short, thus ideal for women or men who do not plan to wear their hair short in the future Transection rate reproducibly low	Minimal processing of grafts after harvesting is required, thus minimal support staff needed Resultant scarring is often not apparent Less invasive, sites heal secondarily in 3–5 days
Cons	Cons
Requires a skilled surgical team to harvest follicular units from the strip There will be a linear scar that will be present if a patient decides to trim their hair short in the future Staples or sutures are required to close the donor area, thus an extra office visit required for removal	Time required to harvest is longer than FUT Requires skill of the clinician to harvest if a robotic system is not used Clinician fatigue during long cases Patient is required to trim the entire donor area short Transection rate is more variable

area for both techniques is located on the occipital scalp. Hair in this area is largely exempt from pattern hair loss. The procedure is performed as an outpatient under local anesthesia.

In FUT, an elliptical strip ranging in width from 0.7 to 1.2 cm is excised after trimming the hair in the donor area. This is done after anesthetizing the area with lidocaine and epinephrine, as well as adding normal saline to increase dermal turgor and thus reduce transection of hair follicles. The defect is then closed with either staples or suture. In order to determine the width and length of the strip needed, the density of hair in the donor area and the number of desired grafts must first be known. Individual follicular units are then created carefully from the harvested strip by surgical assistants with or without the use of magnification. This is a time-consuming process and requires expert technique to perform this in an efficient manner with minimal transection or trauma to the follicle. A long-term consequence of harvesting grafts via FUT is the resultant linear scar in the donor area. This scar is usually only noticeable if a patient wears their hair very short in the back, although rarely a hypertrophic scar can occur. The number of grafts obtained is equivalent to FUE. FUT is the ideal method for harvesting grafts in women, because only a small strip of hair needs to be trimmed and, upon leaving, the linear closure can be covered by the surrounding hair. This is also a viable option for males who never plan to wear their hair short enough to reveal the scar created from the ellipse.

Since its creation in 2002, FUE has become an increasingly popular method of donor harvesting [2]. Hair in the donor area is trimmed to 1 mm in length via clippers and then anesthetized with lidocaine and epinephrine. FUE can be performed manually with 0.75–1.2 mm sharp or blunt punches, manually with the help of motorized hand-held systems or by utilizing a completely robotic system (i.e., the ARTAS hair restoration system) (5) [25]. Manual FUE relies on the skilled eye and hand of the practitioner to correctly assess the angle of exit for each follicular unit and harvest the grafts in a random pattern. Depending on the size of the surgery planned and skill of the clinician performing the FUE, this method can be time intensive. The robotic system on the other hand can operate independent of the physician. It autonomously assesses hair density and the angle each follicular unit exits the scalp. It then utilizes a dual sharp/blunt punch system to extract follicular units in a random manner. The clinician can override the software to harvest grafts closer together, further apart, or change the depth at which the graft is cut to. The robotic system allows grafts to be harvested in an efficient manner. The resultant defects left behind from all methods of FUE will heal naturally in 3–5 days without the need for primary closure. The grafts also require very little processing by hair technicians, and thus the procedure could be performed more efficiently in a setting with less support staff. As discussed above, when performing hair surgery via FUE, the transection rates tend to vary more widely and may be higher than FUT performed with experienced hair technicians [4]. The resultant scars left behind tend to be pinpoint, hypopigmented macules and are unnoticeable even when a patient wears their hair clipped short. FUE is thus the preferred method for patients who potentially may wear their hair in the occipital scalp very short in the future. It is also less invasive and ideal for a scenario with younger patients with minimal loss who may only need a smaller surgical restoration.

The hairline and areas for recipient sites to be made should be mapped out and discussed with the patient prior to the procedure with a marking pen. It is important to be cognizant of potential future hair loss when planning the hairline. Planning a receded hairline helps keep cosmetic balance with continued pattern alopecia occurring at the temples and posterior hairline. Once mapped out, the recipient area is then anesthetized with the use of an amide anesthetic combined with epinephrine. The number of sites created should match the total graft count and is commonly made in a random yet even pattern, with the use of a 19–20 gauge needle. Alternatively, several implantation devices have been made that can either just place the hair or also make the site simultaneously. These have been reported to cause less trauma to the follicle and help improve the speed of implantation (5)

[26]. Single-hair follicular units should be utilized for the main part of recreating an irregular natural hair line, whereas follicular units with two to four hairs can be transplanted just posterior to the hairline. The angle of the recipient site should match the hair that is already there, around 30–45 degrees. The angle changes as you approach the vertex and parietal hairlines, and care should be taken as to the direction and angle if the patient has a natural cowlick.

Unfortunately, in all patients, the donor area does not contain enough hair to transplant the entire frontal scalp, mid-scalp and vertex with an acceptable density (5) [27]. From a cosmetic standpoint, the hairline and frontal scalp are key to framing the face, and thus planting the grafts should begin there and be worked back as far as possible based on the number harvested. In patients with an exposed vertex, as the posterior border of transplanted hair is reached, the density should be slowly tapered to create a softer transition between the transplanted area and exposed scalp. Transplanting the vertex should be avoided in most cases. Given that androgenetic alopecia (AGA) is a progressive condition, the surgeon has to operate under the assumption that the patient will continue to progress to a Norwood VII, thus losing all of the hair on the temples/crown/vertex. If this occurs, the hair transplanted to the vertex can appear as an isolated island of hair, almost with the appearance of a donut and thus be a cosmetically regrettable result.

In female pattern hair loss, the frontal hairline usually remains intact and balding begins on the crown, with widening of the part before progressing to involve the crown diffusely. As with males, the frontal hairline and scalp help to frame the face, and a majority of the recipient sites should be made to help fortify this area, prior to reinforcing the crown. In women who bald slowly but diffusely over the entire scalp, transplantation can be difficult, given the lack of density and unpredictable longevity of hair in the donor area. Patients with this pattern are not good candidates for surgery.

Hair transplantation is also successful for patients who have lost density in their eyebrows, which most commonly results from traction alopecia due to years of over-plucking. The same donor area can be used for FUE or FUT via strip or several punch grafts. Unlike scalp surgery, only single-hair follicular units should be utilized for eyebrow surgery, and thus those with two or more hairs should be split under magnification. When planning the donor area, a much more acute angle must be used to create the sites, and they should be placed in a cross-hatched pattern with one another. A patient should be counseled that since scalp hair is being used, they will have to frequently trim the transplanted hairs moving forward.

The average size of any single-hair transplant surgery should be around 1000–2000 grafts. Hair density is a main determinant as to the size of the procedure possible, but scalp laxity and blood supply, as well as support staff and their experience, are other important factors that can play a role depending on the method chosen for harvesting. Many surgeons perform larger surgeries, but graft survival may suffer if the size attempted results in an increased length of time between harvesting and transplanting individual grafts.

Safety

Hair transplant surgery is safe with rare reports of medical or surgical complications. It is performed under local anesthesia and bleeding is minimal. FUT has a small risk of producing a hypertrophic scar. This risk can be reduced but not eliminated by putting minimal tension on the wound. If a hypertrophic scar occurs, it can be improved with intralesional Kenalog and/or a variety of lasers. In FUE, the defects heal secondarily in 3–5 days, and they are usually not noticeable, but there have been reports of a "moth-eaten" alopecia in the donor area of patients who are over-harvested. This can be avoided by spacing grafts out at least 1 mm, but care should be taken to not over-harvest the donor region (4) [28]. No matter the method of harvesting, the risk of infection is minimal in hair transplant surgery. A self-limited folliculitis may be observed. Temporary or permanent numbness in either donor or recipient sites has also rarely been reported. Given the

amount of anesthesia and minor trauma from harvesting and transplanting, a headache and mild discomfort are common. A 3-day course of prednisone 40 mg can help reduce the swelling, and pain can be controlled with extra-strength acetaminophen. Pain after the first day of the procedure is uncommon. If a clinician plans a long, large procedure, it is vital that staff keep track of the total amount of anesthesia utilized to avoid lidocaine toxicity.

Postoperative Care and Follow-Up

If a patient had FUT with a strip performed, there should be a follow-up appointment at 10 days to remove any staples or sutures, unless absorbable sutures were used. If FUE is performed, the sites will heal via secondary intention within 3–5 days, and thus close follow-up is not necessary. All patients are encouraged to contact the office with any questions or concerns.

Appropriate counseling that the transplanted hair will enter telogen directly after the procedure is important so that the patient does not expect there to be any evidence of increased density in the immediate months following the procedure. They should be told that the transplanted hairs will likely begin to grow 6 months after the procedure and that they should hold judgment on the efficacy of the transplantation until 12–15 months postoperatively. One topic of discussion at hair transplant meetings has been focused on using platelet-rich or poor plasma as either a holding solution for the grafts or injected into the recipient area directly in order to have quicker regrowth and higher yield of transplanted hair, but no concrete data is available yet. Regardless, patients should be seen after 1 year to evaluate the growth of the transplanted hair and address any questions or concerns the patients may have regarding the procedure. This is also a good time to reinforce the importance of medical therapy and assess the need or want for further hair transplant surgery.

Alternative Procedures and Modifications

As discussed above, medical therapy should be offered and recommended to all patients who come in for consultation. An in-depth discussion about minoxidil, finasteride, low-level laser light therapy, and platelet-rich plasma injections should precede any discussion of surgical options. For the vast majority of patients, a combination of medical and surgical therapy will create the greatest long-term density and thus cosmesis.

Currently no true alternative exists with respect to hair transplant surgery. Artificial grafts have been tried in the past, but they carried a significant risk of an inflammatory granulomatous reaction and are banned by the FDA (2c) [29]. Research has focused on cloning hair in order to bypass the limited donor area, something that could render full restorations possible in the future. Hair extensions, hair pieces, scalp micropigmentation, and the use of topical artificial hair fibers (i.e., Toppik) are appropriate options for some patients.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Finasteride has the highest likelihood of all current medical treatments to halt hair loss long term and potentially regrow hair and should be offered to all male patients seeking hair transplant	A
Minoxidil is an effective method for stabilizing and potentially re-growing hair in both males and females and should be offered to all patients (non-pregnant or breastfeeding) with pattern alopecia	A
Platelet Rich Plasma is newer and requires more well-designed trials, but enough evidence exists to support its use as a standalone or adjunct treatment in pattern alopecia. Low level laser light therapy has been well studied but it is more modestly efficacious than other treatment options such as finasteride/minoxidil/PRP and should be used more as an adjunctive therapy.	C
Size of surgery should be limited to what staff can handle and where grafts can be placed safely for natural long-term cosmetic results in an efficient manner to limit the length of time the grafts are ex vivo	B
Given that the donor area does not contain enough follicular units to transplant the entire frontal scalp, mid-scalp, and vertex with an appropriate density, transplanting the vertex should be avoided in the majority of cases due to long-term cosmetic concerns	B
Detailed informed consent, preoperative counseling, and careful patient selection are key predictors of patient satisfaction after surgery	A
Preparation of the recipient bed must include a consideration of continued pattern alopecia when designing the hairline, and care should be taken to create recipient sites at angles naturally occurring in the area of the scalp	C
A well-trained ancillary staff and a well-trained surgeon are associated with minimal transection and optimal outcomes in follicular grafting	B
Hypothermosol, with or without ATP or other holding solutions for grafts may increase graft survival compared to normal saline or lactated ringers	D
Full efficacy of a hair transplant is likely not seen until around 12 months postoperatively	C
FUT should be avoided in patients who desire to wear their hair cropped shortly in the occipital scalp in the future or if they are unsure to	C

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Self-Assessment Questions

1. True/false. Transplanting the vertex is appropriate in most patients.
2. True/false. The only instance where all follicular units should be split to contain only one hair is when transplanting hair to the eyebrow.
3. What is the most appropriate harvesting technique for a 50-year-old woman with pattern alopecia and a normal clinical exam/labwork?
   (a) FUE
   (b) FUT
   (c) Either, it does not matter
   (d) The patient is not a good candidate
4. What is the most appropriate harvesting technique for a 35-year-old male who has androgenetic alopecia that is stable on topical minoxidil and who wears his hair relatively short on the sides and back?
   (a) FUE
   (b) FUT
   (c) Either, it does not matter
   (d) The patient is not a good candidate
5. What is the most appropriate harvesting technique for a 60-year-old female who has had stable hair loss on topical minoxidil for 5 years with significant decreased density and miniaturization in the occipital scalp?
   (a) FUE
   (b) FUT
   (c) Either, it does not matter
   (d) The patient is not a good candidate

Correct Answers

1. False. Given the limited donor area, it is more cosmetically appropriate to focus the most on the frontal and mid-scalp.
2. True. Transplanting follicular units with more than one hair would have a very unnatural appearance. Splitting follicular units in scalp surgery is usually not practiced because of the potential unnecessary trauma or transection.
3. b: Most female patients would not want to have the downtime from trimming the whole donor area necessary for FUE, and since they will likely continue to wear their hair long, the scar from FUT is not a cosmetic issue.
4. a: FUE will allow this patient to continue wearing their hair short without a visible scar in the future.
5. d: Patients with diffuse alopecia lack a good donor area and thus are not good candidates for surgery.

Small Caliber Vessel Sclerotherapy

25

Todd V. Cartee and Sean T. McGuire

Abstract

Sclerotherapy is the procedure of introducing a foreign body into a vein with the intent of ablating the vessel through a controlled thrombophlebitic event with resulting scar formation. Circa 460 BC, Hippocrates described a rudimentary precursor of modern sclerotherapy by inducing thrombosis through serially puncturing a vein with a slender iron rod. In the 1600s, Sigismund Eisholtz used distilled plantain water in the earliest recorded use of an injected substance to induce sclerosis. Refinement of the sclerosant material, injection technique, and the addition of foamed formulations over the past century have elevated sclerotherapy to the gold standard in the treatment of reticular and telangiectatic leg veins and an important therapeutic modality for varicose veins and saphenous reflux.

Keywords

Sclerotherapy · Leg veins · Technique · Safety · Complications

Introduction

Sclerotherapy is the procedure of introducing a foreign body into a vein with the intent of ablating the vessel through a controlled thrombophlebitic event with resulting scar formation. Circa 460 BC, Hippocrates described a rudimentary precursor of modern sclerotherapy by inducing thrombosis through serially puncturing a vein with a slender iron rod. In the 1600s, Sigismund Eisholtz used distilled plantain water in the earliest recorded use of an injected substance to induce sclerosis. Refinement of the sclerosant material, injection technique, and the addition of foamed formulations over the past century have elevated sclerotherapy to the gold standard in the treatment of reticular and telangiectatic leg veins and an important therapeutic modality for varicose veins and saphenous reflux.

Sclerotherapy is utilized to fibrose superficial veins to either address symptomatic venous insufficiency or improve cosmesis. This technique has traditionally been plied for leg veins, but its use on the face, hands, and chest has also been described [1] (Level 4).

Physiology

A working knowledge of the underlying physiology is critical for achieving excellent outcomes. The leg's venous system consists of deep and superficial plexuses that contain 95% and 5% of

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the blood volume, respectively. This innate redundancy permits elements of the superficial system to be ablated with minimal impact on overall venous flow. The superficial venous system is centered about the great and small saphenous veins, as well as the lateral venous system. These vessels communicate with the deep venous system both through major anastomoses—the saphenofemoral and saphenopopliteal junctions—and through hundreds of fascial perforating vessels.

Blood flow from the legs to the heart is analogous to a grain elevator. Contraction of the muscles of the deep posterior compartment of the leg generates the necessary pressure gradient to pump against gravity, and a system of intraluminal valves prevents retrograde flow. Incompetence of the valves or failure of the calf muscle pump results in blood pooling in the legs, increasing intraluminal pressures and ultimately distending the vein. This distension may propagate downstream, mechanically separating otherwise competent valves and extending the apparent extent of disease.

Classification and Scope of Chapter

In 2004, the American Venous Forum revised the CEAP scoring system to reflect an updated understanding of venous disease. (Table 25.1) Sclerotherapy can be used in the treatment of C1–C6 disease; this chapter focuses on the treatment of isolated C1 disease and C2 disease in the absence of clinical or ultrasonographic evidence of saphenous insufficiency (truncal disease). One critical caveat: a physician must always be cognizant of signs suggestive of underlying insufficiency. Whenever there is sufficient suspicion for truncal or deep venous reflux, a complete duplex examination of the venous system is indicated before proceeding with visual sclerotherapy.

Table 25.1 CEAP scoring system

Clinical manifestation	C0	No visible or palpable disease
	C1	Telangiectasia (<1 mm diameter) and reticular veins (1–3 mm)
	C2	Varicose veins (>3 mm)
	C3	Edema
	C4a	Pigmentation and eczema
	C4b	Lipodermatosclerosis and atrophie blanche
	C5	Healed venous ulcer
	C6	Active venous ulcer
Etiologic factors	Ec	Congenital
	Ep	Primary
	Es	Secondary (post-thrombotic)
Anatomic distribution	As	Superficial veins
	Ap	Perforator veins
	Ad	Deep veins
Pathophysiologic classification	Pr	Reflux
	Po	Obstruction
	Pr,o	Reflux and obstruction
	Pn	No venous pathology identifiable

Demographics

The Edinburgh Vein Study found that 84% of participants had (at least) C1 disease [2] (Level 3b). A German population-based study, consisting of 3072 men and women aged 18–79, found isolated C1 disease in 59% [3] (Level 3b). A descriptive study assessed the legs of 291 patients presenting to the University of Hong Kong Medical Center vascular clinic and found C1 and/or C2 disease in 50% of assessed limbs [4] (Level 3b). A more ethnically diverse sampling was included in the San Diego Population Study, wherein 55%, 50%, 45%, and 45% of the included non-Hispanic White, Hispanic, African American, and Asian participants demonstrated isolated C1 disease, respectively [5] (Level 3b). The demographic risk factors for telangiectasias and reticular veins appear to parallel those described in more extensive disease of Caucasian race, namely, advancing age, female gender, family history of venous disease, and pregnancy. Of these, age seems to be the biggest risk factor, with 80% of women aged >80 possessing varicose veins [6] (Level 3b). Age is closely followed by family history as a compelling risk factor, with the chance of having varicose veins approaching 90% if both parents are affected [7] (Level 3b).

Effectiveness of Sclerotherapy

Sclerotherapy is considered the gold standard for the treatment of C1 disease, with up to 90% improvement reported in several randomized, blinded trials utilizing polidocanol (POL) [8] (Level 2b). However, generalizing this degree of effectiveness is difficult due to heterogeneity in the reported outcome measures, small sampling size of many studies, differences in sclerosing agent formulation and concentration, postoperative care, and follow-up interval. Furthermore, a disproportionate amount of the literature constitutes small trials performed by a small group of experts. Yet another variable is noted concentration variance of POL in the United States prior to FDA approval in 2010 [9] (Level 5).

Case Series

A retrospective review of a single private practice compared the use of liquid and foamed sodium tetradecyl sulfate (STS) for reticular veins with subsequent glycerin treatment for telangiectasia. Three hundred and twenty-five patients were contacted after an average of 4 years follow-up (range 1–11), and there was no significant difference in degree of improvement between these two agents, and improvement was rated as moderate to good [10] (Level 4).

Goldman performed a double-blinded study in 20 patients comparing the efficacy of liquid POL to STS in telangiectatic and reticular veins, as well as foam formulations of both agents for varicose veins. In aggregate, no significant difference in efficacy, as determined by an independent physician, nor patient satisfaction was noted at 16-week follow-up [11] (Level 2b).

Randomized Trials and Meta-Analysis

The EASI study—a double-blind, randomized, placebo-controlled trial—compared 160 patients with telangiectasias treated with 0.5% POL, 1% STS, and placebo, as well as 156 patients with reticular veins treated with 1% POL, 1% STS, and placebo. No power calculation is provided in the text. Patients received one to three treatments in a 6-week period. Independent evaluation of standardized photos rated improvement as excellent and similar between the POL and STS groups (4.54 and 4.45; $P < 0.00001$ on a scale from 1 to 5, with 4 being "good improvement" and 5 being "complete treatment success"). There was no change in the placebo-treated arm. This provides compelling level I evidence of the overall efficacy of small vessel sclerotherapy. At 26 weeks, 88% of patients treated with POL and 63% of patients treated with STS were satisfied with their treatment. There were significantly higher rates of skin discoloration and ulceration in the STS group. However, STS is a more potent sclerosing agent than POL, and the 1% concentration of STS used in this study is considerably more concentrated than what is typically used in clinical practice for spider and reticular veins. Therefore, it is unclear if the adverse event profile would have been more similar if equipotent concentrations were employed [12] (Level 1b).

An industry-sponsored randomized, blinded, placebo-controlled study in China investigated the efficacy of liquid POL for the treatment of C1 and C2 disease in a Chinese population. As no officially approved sclerosant was available in China at the time of study, industry sponsorship was instrumental in training and procurement of supplies. Veins smaller than 1 mm in diameter were treated with 0.5% POL or placebo, and veins 1–5 mm were treated with 1% POL or placebo. Patients received up to three treatments at intervals of 2–4 weeks or until they achieved >50% response as graded by blinded investigator assessment. The average number of treatments for the two described groups was 1.93 and 1.74. 87% of both groups were assessed to have >50% improvement at 12-week follow-up. Greater than 85% of patients were either satisfied or very satisfied, and >60% of patients were very satisfied. Both were significantly different from placebo [13] (Level 1b).

Preoperative Evaluation

The literature informing the use of diagnostic testing for varicose veins is limited to expert opinion and small retrospective trials. Patients should undergo a directed history and complete physical exam of the entire legs and feet in a standing position to identify any evidence of varicosities (C2 disease) or chronic venous insufficiency (C3–C6 disease). Varicose veins are often not apparent when a patient is recumbent. Individuals with only telangiectasia likely do not require further evaluation beyond visual inspection [14] (Level 5), although others argue that complete management, even of telangiectasias, includes examining the underlying interconnected plexus to identify the origin of reflux through ultrasound exam [15] (Level 5). The American Society of Dermatologic Surgery (ASDS) Consensus Guidelines do not recommend further evaluation for C1 disease beyond a clinical exam if other findings detailed in Table 25.2 are absent [16]. The authors subject all patients with C2 (visible bulging varicose veins) or greater disease to an ultrasound examination of the superficial venous system to assess for proximal sources of reflux that would be best addressed via endothermal saphenous vein ablation or ultrasound-guided foam sclerotherapy prior to embarking on visual sclerotherapy.

Known patent foramen ovale is a contraindication for foamed sclerotherapy [16]. The second European Consensus Meeting on Foam Sclerotherapy does not recommend screening individuals for patent foramen ovale.

Table 25.2 Scenarios in which one should consider diagnostic ultrasound (from ASDS Consensus Guideline, 2014)

Bulging varicosity >4 mm in diameter, especially when located on the medial leg or posterior calf (zones of GSV and SSV influence)
Significant symptoms consistent with venous insufficiency (throbbing, leg heaviness, etc.)
Lower extremity edema
Cutaneous sequelae of venous disease, such as stasis dermatitis
A “star-burst” cluster of telangiectasia of medial calf especially medial malleolus
History of deep vein thrombosis or thrombophlebitis
Prior sclerotherapy or similar intervention with recurrence or poor results

Best Techniques and Performance

Standard Technique

Basic operational technique has been experientially derived from physiologic principles and continues to be refined as new advances are incorporated. Following appropriate patient selection and any indicated preoperative evaluation, the procedure is begun by reclining the patient flat to reduce the intraluminal pressure of the leg veins. The provider selects the appropriate sclerosant, concentration, and formulation. The material is then loaded into a syringe and topped with a 30 gauge needle. Starting with the larger feeding reticular veins and progressing through the vein’s watershed telangiectasias, the provider cannulates the vessel and injects a small amount of sclerosant. The authors prefer the use of foam sclerosant for the treatment of reticular veins. Foam enables the treatment of higher capacitance vessels with much less agent, but increased efficacy has not been established in clinical trials. When treating reticular veins, negative pressure can be utilized to ensure intraluminal position with the flashback of blood. With experience through and the aid of transillumination, most reticular veins can be successfully cannulated and injected with minimal extravasation of agent without confirmation of placement by flashback. Minimal positive pressure is necessary to infuse the selected sclerosant. Upon successful treatment, the vessel should temporally disappear as blood is displaced by the sclerosant. Following session completion, bandages are placed as needed, and compression stockings are applied to the patient while still recumbent.

Foam vs Liquid Formulation

Selecting a liquid or foam formulation depends on operator experience, variance in the size of

vessels to be treated, and the projected amount of sclerosant to be administered. For vessels <4 mm, the ASDS consensus document on sclerotherapy, acknowledging the lack of general consensus, notes that many clinicians utilize liquid sclerotherapy for the treatment of these vessels. The 2013 European Guidelines for sclerotherapy endorses liquid formulations as the standard but notes that foam is an acceptable alternative.

Several well-conducted randomized controlled trials (RCTs) have demonstrated foam to have superior efficacy when treating saphenous or other large diameter veins [17] (Level 3b) [18] (Level 1b). This experience has prompted the widespread use of foam in treating reticular veins and even large telangiectasia (1–2 mm), but the evidence supporting this approach is sparse.

A meta-analysis of studies comparing liquid to foam sclerotherapy found only two studies concerned with reticular veins; no substantial conclusions could be drawn from these studies [19] (Level 2b). The best single study to date was an un-blinded 100-person investigation comparing the efficacy of polidocanol foam and liquid formulations in vessels <4 mm (with concentration based upon subdivided vessel size). This study demonstrated a nonsignificant trend toward foam superiority (84% vs 72% clearance) [20] (Level 3b).

Another question is how to generate foam. Most practitioners utilize room air, but some have advocated for carbon dioxide, which forms smaller bubbles that dissipate more quickly than nitrogen or oxygen. One observational study comparing experience with carbon dioxide to historical experience with room air-generated foam in the treatment of saphenous tributaries and small saphenous veins found a reduced incidence of foam bubble-related side effects including chest tightness, cough, and dizziness but no significant difference in transient neurological events (e.g., visual disturbances) [21] (Level 3b). Only one small trial (20 participants) has been conducted comparing the use of carbon dioxide and room air to develop foam in the treatment of reticular veins and failed to show any difference in efficacy or side effects [22] (Level 4).

Sclerosant Selection

Sclerosant selection is largely driven by expert opinion, provider comfort, and availability of agent. Head-to-head comparisons are scarce and may not influence daily practice due to their required adherence to government-approved concentrations (although these may not mirror typical use) and the variation in treatment approaches and postoperative care.

The previously mentioned EASI study compared vessel-controlled concentrations of polidocanol and sodium tetradecyl sulfate. Its strengths and weaknesses are available above; the principal findings were a higher patient satisfaction with polidocanol at 26 week and a higher rate of side effects with STS at the tested concentrations [8].

In a randomized study, 129 patients presenting with 1–6 mm varicose veins were treated with either liquid STS or POL. Concentrations were adjusted for size of vessel treated and more closely mimic concentrations utilized in active practice than the EASI study, with vessels <1 mm treated with either POL 0.5% or STS 0.25%, 1–3 mm received 1% POL or 0.5% STS, and those 3–6 mm in diameter were treated with 3% POL or 1.5% STS. At week 16 follow-up, the agents were equally effective as assessed by blinded evaluators (both ranked between moderate and complete resolution) [11] (Level 2b).

A single blinded study compared 100% chromated glycerin (CG), 0.25% liquid POL, and 0.25% foamed POL (Monfreux method) in the treatment of C1 disease in 150 patients. Patients received one treatment. A trend toward higher patient satisfaction was noted in those treated with CG than the other two arms ($p < 0.08$), but no difference was noted between POL liquid and foam. Blinded evaluation found a significantly higher efficiency of CG at 2-month follow-up. A trend toward superior efficacy of the foamed vs liquid polidocanol was noted. Treatment with CG was significantly more painful than either POL regimen. No cases of hyperpigmentation or matting occurred in the CG group, while POL liquid and foam encountered three and four such com-

plications, respectively [23] (Level 1b). The equipotency of these treatments has been debated [24] (Level 5).

Kern et al. also compared the efficacy and pain of treating C1 disease with CG and the same mixed with 1% lidocaine-epinephrine in a 2:1 mixture. One hundred two patients were treated as per the protocol and available for 5-week follow-up. Patients who received the lidocaine mixture had significantly less pain and patient satisfaction was equivalent. Objective review by two blinded experts trended toward superiority for chromated glycerin alone (7.84 vs 7.33 on a 10-point scale, $p = 0.07$) [25] (Level 4).

In a separate study, this mixture was used in a two-step fashion in an attempt to further reduce pain by treating all reticular veins first and then returning to the beginning to treat remaining telangiectasias. Fifty-three women were included and asked to rate their pain immediately after standard therapy (treatment of reticular veins followed immediately by treatment of associated telangiectasias) versus a two-step approach with approximately a 5-minute delay between sweeps. Pain was significantly reduced with the two-step approach but reduced physician and patient economy of movement. The author purports that the vasospasm associated with epinephrine dissipated prior to the treatment of telangiectasia in the two-step group [26] (Level 4).

Thirteen patients received 0.25% STS or glycerin 72% solution in the treatment of vessels 0.2–0.4 mm in diameter. Glycerin 72% mixed 2:1 with 1% lidocaine with epinephrine 1:100,000 is the standard glycerin based scleroing solution used in the US as CG is not available. Both of the patients' legs each received different solutions. At 2 to 6 months following one treatment session, glycerin was noted to cause similar and low levels of pain with injection. Glycerin demonstrated a higher rate of vessel clearance than STS (subjectively assessed) while causing less bruising, swelling, and hyperpigmentation. Given the small sample size, no statistical analysis was performed [27] (Level 4).

In a comparison of hypertonic saline (HS) and liquid POL for C1–C2 disease, Peterson et al. performed a split-leg study between 0.5% POL and 11.7% HS for telangiectasia and 1% POL and 23.4% HS for reticular veins of 63 patients. At 16-week evaluation, no significant difference in efficacy was noted, with both groups reporting approximately 70% improvement. Patients noted significantly more pain with injection of HS, and two episodes of ulceration were recorded in the HS group [28] (Level 2b).

Maximum Volume

The European Consensus Meeting on Foam Sclerotherapy recommends no more than 10 mL of foam for injection of the great saphenous vein; this limit has been exceeded in a small trial without consequence in the treatment of reticular veins [1]. For the treatment of reticular veins, in clinical practice, the current authors as well as most expert sclerotherapists safely use more than 10 mL of foam in a single session [16]. Per the package inserts, no more than 10 mL of 1% POL solution, and no more than 10 mL of 1% or 3% STS should be used in one session.

Safety

POL and STS are both FDA approved for the treatment of varicose veins. The other two agents approved by the FDA for sclerotherapy, morrhuate sodium and ethanolamine oleate, are used principally in the treatment of esophageal varices due to a higher rate of anaphylaxis and extravasation necrosis [16].

Case reports detailing major adverse effects of sclerotherapy, such as pulmonary embolism and cerebral vascular events, exist in the literature and must be respected. However, several meta-analyses have demonstrated that these adverse outcomes are rare. In addition, in almost all cases, patients in these studies were undergoing large vessel sclerotherapy.

A meta-analysis detailing the efficacy and safety of foam sclerotherapy was published in 2012 and included 104 original articles, of which 21% included the treatment of reticular veins. The meta-analysis benefitted from the large number of aggregated patients but was limited due to the heterogeneity of included studies and the lack of well-designed clinical trials. Despite these limitations, as well as larger volumes of foam and the treatment of larger vessels, recorded major adverse effects were rare (Table 25.3) [29] (Level 2a). Another meta-analysis released the same year focused principally on neurological adverse effects of foam and liquid sclerotherapy and reported similarly low occurrence rates (Table 25.4) [30] (Level 2a). The 2013 European Guidelines for sclerotherapy designated these side effects as rare or very rare.

Table 25.3 Side effects of foam sclerotherapy (Rathbun)

	Adverse effect	%	*N*
Neurological	Visual disturbance	1.2	15,058
	Seizure	0.15	545
	Cerebral vascular event	0.63	5600
	Migraine	3	4470
Thrombosis	Deep vein thrombosis	0.9	18,203
	Pulmonary embolism	0.11	12,585
	Thrombophlebitis	11	11,900
Skin	Skin pigmentation	18	3811
	Severe allergy	0.2	11,601
	Injection site ulceration	0.98	10,494
	Paresthesia	1.2	9189
	Ecchymosis	28	2027
Other	Myocardial infarction	0.1	620
	Death	0.01	7152
	Coughing	1.6	8056
	Severe pain	7	495
	Required pain medication	13	1290

Table 25.4 Neurologic side effects of foam sclerotherapy (Sarvananthan). Number of patients = 10.819

Transient ischemic attack (TIA) or amaurosis fugax	0.16%
Cerebral vascular attack	0.11%
Visual disturbances (not TIA)	0.77%
Headache	0.70%
Migraine with aura	0.27%

Alternative Procedures and Modifications

For patients with contraindications to sclerotherapy, significant needle phobia, or the presence of vessels too small to cannulate, laser treatment is a viable alternative. Use of this modality is made difficult due to the high variability in vessel size, depth, and degree of oxygen content. As compared to facial veins, where laser therapy is very successful, leg veins are under significantly higher refill pressures, reducing vessel wall apposition and sclerotic potential [31] (Level 5).

Multiple laser modalities have been successfully trialed for veins less than 1 mm in diameter, including potassium titanyl phosphate (KTP) (532 nm), pulsed-dye laser (595 nm), and intense pulsed light. Larger, deeper vessels may respond better to treatment with alexandrite (755 nm) and Nd:YAG (1064 nm) [32] (Level 2c). Only Nd:YAG has been compared directly to sclerotherapy and was shown to have comparable efficacy [33] (Level 2b).

A randomized, double-blinded intra-leg comparison of Nd:YAG and sclerotherapy was performed in 56 patients with C1 disease. The sclerotherapy was performed using foamed 0.5% POL; patients received two treatments in a 6-week period. More improvement was noted at 6-week follow-up in the sclerotherapy group, but no difference was noted at 6 months. Laser treatment was significantly more painful [34] (Level 1b). A prospective intra-leg trial of 30 patients with lower extremity veins 0.5–1.5 mm telangiectasias compared Nd:YAG with sclerotherapy with 75% glucose. Patients received three treatments at 1-month intervals. Laser settings were 100–120 J/cm2 with a pulse duration of either 15 or 30 msec with epidermal cooling; no compression was utilized after treatment. At follow-up 1 week after the final treatment, patients reported significantly more pain and less satisfaction with the laser-treated leg, but independent assessors found no significant difference in vessel clearance [35] (Level 4).

New modalities are constantly being described. A small randomized trial comparing one treatment of telangiectatic leg veins with a

808 nm diode laser augmented by intravenously injected indocyanine dye to one treatment with a 1064 Nd:YAG found superior clearance with the diode cohort at 3 months; it was also more painful [36] (Level 2b). Fifteen of twenty females who were treated with a high-powered KTP device (fluence 13–15 J/cm2) twice in a 12-week period noted >50% improvement [37] (Level 4).

Combination Therapy

The durability of improvement of varicose veins <4 mm in diameter using POL alone and with the addition of 1064 nm Nd:YAG was compared in 320 patients (640 legs). 298 patients completed the study. Regardless of vessel size, microfoamed POL was formulated using 0.3% POL mixed with room air; the laser fluence was adjusted based on vessel diameter. Patients received two treatment sessions in a 3-week interval and were evaluated by three blinded physicians. Combination therapy was significantly superior in both assessed improvement and patient satisfaction at 3-month, 2-year, and 3-year follow-up. At 3-year follow-up, polidocanol alone resulted in a mean improvement of 15% and 18% of vessels of diameter <0.5 mm and 0.5–1.5 mm, respectively; POL followed by Nd:YAG resulted in 89% and 95% improvement. The results are impressive but are limited by the marked discrepancy between observed improvement with POL alone at the 3-month follow-up versus other studies mentioned above and the authors' personal experience [38] (Level 1b).

Postoperative Care and Follow-Up

The ASDS consensus document recommends 15–20 mmHg stockings following the treatment of telangiectasia and 20–30 mmHg stockings after treating reticular veins. The recommended duration is for 2–3 weeks, most critically for the first 3 days after treatment [16].

This recommendation is supported by few heterogeneous comparative trials.

In a study by Weiss, 40 patients were equally allocated to either the use of no compression stockings or of 20–30 mmHg stockings continuously for either 3 days, 1 week, or 3 weeks following the treatment of vessels <3 mm in diameter. A significant difference was noted in overall efficacy and hyperpigmentation between the four groups at 24-week follow-up. Patient satisfaction was not assessed [39] (Level 4).

A 20-patient split-leg study investigated the effect of an additional 3 weeks of ambulatory 20–30 mmHg compression stockings following 1 week of continuously wearing 30–45 mmHg compression stockings post sclerotherapy in both legs. On a 4-point scale, a statistically significant degree of hyperpigmentation was noted (1.3 vs 2.0). There were no differences in efficacy or thrombosis [40] (Level 4).

The strongest data to date comes from a 100-patient study that compared the ambulatory use of 23–32 mmHg compression stockings for 3 weeks, as opposed to no compression, following sclerotherapy of C1 disease. The investigators found a positive but small benefit in vessel disappearance (7.1 vs. 6.3 on a 10-point vessel disappearance score). No significant difference in hyperpigmentation or matting was observed, but rates of both were very low which was attributed to the use of chromated glycerin as the sclerosant. Patient satisfaction scores were similar between the two groups at 7-week follow-up [41] (Level 3b).

A blinded study of 16 patients received either 0.005% betamethasone solution or saline placebo; patients wore compression stockings for 1 week post procedure. No statistically significant difference in efficacy or adverse effects was found [42] (Level 4).

Complications and Management

Post-sclerotherapy hyperpigmentation is mainly a result of dermal hemosiderin staining related to extravasation of blood inherent in sclerotherapy. A wide range of incidence has been noted in various studies, but it is the most commonly reported adverse event in most [43]. The varia-

tion is at least in part due to the absence of a clear definition of hyperpigmentation in these studies. Spontaneous resolution occurs in 70% of cases in 6 months and 99% in 1 year [44] (Level 4). More cases of hyperpigmentation (64% vs 53%) and necrosis (6.6% vs 0%) were noted in a 129-patient split-leg study between STS and polidocanol (concentration and liquid or foam formulation depended on size of vessel treated) [45]. However, a similar study by Rao found no difference in adverse effects [11]. Patients receiving minocycline at the time of treatment may encounter minocycline-induced hyperpigmentation, which is more dark blue-gray in color than hemosiderin pigmentation [46] (Level 4).

Studies concerning the treatment of this persistent hyperpigmentation are mainly small and underpowered and do not permit definitive conclusions. The highest level of evidence comes from a multicenter trial that investigated the effect of post-sclerotherapy microthrombectomy. One hundred patients were divided into those treated for veins <1 mm in diameter and those with veins 1–3 mm. Areas of varicosities were randomized into two halves that received either microthrombectomy or non-intervention 1–3 weeks following sclerotherapy. Photographs obtained 16 weeks later were reviewed by blinded evaluators. Significant improvement in pigmentation and overall improvement were noted in the <1 mm diameter group but not in the 1–3 mm diameter cohort [47] (Level 1b).

In another study, eight patients with post-sclerotherapy hyperpigmentation persistent for over 1 year were treated with a Q-switched ruby laser. Lightening of 75–100% occurred in 58% of treated areas [48] (Level 4). A novel approach of utilizing an IPL + RF device (model S-E 3200, SUS Photon Technology CO., China) to treat post-sclerotherapy hyperpigmentation present for over 18 months was assessed in 21 individuals. Up to ten treatments at 1-month intervals were performed with an average of seven treatments performed. In 19/21 patients, complete resolution was obtained, and average patient satisfaction was 8.7/10. Different fluences were used based upon Fitzpatrick skin type [49] (Level 4).

In the case of minocycline-induced pigmentation, case reports suggest that Q-switched and picosecond alexandrite laser treatment may provide partial to complete improvement [50] (Level 4).

Telangiectatic matting is the new appearance of fine red telangiectasia following sclerotherapy and is thought to represent dilation of collateral veins or an inflammatory effect of treatment. A retrospective analysis of 2120 sclerotherapy patients found a post-treatment incidence of 16%. Identified risk factors were excessive body weight, hormonal therapy, and longer history of venous disease prior to treatment [51] (Level 3b). In a series of 113 patients treated with sclerotherapy for vessels <2 mm, Weiss and Weiss noted that higher concentrations appear to increase the risk of telangiectatic matting and that many cases noted at 1-month follow-up resolved spontaneously at 6-month follow-up [52] (Level 4).

Whereas significant clinical experience and opinions regarding optimal management are plentiful, evidence-based management is unavailable. This is likely due to the relative subtlety of matting compared to the previously apparent varicosities and its self-resolving nature.

Skin necrosis and ulceration is a rare side effect of sclerotherapy. An estimated incidence of approximately 1% derives from several studies with variance in technique as well as sclerosant selection and volume [53] (level 5). If you perform enough sclerotherapy, you will eventually encounter a punctate ulceration, although in the authors' experience, this occurs in far less than 1% of treatments. These typically heal with small scars usually less than 1 cm (similar to a punch biopsy). More extensive ulcerations are exceedingly rare and presumably result from inadvertent injection directly into arteries, although this has been contested [53, 54] (Level 4, 1). Proper visualization of sclerosant placement, potentially with ultrasound, should minimize risk. Ultrasound guidance must be utilized whenever injecting sclerosant into varicose veins that are not bulging and therefore not extremely superficial.

Conclusion

Reticular and telangiectatic veins are widely prevalent in all ethnicities that have been studied. Not surprisingly, therefore, sclerotherapy is a skill in high demand. The treatment of reticular veins and telangiectasias of the leg with sclerotherapy has been shown to be effective with a low incidence of adverse events. While viable alternatives exist, such as laser-based therapy, chemical sclerotherapy remains the gold standard due to its efficacy, tolerability, safety, and relatively low cost. Interestingly, available research, regarding elemental issues, such as sclerosant selection, treatment of complications, and post-treatment care, consists largely of small, underpowered, single provider studies. These limitations affect the conclusiveness and generalizability of their results. Thus, expert opinion and consensus documents currently inform much of clinical practice. With further research efforts, iterative improvements will continue to elevate the general caliber of sclerotherapy.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Venous disease is remarkably common	A
Sclerotherapy is highly effective for C1 disease	A
POL and STS are equally effective	B
POL may have less hyperpigmentation risk, but this has not been clearly established	C
For C1 disease, liquid is the preferred formulation, but foam may be equally or more effective for reticular veins	B
Post-sclerotherapy compression modestly increases overall improvement; some weak evidence supports a decreased incidence of side effects with its use	B
The optimal duration and amount of compression necessary to produce benefit is unclear	C
Microthrombectomy reduces persistent post-sclerotherapy hyperpigmentation	B
Nearly all hyperpigmentation resolves by 1 year	B
Laser is an appropriate alternative in the correct patient but is more painful	A
Major adverse effects are rare	A

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Self-Assessment Questions

1. Which of the following is *not* an FDA-approved sclerosant in the United States?
   (a) Polidocanol
   (b) Sodium tetradecyl sulfate
   (c) Sodium morrhuate
   (d) Glycerin
   (e) Ethanolamine oleate
2. What percentage of patients experience post-sclerotherapy telangiectatic matting?
   (a) 6%
   (b) 16%
   (c) 26%
   (d) 36%
   (e) 46%
3. What percentage of adult females demonstrate isolated C1 disease?
   (a) 0–20%
   (b) 20–40%
   (c) 40–60%
   (d) 60–80%
   (e) 80–100%
4. Which statement regarding post-treatment hyperpigmentation is true?
   (a) 30% of cases resolve within 6 months.
   (b) Incidence is unaffected by compression therapy.
   (c) The underlying mechanism is the extravasation of blood.
   (d) Pretreatment with minocycline is preventative.
   (e) Use of hypertonic saline is a relative risk factor.
5. Which is the correct CEAP classification for a patient with reticular veins 2 mm in diameter due to reflux without evidence of underlying disease?
   (a) C0EsAsPo
   (b) C1EpAsPr
   (c) C2EsApPr
   (d) C2EcAdPr,o
   (e) C2EpApPo

Correct Answers

1. d: a and b are approved for the treatment of leg veins, whereas c and e are approved for the treatment of esophageal varices.
2. b: In a retrospective study by Davis involving 2160 patients, 16% experience telangiectatic matting after sclerotherapy. Risk factors identified in this study were excess body weight, use of hormones at the time of sclerotherapy, family history of spider veins, and a longer duration of spider veins.
3. c: According to results from population-based studies conducted in Germany, China, and the United States, isolated C1 disease was identified in 40–60% of patients. In the Edinburg Vein Study, 84% patients had AT LEAST C1 disease.
4. c: 70% of cases resolve by 6 months. Compression therapy has been demonstrated to reduce incidence. Minocycline use is a risk factor for hyperpigmentation which may be more blue-gray in color. Hypertonic saline has the highest reported rates of the studied sclerosants and glycerin the lowest.
5. b: The C1 designation is for vessels less than 3 mm in diameter, Ep designates no underlying disease, anatomically the veins as superficial, and the underlying etiology is related to reflux.

26

Endovenous Laser and Radiofrequency Treatments

Rachel Redenius and Margaret Mann

Abstract

Chronic venous disease affects approximately 15% of men and >25% of women in the United States and can cause significant morbidity in those affected (2c) (Beebe-Dimmer et al., Ann Epidemiol 15:175–184, 2005). The preferred treatment options have shifted in the last decade from surgical ligation and stripping in the operating room to minimally invasive procedures such as endothermal ablation in the outpatient setting. Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are the two most commonly used thermal techniques. The heat produced by these methods causes denaturation of collagen proteins in the vessel wall resulting in inflammation, thrombosis, and fibrosis of the vein. RFA received Food and Drug Administration (FDA) approval for the treatment of varicose veins in 1999 followed shortly by EVLA with an 810-nm wavelength in 2002. Additional available lasers include the 810-, 940-, 980-, 1319-, 1470-, and 1500-nm diode lasers and the 1064- and 1320-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers. The procedures are safely performed under local anesthesia and are well tolerated with minimal downtime for the patient. Due to their clinical effectiveness and safety profile, endothermal treatments are increasingly supplanting surgery as the treatment of choice for chronic venous disease.

Keywords

Varicose veins · Endovenous ablation · Chronic venous disease

Introduction

Chronic venous disease affects approximately 15% of men and > 25% of women in the United States and can cause significant morbidity in those affected (2c) [1]. The preferred treatment options have shifted in the last decade from surgical ligation and stripping in the operating room to minimally invasive procedures such as endothermal ablation in the outpatient setting. Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are the two most commonly used thermal techniques. The heat produced by these methods causes denaturation of collagen proteins in the vessel wall resulting in inflammation, thrombosis, and fibrosis of the vein. RFA received Food and Drug Administration (FDA) approval

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for the treatment of varicose veins in 1999 followed shortly by EVLA with an 810-nm wavelength in 2002. Additional available lasers include the 810-, 940-, 980-, 1319-, 1470-, and 1500-nm diode lasers and the 1064- and 1320-nm neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers. The procedures are safely performed under local anesthesia and are well tolerated with minimal downtime for the patient. Due to their clinical effectiveness and safety profile, endothermal treatments are increasingly supplanting surgery as the treatment of choice for chronic venous disease.

Indications and Contraindications for Endovenous Laser and Radiofrequency Treatments

The primary superficial veins of the lower extremity are the great saphenous vein (GSV), which runs medially from the ankle to the groin, and the small saphenous vein (SSV), which runs laterally from the ankle to the popliteal fossa. These veins drain blood from superficial collecting veins into the deep venous system for return to the heart. Numerous perforating veins pass through the fascia and connect the deep and superficial systems. Venous disease results when any point in this process is interrupted, though incompetent superficial veins are the most common cause. All veins contain one-way valves to prevent retrograde flow. When these valves are dysfunctional, either secondary to trauma or congenital abnormality, reflux occurs, creating high pressures in the superficial veins and subsequent dilation.

The presence of venous insufficiency increases with age and affects <1% of men and <10% of women <30 years and 57% of men and 77% of women ≥70 years (2c) [2]. The severity of the disease has also been shown to worsen with time, with a third of patients in one study showing progression in 6 months (4) [3]. Risk factors include obesity, standing occupation, reduced levels of physical activity, and family history (2c) [2, 4]. Many women report development of varicose veins in pregnancy; however, pregnancy has been inconsistently associated with venous disease in epidemiological studies (2c) [4, 5]. More recently, a large meta-analysis showed pregnancy significantly increased the prevalence of venous disease by 82% ((OR) odds ratio 1.82; 3b) [6]. One theory is that valvular insufficiency may result from the inhibition of smooth muscle contraction and vasodilation caused by progesterone and estrogen, respectively. Additionally, the gravid uterus may obstruct venous return and cause increased hydrostatic pressure. Multiparous women had the highest risk of developing varicose veins in one study, and the risk increased with age and a positive family history (3b) [7]. It is therefore unclear if pregnancy contributes to the development of varicose veins in women who are already predisposed or if it serves as an independent risk factor.

Patients with symptomatic venous insufficiency that is refractory to conservative therapy may be candidates for endothermal ablation. A 2012 international consensus meeting suggested the following veins could be treated with thermal ablation (5) [8]:

GSV (1a)
SSV (1a)
Anterior and posterior accessory saphenous veins (1b)
Giacomini vein and cranial extension of the SSV (1b)
Other superficial veins in the subcutaneous tissue (1c)
Pathologic perforating veins (1c)
Residual intrafascial veins after treatment (1c)
Venous malformations (1c)

All patients are not good candidates for these elective, thermal techniques, and appropriate patient selection following a thorough evaluation is key. Absolute contraindications include acute deep venous thrombosis (DVT), active infection, active superficial phlebitis, and the presence of deep venous obstruction when a collateral vein is the treatment target [8]. Relative contraindications include patients with poor ambulatory status, severe peripheral arterial disease ((ABI) Ankle Brachial Index < 0.5), pregnancy, thrombophilia, and anesthetic allergy precluding the use of tumescent anesthesia.

The anatomical characteristics of the vein may create technical issues and must be considered prior to treatment selection. Tortuous veins may prevent advancement of the laser fiber or radiofrequency catheter and are not ideal for treatment with thermal techniques. Veins that are too small (<3 mm) may be at increased risk of perforation, while large-diameter (>10 mm) veins may be more prone to treatment failure due to decreased contact with the treatment source (2b) [9]. Conflicting reports exist regarding vein size and treatment success; however, one study showed no significant difference in closure rate with the ClosureFAST catheter for veins >12 mm in diameter (2b) [10]. The length of the treated vein (at least 10 cm for the 7-cm catheter and 5 cm for the 3-cm catheter) should also be considered when using the ClosureFAST catheter since segmental ablation is performed.

Effectiveness of Endovenous Laser and Radiofrequency Treatments

A Cochrane review of 13 randomized controlled trials (RCTs) with a combined total of 3081 patients evaluated the effectiveness of EVLT and RFA in comparison to high ligation and stripping (1a) [11]. Eight trials compared EVLT with surgery, five compared RFA with surgery, and an additional three trials compared foam sclerotherapy with surgery (two of the trials compared multiple techniques). There was no significant difference in clinical (as determined by duplex ultrasound [DUS]) or symptomatic recurrence between any endothermal treatment and surgery. Recanalization rate was equal among all groups, but there was significantly less neovascularization and technical failure in the laser group compared to surgery. EVLT has been reported to have an effectiveness >90% in most studies, though this decreases with time. Min et al. reported a closure rate of 99.3% at 3 months falling to 93.4% at 2 years with the 810-nm laser (2b) [12]. Selected studies evaluating the success of EVLT can be seen in Table 26.1.

The first-generation radiofrequency system (Closure, VNUS Medical Technologies, San Jose, CA) showed significantly more treatment failures at 1 year compared to the 810-nm laser, though quality of life and Venous Clinical Severity Score (VCSS), see (Table 26.4) did not differ between groups (1b) [16]. The Closure model was replaced by the second-generation system (ClosureFAST, VNUS Medical Technologies, San Jose, CA) in 2006. This system utilizes higher temperatures (120 °C vs. 85 °C) and segmental ablation rather than a continuous pull-back, making it much quicker than the previous model. There was no difference in effectiveness between the 980-nm laser and the ClosureFAST catheter; however, RFA resulted in less postoperative pain, bruising, and analgesic use in the first 10 days (2b) [17]. This may be due to vein wall perforations caused by hemoglobin-specific lasers, which are not seen with RFA in an animal model (2b) [18]. The perforations lead to extravasated blood in the perivascular space, resulting in increased postoperative bruising and discomfort. In a study comparing the 1470 nm diode laser to RFA in the same 60 patients with bilateral disease, both methods had similar success rates but postoperative pain and time to return to activity were significantly less in the EVLT group (2b) [19].

The Endovenous Radiofrequency Obliteration Versus Ligation and Stripping (EVOLVeS) study evaluated 85 patients treated with RFA or high ligation and stripping (1b) [20]. Treatment success was similar between the two groups with less postoperative pain, analgesic use, earlier return to work and daily activities, higher quality

Table 26.1 Outcomes of selected EVLT studies

References	No. of treated limbs	Wavelength of device (nm)	Closure rate (%)	Follow-up
Min et al. [12]	121	810	93.4	2 years
Agus et al. (2b) [13]	1076	810–980	97	3 years
Schwarz et al. (2b) [14]	312	1470	100	3 months
Moul et al. (4) [15]	1171	1320	99.9	11.4 months

Table 26.2 Outcomes of selected RFA studies

References	No. of treated limbs	RFA device	Closure rate	Follow-up
Merchant and Pichot (2b) [22]	1222	Closure	87.2%	5 years
Proebstle et al. (2b) [23]	256	ClosureFAST	92.6%	3 years
Creton et al. (2b) [24]	220	ClosureFAST	96.9%	1 year
Bisang et al. (2b) [25]	118	ClosureFAST	94.1%	12.2 months

Table 26.3 CEAP classification - Clinical, Etiology, Anatomy, Pathophysiology

C = Clinical	E = Etiology	A = Anatomy	P = Pathophysiology
C0—No visible venous disease	Ec—congenital	As—superficial veins	Pr—reflux
C1—telangiectasias or reticular veins	Ep—primary	Ad—deep veins	Po—obstruction
C2—varicose veins	Es—secondary (post-thrombotic)	Ap—perforator veins	Pr,o—both reflux and obstruction
C3—edema			Pn—no venous pathophysiology identifiable
C4—skin changes C4a—pigmentation /eczema C4b—lipodermatosclerosis or atrophie blanche			
C5—healed ulcer			
C6—active ulcer			

of life scores, and fewer complications in the RFA group at 4 months. The follow-up study 2 years later showed no significant difference in recurrence rates between the two groups (20.9% surgery vs. 14.3% RF) with less neovascularization in the RFA group (1b) [21]. Of note, GSV diameter has continued to decrease over time with a mean size of 6.3 mm 72 h post treatment and 2.9 mm at follow-up 2 years later. Outcomes of selected studies evaluating the effectiveness of RFA can be seen in Table 26.2.

Preoperative Evaluation

Prior to treatment, patients should provide a detailed history and undergo physical exam [8]. Providers should elicit the patient's reason for seeking treatment (medical vs. cosmetic) and document any symptoms suggestive of venous disease such as heaviness, aching, restless legs, pain, tightness, tingling, burning, swelling, skin irritation, and muscle cramps. These symptoms tend to be exacerbated by heat and dependent position, worsen thoughout the day and relieved by leg rest or elevation. Persistent disease can lead to skin changes such as edema, stasis dermatitis, lipodermatosclerosis, and ulcers. Symptoms likely associated with a venous etiology are commonly worse at the end of the day or after prolonged sitting or standing. Elevation and compression may provide symptomatic relief, though long-term treatment with these methods is often impractical.

In addition to the above history, the patient's past medical and surgical history, including any previous venous stripping or thermal ablation, should be obtained. A personal or family history of venous thromboembolism warrants special attention. Though there is no consensus, clinicians often utilize some thrombotic risk assessment such as Caprini's assessment to decide whether thromboprophylaxis should be prescribed (5) [26]. Both EVLT and RFA can be safely performed in the setting of anticoagulation (2b) [27].

A clinical examination is performed to help establish if symptoms are secondary to venous disease or another cause. The presence of bulging varicosities, telangiectasias, corona phlebectasia (cluster of telangiectasias and reticular veins overlying the medial malleolus), edema, and skin changes is documented. The CEAP classification system (Table 26.3) is used to grade the severity

Table 26.4 Venous Clinical Severity Score (VCSS)

	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, no activity limitation	Daily, moderate activity limitation	Daily, severe activity limitation
Varicose veins (>3 mm in diameter)	None	Few or corona phlebectasia	Multiple, confined to calf or thigh	Extensive, involving calf and thigh
Venous edema	None	Foot and/or ankle	Above ankle but below knee	Knee and above
Pigmentation	None	Perimalleolar	Diffuse, lower 1/3 calf	Wider distribution, above lower 1/3 calf
Inflammation	None	Perimalleolar	Diffuse, lower 1/3 calf	Wider distribution, above lower 1/3 calf
Induration	None	Perimalleolar	Diffuse, lower 1/3 calf	Wider distribution, above lower 1/3 calf
No. of active ulcers	0	1	2	>2
Active ulcer duration	None	<3 months	>3 months but <12 months	>12 months
Active ulcer size	None	<2 cm diameter	2–6 cm diameter	>6 cm diameter
Compressive therapy	Not used	Intermittent	Most days	Full compliance

of venous insufficiency but cannot assess response to treatment. A standardized outcomes measure such as the Venous Clinical Severity Score is recommended before and after therapy to determine the treatment impact (Table 26.4) [8].

A duplex ultrasound (DUS) is performed to scan the entire deep and superficial venous systems. The diameter of the veins as well as the duration of reflux (if present) is recorded. Reflux ≥0.5 s in the superficial venous system and ≥ 1 s in the deep venous system is considered abnormal. Ruling out obstruction in the deep venous system is also necessary prior to treatment as this may be a cause for insufficiency and a contraindication for thermal ablation.

Best Techniques and Performance

Prior to both techniques, the great saphenous vein is mapped with ultrasound, and the most caudal point of reflux is documented to determine the access point. The physician also checks for tortuous or aneurysmal segments and for areas where the vein may be too small to cannulate. For most patients, access is obtained just above or below the knee. The patient is prepped and draped with sterile technique [8], and 1% lidocaine with epinephrine is injected at the access site. The vein is accessed either percutaneously (Seldinger technique) with a 16–19G needle or directly with a phlebectomy hook. Placing the patient in reverse Trendelenburg position will increase venous filling and make access easier. A warm room, heating pad, or 2% nitroglycerin paste on the access site can also help to minimize vasoconstriction.

RFA

When venous return is observed, a guidewire is passed through the hollow needle into the vein. An introducer sheath is then inserted over the guidewire and the guidewire is removed. The RFA catheter is inserted through the sheath and followed by ultrasound to a location at least 2–3 cm caudal to the saphenofemoral junction, just distal to the epigastric vein. The ends of the catheter contain electrodes, which contact the vein wall and release radiofrequency energy from a generator. Once in place, the provider administers tumescent anesthesia, most commonly 0.1% lidocaine, into the perivenous space under ultrasound guidance to confirm the appropriate placement of the anesthetic circumferentially in the saphenous sheath. The anesthesia serves to numb the area, facilitate compression to improve vein contact with the fiber or catheter, and act as a heat sink to prevent skin burns and damage to surrounding nerves and other structures. The distance from the skin to the treated

vein should be at least 1 cm to prevent skin burns [8]. An infiltration pump can be used to deliver the solution. After anesthetic administration is complete, the location of the catheter is again confirmed with ultrasound. Through retrofeedback, the control unit delivers the minimum power necessary to maintain the temperature at the electrodes. The power starts at 40 W (18 W for a 3-cm catheter) but typically drops to below 20 W (10 W for a 3-cm catheter) within 10 s if the vein is adequately compressed and blood is not flowing to cause cooling. If this does not occur, treatment should be stopped and catheter position should be confirmed (5) [28]. Placing the patient in Trendelenburg position during the procedure helps to empty the vein and increase contact between the device and the vein wall. Two heat cycles may be used near the junction or at wide aneurysmal segments and may even improve outcome without an increase in side effects when used along the entire length of the treated segment (2b) [29, 30]. As mentioned previously, the first-generation system heated the vein to 85 °C and was advanced via continuous pullback at a rate of 2.5 cm/min. The ClosureFast system ablates the vein in 7-cm segments (3-cm segments with the smaller catheter) with 20-s treatment cycles and maintains a temperature of 120 °C. ClosureFast was significantly more effective than the first-generation ClosurePlus in one study with 98% vs. 88% occlusion at 1 week (2b) [31].

EVLT

The GSV is accessed in the same manner as above, and a 200–600-μm laser fiber is advanced through the introducer sheath to a point at least 2–3 cm caudal to the saphenofemoral junction, just distal to the epigastric vein. An aiming beam can be visualized through the skin when the laser is turned on; however, this should not replace the use of ultrasound for localization. Ultrasound should be used in both the transverse and longitudinal views to verify fiber-tip location following tumescent anesthesia [8]. Once the position is confirmed and tumescent anesthetic has been infiltrated, treatment can begin. Protective eyewear specifically designated for the wavelength in use should be worn while the laser is in operation.

The exact mechanism of action of EVLA is still under debate, which has led to a variety of treatment protocols and new devices, each claiming to be superior to its predecessor. There have been five proposed mechanisms for the effectiveness of EVLA (5) [32, 33]. The first is the direct contact between the laser fiber tip and the vein wall. The second is the interaction between the emitted laser light and the vein wall, either through direct absorption of light scattered by blood or conduction of heat from the blood to the wall as the blood absorbs the light. The third mechanism is formation of steam bubbles in front of the laser tip. The fourth mechanism involves the heat transferred from carbonized blood that forms on the fiber tip. The blood surrounding the fiber sticks to the tip and strongly absorbs the emitted light, reaching temperatures up to 1000 °C. The contact between this extremely hot tip and the wall can lead to permanent injury. The fifth proposed mechanism involves formation of a coagulum in the vessel lumen as a result of thermal injury, which may release substances that interact with the vein wall. Doubts exist, however, that enough blood is present in the treated vein for this to be a key contributor. It is currently unclear how these mechanisms interact and which predominate. Increasing our understanding will hopefully prevent overtreatment and lead to more refined techniques that can reduce side effects.

Throughout the published literature, laser settings are often reported as linear endovenous energy density (LEED), the energy delivered per centimeter of the vein. It has been reported that a threshold of 60 J/cm exists for successful obliteration (3b) [34]. Critics feel that this parameter provides very little information and that laser power rather than energy is more important [32]. For example, an LEED of 50 J/cm can be achieved with both 10 W of power and a pullback velocity of 2 mm/sec or 0.1 W of power and a 0.02 mm/sec velocity, though clearly these settings are very different. Providing the exact power and pullback velocity settings rather than LEED allows the procedure to be duplicated by other clinicians. Power settings and pullback rates are dependent on the

laser device used, and the reader should refer to the protocol inherent to each device.

As mentioned previously, there are many different wavelength devices available for EVLA, and it is unclear whether vein wall injury occurs from direct absorption of scattered light or from heated blood. Hemoglobin-specific wavelengths (810, 940, 980, and 1064 nm) were the first developed followed by newer wavelengths (1319, 1320, 1470, and 1500 nm) which target water. Though these newer wavelengths are promoted as targeting the water in the vein wall, significant absorption by the water in blood also occurs, which may explain the minimal, if any, difference in the effectiveness of these devices in studies [32]. Water-specific lasers have been reported to have fewer postoperative side effects, such as bruising and discomfort, which may be related to a lower depth of thermal injury (2b) [35]. Unfortunately, many studies comparing wavelengths also use different fiber tips and energy settings, making it difficult to draw conclusions regarding the exact contribution of wavelength. In an RCT comparing the 940-nm diode laser with the 1470-nm diode laser, there was no difference in treatment success, but the water-specific laser results in significantly less postoperative pain in the first week (1b) [36]. This study used the same fiber tip and settings for both devices. Another study found the same results when a 940-nm diode laser was compared to the 1320-nm Nd:YAG laser; however, this study used lower power settings in the latter group, which may also explain the reduced side effects (2b) [37].

The laser can be fired in a pulsed mode or continuous mode. The pulsed mode exposes the vein to a fixed amount of energy at each distance, and the total energy is dependent on the distance between pulses, the pulse duration, and the power setting. When operating in continuous mode, the laser fiber is pulled back at a constant rate. The total energy in this mode is a result of the pullback speed and power used. Lasers fired in pulsed mode have been associated with fewer vein wall perforations (2c) [38, 39]. As mentioned previously, blood coagulates on the fiber tip, resulting in carbonization and extremely high-tip temperatures that can lead to perforation. Short pulse durations prevent this coagulum from forming on the fiber tip. The short pulse duration also allows a slower heating, which may reduce perforation risk. Many providers prefer the continuous mode with a rate of 1–2 mm/sec due to reduced treatment time. There is also some concern that pulsed mode may lead to undertreatment or skip areas. In one study using an ex vivo model of human veins harvested during phlebectomy, six different lasers were compared, two of which were used in pulsed mode [38]. All devices were operated at the same power. The fewest perforations were seen with use of a protected-tip fiber and with a 1320-nm pulsed Nd:YAG laser. Though different wavelengths were used, this study suggests that delivery mode may also be an important factor in the development of side effects.

The type of laser fiber used may also impact treatment success. In a retrospective study comparing the gold-tip NeverTouch VenaCure laser fiber (AngioDynamics, Queensbury, NY) with the bare-tip fiber, Prince et al. found a statistically significant increase in treatment failures with the gold-tip fiber (11.1% vs. 2.3%) (4) [40]. The authors noted difficulty withdrawing the gold-tip fiber smoothly, which may have resulted in undertreated skip areas along the vein. However, the gold-tip fiber was associated with fewer complications and was also felt to be easier to visualize on ultrasound. There are many types of protected fibers such as jacket-tip fibers [35], radial fibers (2b) [41], and tulip fibers (1b) [42] which have been associated with fewer vein wall perforations and side effects compared to bare-tip fibers, though no difference in treatment effectiveness was observed. There are multiple theories for this reduction in side effects. The construction of the different fibers may disperse energy over a greater surface area compared to the bare-tip fiber, which allows them to be used at lower energy settings [35]. The protected tips prevent direct contact with the vein wall, and in vitro analysis demonstrated a significantly reduced depth of thermal injury with jacket-tip fibers compared to bare-tip fibers at the same energy settings [35]. Additionally, the protected

tips may prevent tip carbonization, which can lead to perforation as discussed above [38, 39].

After completion of the treatment, the laser is placed in standby just prior to withdrawal of the fiber. The vein and junction may be visualized with ultrasound, although it is difficult to determine treatment outcome at this time since the vein has already collapsed from tumescence [8].

Safety

Thermal techniques are minimally invasive and very safe. The safety profile has continued to improve with time as providers become more familiar with the treatments and refine their techniques. Skin burns may occur at the access site as the laser is withdrawn or when a superficial vein is treated. Merchant et al. reported skin burns in 4.2% of patients treated with RFA which decreased to 0% with better use of tumescent anesthesia (2b) [22]. Ensuring that the treated vein is >1 cm below the skin surface prevents this complication. If a burn does occur, it is often self-limited and treated with local wound care.

Thermal injury to a nerve can occur when it lies in close proximity to the treated vein. Though the risk is much less than with surgery (7% with short stripping and 40% with long stripping of the GSV) [43, 44], permanent paresthesias can rarely occur. The saphenous nerve is closest to the GSV below the knee and is at greatest risk when ablation starts at the ankle. The sural nerve lies adjacent to the SSV in the calf, and the rate of injury ranges from 1.3 to 11% (2b) [45]. The overall frequency of paresthesias in a recent Cochrane review was 2.4% with EVLT and 11.7% with RFA, though RFA dropped to 1.7% for studies with follow-up longer than 3 months [11]. Foot drop may also occur with injury to the common peroneal nerve near the fibular head, either due to treatment at the saphenopopliteal junction or with ambulatory phlebectomy. The provider should be aware of these "danger zones" and liberally use tumescent anesthesia to prevent nerve injury.

Deep vein thrombosis (DVT) is the most concerning complication of thermal ablation. Endovenous heat-induced thrombosis (EHIT) is a thrombus that extends from the superficial system into the saphenous junctions and possibly the deep system following recent thermal ablation (Table 26.5).

Table 26.5 Endovenous heat-induced thrombosis (EHIT) classification and treatment

Class	Criteria	Treatment
I	Thrombosis to the saphenofemoral or saphenopopliteal junction, not extending into the deep system	Observe with serial ultrasound
II	Nonocclusive venous thrombosis, extending into the deep system with a cross-sectional area of < 50%	Observe with serial ultrasound Treat with LMWH
III	Nonocclusive venous thrombosis extending into the deep venous system with a cross-sectional area > 50%	Treat as DVT
IV	Occlusive deep venous thrombosis	Treat as DVT

Risk factors for EHIT include GSV diameter > 10 mm, SSV diameter > 8 mm, male gender, and multiple phlebectomies (3b) [46]. Previous history of superficial thrombophlebitis has also been associated (2b) [47]. In a retrospective study of 2470 limbs treated with RFA and 350 limbs treated with EVLA, DVT was found in 0.7% (four were EHIT) and 1% (three were EHIT), respectively (2b) [48]. There was no significant difference between the two thermal techniques [48, 49]. Risk of DVT is accepted to be less than 1% with either technique, and routine use of prophylactic anticoagulation is not recommended [8]. Patients should have a duplex ultrasound done within 10 days of treatment to evaluate for thrombus and be treated accordingly if one is present. Most providers observe EHIT I and treat EHIT III and IV as DVTs. Management of EHIT II is undefined as some providers treat with low-molecular-weight heparin while others observe. Sadek et al. found that increasing the distance from the saphenofemoral junction (SFJ)/ saphenopopliteal junctoin (SPJ) to ≥2.5 cm reduced the incidence of EHIT II, though this difference was not significant (2b) [49].

The most common side effects following thermal ablation are pain and ecchymoses. While

these side effects are expected to some degree in all patients, they are more common with hemoglobin-specific lasers and bare-tip fibers as mentioned previously. Postoperative pain in the first week was significantly less following ETA compared to surgery (1a-) [50]. Patients can be counseled to expect pain for up to 2 weeks following treatment and to take acetaminophen or NSAIDs if needed. Bruising and hyperpigmentation have been reported in 31.3% of EVLT patients and 12.3% of RFA patients [11].

Superficial thrombophlebitis is another common side effect reported in 8.8% of RFA patients and 6.5% of EVLT patients [11]. Treatment is often conservative with NSAIDs and warm compresses, though evacuation of trapped coagulum may be beneficial.

Postoperative Care and Follow-Up

At least two follow-up visits following any endovenous thermal ablation are recommended [8]. The first visit is for a duplex ultrasound within 10 days to ensure a thrombus has not developed. The second appointment is a clinical follow-up with duplex ultrasound 3–6 months later to document successful vein closure.

Compression stockings are typically recommended following ablation to reduce pain and edema and improve treatment outcome. High-quality evidence supporting their use is lacking, however, and the appropriate strength and duration of compression therapy are unknown. A randomized controlled trial of 400 patients examined the benefit of class II compression versus no compression following EVLA (1b) [51]. Patients who wore compression stockings had significantly less pain and edema in the first week, but there was no significant difference at 2 weeks. Additionally, there was no significant difference in quality of life or time to return to work. Another small study found that patients wearing compression stockings for 1 week had reduced pain and improved physical function compared to those wearing stockings for only 2 days post EVLA (2b) [52]. Conversely, Ayo et al. found no significant difference in VCSS scores, pain, or bruising whether compression was used or not (1b) [53]. Patients often find compression stockings uncomfortable and difficult to wear, which results in poor compliance. The available evidence suggests only a mild benefit to compression, and patients may be able to weigh the improvement in postoperative pain and edema with the inconvenience of use.

Alternative Procedures and Modifications

Surgical ligation and stripping has long been the standard of care for treatment of varicose veins and venous insufficiency. The GSV is ligated at the saphenofemoral junction and stripped to the knee or ankle. The SSV is ligated at the saphenopopliteal junction. Recurrence is high at 30–50% in 3–5 years due to neovascularization (2b) [54]. Additionally, surgery requires general anesthesia and is associated with more postoperative pain, wound infections, hematomas, and 3–5 days of additional downtime from work or normal activities [50].

The steam vein sclerosis (SVS) system, which is not currently FDA approved, heats the target vein wall through micropulses of steam at 120 °C. The vein is accessed percutaneously and a 16G infusion catheter is placed. The flexible stainless steel SVS catheter is inserted through the infusion catheter and passed through the vein to a level 2–3 cm caudal to the SFJ. Since the catheter is flexible, it can act as its own guidewire and travels through tortuous vein segments. One pulse of steam has 60 J of energy. In a study by Milleret et al., two pulses were administered every 1 cm for veins up to 7 mm in diameter (4) [55]. Three pulses were used for veins over 7 mm and four pulses for veins over 12 mm. The pulses were delivered every 1 cm of vein as the catheter was withdrawn. Tumescent anesthesia is required with this technique to prevent perivenous damage. In a series of 75 veins, 96% occlusion was observed at 6 months. Side effects were minimal and similar to other endothermal techniques. Further head-to-head studies are needed.

In foam sclerotherapy, a liquid sclerosant is mixed with air and injected into the target vein to cause inflammation, fibrosis, and ultimately occlusion. The foam replaces blood in the vein, which increases the efficacy and reduces the volume of sclerosant needed. Foam is four times more effective than liquid due to increased contact time with the vein wall and significantly more effective in the treatment of truncal veins (2b) [56]. Physician-compounded foam is often mixed with room air in a 1:4 ratio using the Tessari technique (4) [57]. CO_2 may also be used. A low-nitrogen proprietary foam, FDA approved in the United States as Varithena™, was developed following rare reports of serious neurologic events thought to be due to embolism from persistent, large nitrogen bubbles [58]. It is reported to have more consistent bubble size and longer contact time with the vascular endothelium. The GSV is accessed percutaneously under ultrasound guidance, and sclerosant foam is injected once venous return is observed. There is no high-quality evidence regarding injection location (distal or proximal portion of vein) or maximal volume of foam that should be used, though higher volumes are felt to have increased risks of side effects. Experts recommend limiting the volume of foam to 10 mL in a single session (5) [59]. The success rates have been reported to be 88–93% (2b) [60]. Multiple treatments may be required, particularly for larger veins. Local side effects such as phlebitis, hyperpigmentation, and pain are most common (4) [61]. Rare side effects include migraines, neurologic symptoms, and visual changes, which may be more common in a patient with a patent foramen ovale [59].

A disadvantage of all endothermal techniques is the need for tumescent anesthesia, which can cause patient discomfort and add considerable time to the procedure. It is also often the most difficult aspect of the procedure for the physician to learn. Though foam sclerotherapy does not require anesthesia, current studies show it to be inferior to endothermal techniques for treatment of the truncal veins, and it often requires multiple treatments. A newer hybrid technique, referred to as mechanochemical ablation (MOCA), combines endothermal ablation and sclerotherapy. The device, ClariVein, is FDA approved and utilizes a catheter to infuse the sclerosant into the target vein. The end of the catheter has a rotating wire that simultaneously mixes the fluid and injures the intima of the vein wall. The distal tip of the wire is placed 2 cm caudal to the SFJ, and the catheter is withdrawn at a rate of 1–2 mm per s. The wire is reportedly even capable of traversing tortuous GSV segments. In the initial trial, all patients received 12 cc of 1.5% liquid sodium tetradecyl sulfate (4) [62]. A closure rate of 96.7% at 260 days was reported with no cases of DVT, skin injury, or nerve injury, suggesting it is a safe and efficacious procedure that does not require tumescence. A randomized controlled trial comparing MOCA to RFA found no significant difference in occlusion rates, clinical severity scores, or disease-specific quality of life scores at 1 and 6 months (2b) [63]. Patients reported significantly less procedural pain with MOCA compared to RFA. This study also showed that concomitant phlebectomy with MOCA was safe and effective, though it should be noted that pain scores were gathered prior to phlebectomy. Additional head-to-head studies comparing MOCA to endothermal treatments are needed.

Another nonthermal technique that eliminates the need for tumescent anesthesia is VenaSeal closure system (VSCS; Medtronic, Plymouth, Minn), which was FDA approved in 2015. This system uses a modified cyanoacrylate, which is a flexible and viscous substance that rapidly polymerizes on contact with blood or tissue. Its flexibility allows it to withstand the movement of the legs without being perceived by the patient, and its viscosity limits the risk of embolization. An initial case series demonstrated a 92% closure rate at 12 months (4) [64]. No tumescent anesthesia or postoperative compression was used. The vein is accessed percutaneously through ultrasound guidance similarly to other techniques. A 5F introducer sheath is passed through the vein to a level > 5 cm caudal to the SFJ where approximately 0.10 mL of cyanoacrylate is injected at two locations 1 cm apart. This is followed by a 3-min period of compression. Repeat injections are carried out along the length of the vein, each followed by

local compression with a hand or ultrasound probe. The sheath is removed and a bandage is applied. Cyanoacrylate was found to be non-inferior to RFA with a closure rate of 99% at 3 months compared to 94% with RFA in an industry-sponsored RCT (1b) [65]. Adverse events were similar between groups and no serious events occurred.

In addition to incompetent truncal veins, patients may also have symptomatic tributary varicose veins. Some providers advocate observation since they may resolve following treatment of the GSV, while others recommend concomitant phlebectomy to spare the patients a second procedure. Carradice et al. randomized 50 patients to EVLT alone vs. EVLT with phlebectomy (2b) [66]. There was no difference in quality of life scores or postprocedural pain scores, and VCSS scores were significantly lower at 3 months in the group that underwent phlebectomy. In a larger study of 507 limbs with symptomatic tributary varicosities, 30% did not undergo concomitant phlebectomy at the time of RFA, and only 5% of those had resolved with the ablation alone at the time of follow-up (4) [67]. Other patients developed new varicose tributaries post ablation requiring phlebectomy at a later date. The findings in this study support the safety and efficacy of concomitant phlebectomy in patients with symptomatic tributary veins who require saphenous ablation.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Endovenous laser ablation is effective and safe for the treatment of venous insufficiency	A
Radiofrequency ablation is effective and safe for the treatment of venous insufficiency	A
Hemoglobin-specific lasers are associated with increased postoperative bruising and pain compared to water-specific lasers	B
Bare-tipped fibers are associated with increased postoperative bruising and pain	B
Tumescent anesthesia during endothermal ablation reduces side effects	A
Thromboprophylaxis should be considered in individuals at increased risk of thrombus	D
Compression stockings should be worn following endothermal ablation	C

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Self-Assessment Questions

1. Which of the following is not an absolute contraindication to treating with endothermal ablation?
   (a) Acute DVT
   (b) Active infection
   (c) Allergy to tumescent anesthesia
   (d) Active superficial thrombophlebitis
   (e) Deep venous obstruction when treating a collateral vein
2. Which wavelength of laser is most associated with increased postoperative pain and bruising following EVLA?
   (a) 1320
   (b) 1470
   (c) 810
   (d) 1064
   (e) 1500
3. Which fiber type is associated with more postoperative complications?
   (a) Jacket-tip fiber
   (b) Tulip fiber
   (c) Gold-tip fiber
   (d) Bare-tip fiber
   (e) Radial fiber
4. What is the approximate risk of DVT following ETA?
   (a) 5%
   (b) 1%
   (c) 3%
   (d) 10%
5. MOCA and VenaSeal have which of the following advantages over endothermal techniques?
   (a) No need of tumescent anesthesia
   (b) Fewer side effects
   (c) Increased venous occlusion
   (d) a and b only
   (e) a, b, and c

Correct Answers

1. c: An allergy to tumescent anesthesia is considered a relative contraindication to thermal ablation. The other options listed are absolute contraindications.
2. c: The 810-nm laser is hemoglobin-specific, while the other options are water-specific. The hemoglobin-specific lasers have shown an increase in postoperative bruising and discomfort, possibly secondary to increased vein wall perforations, though additional studies using the same laser settings in both groups are needed.
3. d: Bare-tipped fibers have shown an increase in postoperative pain and bruising compared to the other fiber types, likely due to increased depth of injury and vein wall perforation.
4. b: Risk of DVT with both RFA and EVLA is approximately 1%.
5. a: Neither technique requires tumescent anesthesia, which is an advantage over the endothermal options. While one study showed less procedural pain with MOCA compared to RFA, adverse effects with VenaSeal were similar to RFA. Both options showed similar occlusion rates to the endothermal treatments.

Blepharoplasty

27

Isabella Lai and R. Sonia Batra

Abstract

Blepharoplasty is an operation focused on functional and/or cosmetic restoration of the eyelid by removal of redundant tissue. It is one of the most popular cosmetic procedures due to its relatively low risk profile and rapid visible improvement in facial aesthetics. Current methods of periorbital rejuvenation to restore youthful appearance are more conservative—grounded on concise preoperative evaluation and focused on limited skin resection. In this chapter, the authors present evidence for preoperative evaluation, decision-making and counseling of patients, surgical planning, various operative techniques, and postoperative care in functional and aesthetic blepharoplasty. Evidence on the postoperative complications and alternative complementary procedures is also discussed.

Keywords

Blepharoplasty · Aesthetic facial surgery · Upper eyelid · Lower eyelid · Transconjunctival incision · Transcutaneous incision · Dermatologic surgery

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Introduction and Definition

The eyes and periorbital areas are expressive points of human interactions, but they are also points that reflect facial aging. As people age, their skin loses elasticity, leading to excess laxity and skin folds over eyelid margins. These changes in eyelid appearance create an illusion of sadness, fatigue, and loss of energy, all of which decrease the aesthetic appeal of the human face. Furthermore, in severe cases, excess laxity of the skin can obstruct vision.

Blepharoplasty is formally defined as an operation for the restoration of a defect in the eyelid. The goal of the procedure is to repair ptosis, eyelid retraction, entropion, ectropion, trichiasis, or defects resulting from tumor excision. More commonly, this term specifically refers to removal of redundant tissue (e.g., skin, muscle, and fat) from the upper or lower eyelids to provide the eye with a more youthful appearance.

The role of blepharoplasty can be multifold: either cosmetic, to rejuvenate the appearance of the eyes, or functional, to improve visual fields. Blepharoplasty is one of the most popular cosmetic procedures performed in the United States [1]. According to the American Society of Plastic Surgeons, more than 200,000 eyelid procedures were performed in 2016. The popularity of this procedure is derived from its ability to provide a natural, younger appearance with a limited operation time and a low risk profile.

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Currently, there are very few high-quality, evidence-based articles on blepharoplasty because aesthetic surgery is still in its infancy. Most articles on this subject are of level IV evidence (case series) and level V evidence (case reports or expert opinion). There are few articles of level III evidence (retrospective comparative case series) and even fewer of level II evidence (prospective comparative studies). Given the nature of the subject, it would be very difficult to create level I evidence studies that are blinded, prospective, randomized, and controlled. Given the current quality of evidence and the variability in published data, meta-analyses have not been performed. Additionally, no consensus statements have been made by the American Academy of Dermatology, American Society for Dermatologic Surgery, American Academy of Cosmetic Surgery, American Society of Plastic Surgeons, American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), or American Academy of Facial Plastic and Reconstructive Surgery. This is expected as there are few controversies in this field.

This chapter contains different aspects of blepharoplasty and presents evidence from published works and current trends in this surgical technique.

Table 27.1 Indications for blepharoplasty and definitions

Indications for blepharoplasty and definitions
Blepharochalasia Redundant skin of the upper eyelid hangs down, impairing the visual field
Blepharospasm Muscles in the eyelids and around the eyes twitch uncontrollably
Dermatochalasis Excess of eyelid skin; underlying muscle, connective tissue, and fat Most often results from natural aging but can result from specific disorders (e.g., thyroid eye disease, floppy eyelid syndrome, blepharochalasis syndrome, trauma)
Ectropion Turning out or sagging of the upper or lower eyelid; mainly affects the lower eyelid, leaving the eye exposed and dry (excessive tearing is common)
Entropion Abnormal inward rotation of the eyelid; occurs most commonly as a result of aging but may occur after trauma and scar contraction or after surgery
Epiblepharon A congenital horizontal fold of the skin stretches across the border of the eyelid, pressing the eyelashes inward against the eyelid
Rejuvenation
Thyroid disease May cause unilateral or bilateral upper eyelid retraction and proptosis (protruding eye)
Trauma

Indications

Upper and lower eyelid blepharoplasty is performed for various functional or cosmetic indications (Table 27.1 summarizes indications and definitions). Patients undergoing cosmetic blepharoplasty may have different expectations than those undergoing functional blepharoplasty. For this reason, a thorough discussion of anticipated results with the patient is critical prior to the procedure in order to achieve the best outcomes.

Upper Eyelid

The signs of aging on the face are most prominently noticed in the upper eyelids. The current signs of eyelid aging are total orbital volume loss, tissue descent, and increased skin laxity [2]. Apart from causing undesirable aesthetics, these signs of aging can also cause eyelid droopiness and obstruction of the superior visual field. Upper eyelid blepharoplasty can therefore be performed to relieve this obstruction. Repair of blepharoptosis and upper eyelid dermatochalasis provides significant improvement in vision and quality of life.

Functional indications for reconstructive upper blepharoplasty include visual axis obstruction and comprise three essential elements: (1) patients should notice improvement in vision with eyelid skin elevation, (2) visual field testing is needed prior to procedure to document visual field impairment, (3) and there is photographic evidence of upper eyelid skin laying across eyelashes (3b) [3]. Evidence from one retrospective analysis studying downgaze (3b) [3] and from a

case series on superior visual field defects (4) [4] demonstrated that visual impairment from upgaze or downgaze should be a key functional indication. In a prospective survey of patients preoperatively and postoperatively, blepharoplasty was found to be qualitatively beneficial in addressing visual impairment in the head-tilt/chin-lift test, symptoms of discomfort, eye strain, and visual interference (4) [5]. Other functional surgical indications currently considered, albeit with limited evidence, are dermatitis, difficulty wearing a prosthesis in an anophthalmic socket, and temporal visual field impairment; thereby preventing patients from meeting driver licensing standards (4) [5].

Cosmetic upper eyelid surgery is an elective procedure, and its main indication is to improve the appearance of the eyes. Often-cited cosmetic requests of patients are to correct "tired" or "droopy" eyes, improve eyelid symmetry, improve eyelid contour, and rejuvenate the face (5) [6].

Lower Eyelid

Lower eyelid blepharoplasty is performed for both aesthetic and functional concerns. Functional indications include reading difficulty secondary to prolapsed orbital fat and skin covering the bifocal spectacle segment. Other functional indications are trauma, inflammatory disorders of the orbit and eyelids, entropion (inversion of the eyelid margin), and epiblepharon (congenital abnormality where eyelashes are forced against the cornea) (5) [7].

Although there are functional indications, lower eyelid surgery is most commonly performed to correct cosmetic concerns associated with aging. As a person ages, the increasing laxity of the structural supportive tissues and decreasing integrity of the orbital septum cause orbital fat pseudoherniation and appearance of bags in the lower eyelid. Laxity can be hereditary and appear in adolescents as well as the elderly. Orbital fat pseudoherniation leads to deepening of the nasojugal fold and causes the eyes to appear fatigued [8]. Additionally, below the orbital rim, the fatty tissues of the midface, cheek, and suborbicularis oculi fat also lose volume and descend. In a youthful face, cadaveric studies have demonstrated that the suborbicularis oculi fat attaches to the arcus marginalis at the level of the inferior orbital rim [9]. These changes in the midfacial fat, suborbicularis oculi fat, and orbicularis oculi contribute to the increasing potential for eyelid malposition, deepening of the tear trough, and rounding of the eye [9]. Additionally, skin elasticity loss also leads to progressive dermatochalasis with fine and deep rhytids [10]. Rizk and Matarasso conducted a retrospective study of 100 patients to analyze the indications and treatment of lower eyelid blepharoplasty. They concluded that orbicularis oculi muscle hypertrophy is also an absolute indication for lower eyelid transcutaneous blepharoplasty as this requires resection of the preseptal orbicularis muscle (5) [11].

Therefore, aesthetic indications for lower blepharoplasty include patients with lower eyelid fat pseudoherniation with or without orbicularis hypertrophy, excess lower eyelid skin, the appearance of circles under the eyes, or prominent depth in the tear trough deformity (5) [12].

Effectiveness of Blepharoplasty

Blepharoplasty is a procedure associated with a high level of satisfaction for both patients and surgeons. For the patient, blepharoplasty affords the opportunity to achieve a youthful and rejuvenated appearance. For the surgeon, it is a short, in-office procedure that has immense, long-lasting results, and it allows the surgeon to restore facial harmony, preserve anatomical landmarks, and avoid undesirable surgical stigmata.

Although there is a marked increase in medical articles documenting the successes of blepharoplasty, these studies usually focus on patient satisfaction. This is due to the subjective nature of outcomes that hinge on aesthetics. A study by Viana GA et al. surveyed 50 patients after lower blepharoplasty and concluded that blepharoplasty was a safe and effective procedure, had low complication rates, and led to significant improvement of self-esteem assessed 6 months

after the operation (4) [13]. However, although all participants had positive changes in their social lives, seven patients had decreased self-esteem. The researchers believed that the worsening self-esteem of these patients can be explained by external social factors: Three patients were divorced, three had problems with children, and one unexpectedly became a widow during the study period. In a literature review, Figueroa showed that pain and loss could be responsible for the rupture with significant change in body image self-esteem, which could last up to 1 year after the event (5) [14].

To address the issue of biases of patient surveys in determining the efficacy of blepharoplasty, Chauhan et al. sought to create a more objective measure of efficacy (4) [15]. One of the chief motivations of blepharoplasty is to restore a youthful appearance and minimize aging. For this reason, the authors conducted a prospective study to quantify the degree of perceived age change after facial surgical procedures. Patients were separated into three groups based on surgical procedures completed: 22 patients in face- and neck-lift, 17 patients in face- and neck-lift and upper and lower blepharoplasty, and 21 patients in face- and neck-lift and upper and lower blepharoplasty plus forehead-lift. The adjusted means demonstrated that patients were perceived to be 8.9 years younger than their chronological age after surgery. The effects were most dramatic in those who had undergone all three aging face surgical procedures. This study demonstrates that aesthetic facial surgery leads to a significant and consistent reduction in perceived age after aesthetic facial surgery. This effect is more substantial when the number of surgical procedures is increased, an effect unrelated to the preoperative age of a patient and unaffected by other variables (4) [15].

There lacks evidence on the lasting effects of blepharoplasty. It is estimated that these procedures usually last for 10–15 years (5) [15]. This is due to the inevitable fact that treated areas are also subjected to the same aging process as that of the rest of the body.

Preoperative Evaluation

The preoperative evaluation prior to blepharoplasty should include a detailed general medical and ophthalmologic history, focused physical exam, and thorough discussion of expectations with the patient.

Medical History

Multiple review articles have highlighted the importance of a thorough medical history (5) [16, 17]. This history should include chronic medical conditions, e.g., hypertension, diabetes mellitus, cardiac disease, bleeding or hematologic disorders, and thyroid abnormalities. Furthermore, current medications and previous surgeries should also be queried as they can have an impact on wound healing.

Ophthalmologic History

An ophthalmological history is critical during preoperative evaluation. This should include information about vision, prior traumas, and ophthalmologic conditions (e.g., glaucoma, allergic reactions, dry eyes). Dry eye syndrome is a common dysfunctional tear syndrome, described by the patient as dryness, burning, foreign body sensation, blurred vision, photophobia, itching, redness, tearing, and discharge of mucus. Hamawy et al. have published an algorithm for treating dry eyes (3b) [18].

The Schirmer test is no longer indicated for predicting dry eye syndrome. The role of the Schirmer test was evaluated by Rees and LaTrenta in a prospective analysis of 100 patients. Because blepharoplasty can mechanically alter eyelid closure and impair the lubricating mechanism, subclinical dry eye syndrome is an important consideration in any patient contemplating blepharoplasty, especially those with morphologically prone eyes. The authors found that the Schirmer test could not reliably predict the development of postoperative dry eye syndrome

(4) [19]. They state that the morphology of the orbit is a more reliable indicator to signal the predilection to develop this complication (5) [19].

It is especially important to ask regarding prior ocular procedures such as laser-assisted in situ keratomileusis (LASIK) and other refractive surgeries. Patients who have had refractive surgery within the past 6 months are not suitable candidates for blepharoplasty (2b) [20–22].This patient population is at risk for dry eyes and keratopathy because of the alteration in corneal sensation, tear production, and tear film formation [20–22].

Alterations in tear secretion and tear film stability after LASIK and subsequent blepharoplasty were studied by Griffin et al. [23] They performed blepharoplasty on nine patients who had undergone bilateral LASIK in the previous 18 months. This group was compared to a control group of nine patients with no history of LASIK, dry eyes, or contact lens use. The authors found no statistically significant difference in tear characteristics after blepharoplasty between both groups. They concluded that blepharoplasty may be performed after LASIK if an interval of time has passed (3b) [23].

Lifestyle History

A review by Trussler and Rohrich also recommends lifestyle history: e.g., smoking, alcohol consumption, illicit drug use, and over-the-counter herbal supplements as these substances can affect wound healing (5) [21].

Physical Exam

Many surgeons may require a full preoperative ophthalmologic exam to assess visual fields, visual acuity, adequacy of tear film, functionality of periocular muscles, and underlying glaucoma and macular diseases. A detailed periorbital physical exam is recommended; this should include examining the periorbital structures and analyzing the presence of upper and lower eyelid dermatochalasis, lateral hooding, ptosis, angle of the lateral canthal tilt, and lower eyelid laxity [20–22].

The orbicularis and lower lid ligaments are part of the periorbital structures and should be examined with a snap test or attempting to pull the eyelid more than 6 mm from the eye to see if laxity exists. Blepharoplasty in a lax lower lid can worsen lid malposition and cause scleral show or ectropion. If laxity exists, a canthopexy or canthoplasty should be discussed. Additionally, the patient needs to be evaluated for the presence of canthal tilt: when the medial canthal position is 2 mm inferior to the lateral canthal position. If this is not the case, lateral canthal repositioning may be required. Fat excess and appearance should be assessed as well as the tear trough (nasojugal groove) deformity. The orbital rim's position relative to the cornea in the lateral view is important to assess. If the rim is located posteriorly, a negative vector or prominent eye will make lower eyelid surgery more challenging (4) [24].

The upper lid margin normally covers 2–3 mm of the iris. A lower position may indicate ptosis, which needs to be documented and addressed preoperatively. Ptosis in conjunction with a high tarsal fold is indicative of levator dehiscence. The position and shape of the brow needs to be assessed to see if brow lifting or shaping is required in addition to blepharoplasty. The key elements in the problem of the lower eyelid blepharoplasty are the negative vector, sagging lower eyelid, and prominent tear trough. These elements are difficult to correct and their postoperative results may be suboptimal. These elements need to be pointed out to patients preoperatively.

Patient Counseling

With any procedure, managing patients' expectations is crucial to satisfactory outcome (5) [25]. Patients should understand that upper blepharoplasty will make eyes large and more prominent but will not elevate the brows, reduce rhytides, or

lines of expression. Middle-aged patients should not expect to appear as they did in their 20s or 30s. For lower blepharoplasty, patients will have improved infraorbital contour and appear better rested. However, they should not expect this procedure to address sagging malar eminence because this is done through a different procedure.

A discussion of complications postoperatively should also be explained during the session. Patients should also be informed regarding postoperative care and length of recuperation. This is best done in the form of a handout which details expectations following surgery.

Although upper eyelid blepharoplasty requires minimal bandaging, upper eyelid visibility and swelling will be noticeable and may take months to resolve. Ointments may help with wound healing, but depending on the components within the ointment (e.g., antibiotics), contact dermatitis may result.

For lower lid blepharoplasty, the patient should be aware of the risk of conjunctival irritation and dry eyes. Artificial tears can be provided for these conditions.

If laser resurfacing is to be performed, then the patient needs to be educated about prolonged erythema and wound care. Most importantly, patients should be informed that due to postoperative swelling, the final results of the surgery may not be fully apparent for 3 months.

Surgical Treatment

In blepharoplasty, the current trend is toward minimalism—preserving and even augmenting volume loss (5) [26]. While aggressive procedures can have outstanding results, more complications can also arise; as such, "less is more." In this section, we will discuss the evidence behind the surgical techniques of blepharoplasty, as it relates to preoperative markings, instruments used, and the various types of incisions (Table 27.2).

Table 27.2 Level of evidence

Evidence-based summary	
Findings	Evidence level
Blepharoplasty is a safe and effective procedure, with low complication rates, and leads to improvement of patient self-esteem assessed 6 months after the operation	A
Functional indications for reconstructive upper blepharoplasty is indicated when visual axis is obstructed. Functional indications for lower eyelid blepharoplasty include reading difficulty secondary to prolapsed orbital fat and skin covering the bifocal spectacle segment	B
Patients undergoing blepharoplasty should have a thorough periorbital and ophthalmologic examination. They should be asked about specific medical conditions which could affect the procedure and postoperative healing	C
Patients who have had refractive surgery (LASIK) within the past 6 months are not suitable candidates for blepharoplasty	B
Managing patients' expectations is crucial to satisfactory outcome	D
In blepharoplasty, the current trend is toward minimalism—preserving and even augmenting volume loss	D
Compared to cold steel surgery, the CO_2 laser leads to improved hemostasis, reduced operative time, less bleeding, greater intraoperative visibility, and decreased ecchymosis and edema	D
The laser diamond scalpel and Colorado needle offer the surgeon tactile feedback	B
No statistical difference was noted when comparing radiofrequency device with CO_2 laser for blepharoplasty incision	B
No statistical difference was noted when comparing the Colorado needle with traditional scalpel in terms of ecchymosis, cosmesis results, or scar formation	B
Electrocautery was not inferior to cold steel scalpel in terms of healing/scar formation of the skin incision	C
Upper eyelid skin removal is often more liberally done than lower eyelid skin removal because showing of the tarsal skin (2–3 mm above the eyelid margin) is desirable in the upper eyelid for makeup application and visibility	D

Table 27.2 (continued)

Evidence-based summary	
Findings	Evidence level
Lower eyelid blepharoplasty is based on the more conservative removal of a pinch of skin, as excessive skin removal leads to scleral show	D
Malposition of the eyelid is the most frequently reported complication associated with transcutaneous lower eyelid blepharoplasty	D
Inadequate removal of fat is the most common complication after transconjunctival lower eyelid blepharoplasty	C
Due to ethnic anatomical differences and perception of aesthetics, Asian eyelid surgery requires modified techniques	C
While rare, blepharoplasty does incur complications, including bleeding, structural, infection, and vision loss. Patients should be informed of these complications	B
The most feared complication of blepharoplasty is permanent vision loss, most commonly secondary to retrobulbar hemorrhage; however, vision loss can also be caused by globe perforation, ischemic optic neuropathy, and angle closure glaucoma	B
Even though rare because of the extensive vascularization of the region, infections postblepharoplasty do occur and require early appropriate treatments (i.e., antibiotics, debridement, drainage, and possible hyperbaric oxygen)	B
Lower eyelid malposition is the most commonly reported complication of lower eyelid blepharoplasty. Addressing this complication requires identification of the affected lamella.	B
If initial ocular lubrication fails to address dry eye symptoms, anti-inflammatory eye drops (such as topical cyclosporine) should be used, followed by punctal occlusion	A
Consistent use of lubricating eye drops can prevent corneal abrasions during the early postoperative period	A
While they do not offer outcomes comparable to those of blepharoplasty, botulinum toxin A and hyaluronic acid injections are alternative procedures that address eyelid concerns	C

Preoperative Markings

Zoumalan and Roostaeian summarized preoperative markings in their review on blepharoplasty [27]. These incisional markings are individualized for patients and their desires. Markings should be performed when patients are sitting upright with eyebrows and eyelids in neutral position.

Instruments

There are various options for cutting devices in blepharoplasty: cold steel scalpel, cautery, radiofrequency (RF), Colorado needle, and laser. Each instrument offers its own advantages and disadvantages (Table 27.3).

Cold steel scalpel and laser have been compared in some studies. In an observational study on patients who underwent blepharoplasty, Coleman et al. note that while laser can create less bleeding, it increases inflammatory response when compared to scalpel (5) [28]. In contrast, a review by Gladstone reported laser improved hemostasis and less collateral damage with laser incision (5) [25]. Biesman discussed in a review article the perceived efficiency of utilizing the carbon dioxide (CO_2) laser, as it serves as both a blunt dissection device and a cautery unit (5); additionally, he also noted improved hemostasis with CO_2 laser [29]. Further studies by David and Sanders on 13 patients showed reduced operative time, less bleeding, and decreased ecchymosis and edema. Scars were indistinguishable at 30 days in both groups (2a) [30]. In a randomized study, Morrow and Morrow did not observe differences in healing; however, the authors noticed increasing patient comfort and shorter recuperation time with laser (2a) [31]. In a study by Baker et al., blinded observers were not able to distinguish clinically significant outcomes between diamond scalpel and CO_2 laser; however, the scalpel provided improved tactile feedback to surgeons and allowed for the ability to incise at varying levels of hemostasis (2a) [32].

Table 27.3 Instruments used for incision in blepharoplasty: evidence-based advantages and disadvantages

Cold steel scalpel	Electrocautery	Colorado needle	Radiofrequency	CO_2 laser
Advantages				
Decreased inflammation Decreased collateral damage Allows tactile feedback	Simultaneous incision and hemostasis	Decreased thermal damage Allows tactile feedback	Simultaneous incision and hemostasis Decreased collateral damage Allows tactile feedback	Simultaneous incision and hemostasis Improved intraoperative visibility Decreased operative time Decreased collateral damage Increased patient comfort Decreased ecchymosis/edema Decreased recuperation time
Disadvantages				
Requires separate device to achieve hemostasis	Possible increased inflammation	Possible necrosis	Possible greater depth of tissue damage	Possible increased inflammation No tactile feedback

The short-pulse CO_2 laser was compared to the Colorado needle tip with electrocautery in a randomized trial by Rokhsar et al. [33] Twelve patients were studied. Mean intraoperative time with the Colorado needle was shorter than that with the laser. Histologic examination revealed less thermal damage of the tissue harvested with the Colorado needle. However, no difference in healing parameters was noted by the patient or physician 1 month postoperatively. The Colorado needle offers the advantages of the short-pulse CO_2 laser along with greater tactile feedback (3a) [33].

A radiofrequency device was compared with CO_2 laser in a randomized controlled trial by Niamtu on 30 patients. Each eye was randomly treated with one modality. Five blinded board-certified surgeons did not observe any statistically significant difference in scar quality at 12 months. The author concluded that both devices incise and provide coagulation simultaneously, minimize collateral damage, and produce indistinguishable scars (2a) [34].

Radiosurgery has also been compared with conventional scalpel surgery. In a prospective study on opposite eyelids by Ritland et al., 13 patients found better wound healing and a higher Hollander score at 1 week ($p = 0.014$) with radiosurgery, but no statistically significant difference at 3 months (3b) [35]. In a prospective, randomized, blinded, comparative, interventional study by Kashkouliet al. in 2008, eyelid scar formation and histology on 46 eyelids were assessed by two masked observers. They found that while scar formation was insignificantly less in the radiosurgery group ($p = 0.055$), the histologic zone and depth of tissue damage was greater in the radiofrequency group (2b) [36].

The Colorado microdissection needle and scalpel were studied in a prospective, comparative case series by Arat et al [37]. A total of 254 eyelids of 101 patients underwent bilateral upper or transcutaneous lower blepharoplasty, and ecchymosis, cosmesis, and histologic tissue damage of incisions made by a scalpel versus a Colorado needle were compared. Histologically, necrosis was only noted with the Colorado needle sides ($p = 0.001$). No clinical difference was noted between the two groups in terms of ecchymosis, cosmesis results, or scar formation (2b).

Albeit the numerous studies that have shown the benefits of electrocautery when compared to traditional scalpel, electrocautery is not commonly thought of as a cutting device due to deep fears for

burns, poor wound healing, and excessive scarring. It is usually thought of as a device for underlying dissection and hemostasis. In a prospective, randomized, double-blind study by Afuwapeet al., electrocautery and scalpel were compared in 197 native African patients as it relates to postoperative pain, duration of wound healing, and occurrence of infection. It was concluded that electrocautery in making a skin incision is associated with reduced incision time ($P < 0.001$), incisional blood loss ($P < 0.001$), and postoperative pain ($P < 0.001$). However, there was no statistically significant difference in wound infection and wound epithelialization time ($P = 0.206$) (2b) [38]. In a comparative, observational study by Lee et al., patient and blinded observer perspectives on wound healing and scar formation were assessed. The observers rated incision vascularization, pigmentation, thickness, and relief. Patients rated incision pain, itching, discoloration, stiffness, thickness, and irregularity. Results showed that electrocautery was not inferior to cold steel scalpel in terms of healing/scar formation of the skin incision (3b) [39]. To summarize, many studies have shown that electrocautery does offer advantages such as rapid hemostasis, faster dissection, and reduced blood loss, without affecting wound healing time, rates of infection, and postoperative complications [40–45].

Laser blepharoplasty offers many advantages. A review of laser blepharoplasty by Lessner and Fagien found the same advantages to the laser technique as mentioned previously. The authors caution surgeons to remove less skin during blepharoplasty if resurfacing is planned for the same site as thermal collagen contracture will occur after laser resurfacing (5) [46]. In a review article by Leciere et al., long-term outcomes of CO_2-laser assisted blepharoplasty were studied in a prospective controlled trial of 52 patients. It was found that ptosis surgery is a safe and reproducible technique particularly appreciated by patients. The procedures led to improved hemostasis, decreased operating time, and improved postoperative appearance (2c) [47].

No studies in humans have been performed to directly compare carbon dioxide laser, radiosurgery, and scalpel incision. However, these three modalities were compared in Hodson et al. study on snakes. The design of the study was to examine the histologic skin response in snakes after a 2 cm skin incision was made by either CO_2 laser, radiosurgery, or scalpel incision. Necrotic and fibroplastic tissue were measured in histologic sections; samples were assessed and scored for total inflammation, histologic response (based on the measurement of total inflammation score, necrotic tissues, and fibroplastic tissues), and other variables. Frequency distributions of gross and histologic variables associated with wound healing were calculated. It was found that skin incision using a scalpel was less necrotic, followed by radiosurgery, and then laser (5) [48].

Upper Eyelid

Upper eyelid blepharoplasty is performed by an external incision in the upper eyelid crease and excision of redundant skin by various modalities as discussed previously. In general, upper eyelid skin removal is often more liberally done than lower eyelid skin removal. This is because showing of the tarsal skin (2–3 mm above the eyelid margin) is desirable in the upper eyelid for makeup application and visibility (5) [49].

Along with the skin, the underlying orbicularis oculi muscle and fat can also be removed if redundancy is observed. Surgeons often consider preservation of the orbicularis oculi muscle to prevent development of lagophthalmos [27]. Nasal herniated fat pads are removed, while central fat pads are often kept to maintain upper eyelid fullness. The wound is then carefully closed with either interrupted, simple running, or running subcuticular closure. Glue and Steri-Strips can also be placed depending on the surgeon's preference.

For upper eyelid surgery, ptosis correction is most commonly encountered. For the correction of involutional ptosis, Ben Simon et al. retrospectively compared an external approach for levator advancement (81 eyelids, 37 with blepharoplasty and 51 alone) with a Muller's muscle–conjunctival resection (184 eyelids, 104 with blepharoplasty and 80 alone) [50]. Patients who underwent

Muller's muscle–conjunctival resection attained a better cosmetic outcome and had a lower reoperation than the other patients (3b). Brown and Putterman showed that a decreased eyelid raising effect of a Muller resection ptosis procedure can be accomplished with concomitant blepharoplasty that includes orbicularis resection [51]. Erb et al. showed that after levator advancement for unilateral ptosis repair, 17% of patients had a decrease in contralateral eyelid height of more than 1 mm due to the Hering dependence phenomenon with 5% of patients requiring surgical repair during the first postoperative year (3b) [52].McCulley et al. found that 8.7% of patients with primary acquired good-function blepharoptosis underwent additional surgery after external levator aponeurosis advancement (3b) [53]. The authors observed an increased risk of persistent postoperative blepharoptosis in patients with severe ptosis [53].

Lower Eyelid

Lower eyelid blepharoplasty is based on the more conservative removal of a pinch of skin, as excessive skin removal leads to scleral show (4) [54]. The ideal approach for treating lower eyelid blepharoplasty is under debate. There exist two distinct methodologies: (1) external transcutaneous incision and (2) internal transconjunctival incision.

The transcutaneous method involves an external skin incision to remove excess skin while accessing the underlying fat compartments and the orbicularis muscle. This is performed by a subciliary incision under the lower eyelash line to remove redundant skin. After the removal of redundant skin, an incision is made in the orbital septum to remove the orbicularis oculi muscle flap and the pseudoherniated fat pads. There are variations in the transcutaneous approach—e.g., skin-only flap, skin–muscle composite flap, and separate skin and muscle flap. Currently, there are no prospective comparative studies on these techniques; the current studies are based on surgeons' experiences on a particular technique.

The transconjunctival technique involves a retroseptal approach. This allows the surgeon access to the fat compartment while avoiding the anterior and middle lamellae. An incision is made in the tarsoconjunctival aspect of the lower tarsal plate. The lower eyelid fat pads herniate through this incision. In a study by de Castro in 2004, a transconjunctival approach was performed on 100 blepharoplasties, and preoperative, intraoperative, and postoperative periods were analyzed. The patients, surgeon, and a third person evaluated the results, and photographs of postsurgical eyelid positions were displayed in the article [26].

The transcutaneous approach has not only variations of the techniques but also multidisciplinary principles that affect the results. In a prospective study on lower eyelid physiology, the Atlanta group showed that there is very little muscle denervation (by preoperative and postoperative electromyography determination) with a transcutaneous incision, skin–muscle flap, and orbicularis suspension (5) [55]. In a study by Liao et al., a total of 408 female patients underwent modified subciliary lower blepharoplasty between 2002 and 2010 [56]. The severity of eyebags (dynamic wrinkle numbers and prolapse) was compared through preoperative and postoperative photos. While this modified transcutaneous approach led to improved dynamical wrinkles and prolapse in the eyebags, the results were dependent on periorbital aging and dynamic wrinkle numbers ($P < 0.001$) prior to the procedure (2b).

The transcutaneous incision results in high patient satisfaction. In a prospective, randomized, controlled trial conducted between April 2005 and May 2007, Viana et al. studied the satisfaction of aesthetic results of 50 surgical patients following two variations of the transcutaneous lower eyelid blepharoplasty. It was concluded that the transcutaneous approach was safe and effective and led to improvement in self-esteem assessed 6 months after the operation (2b) [13].

Gladstone examined the two parallel approaches to treat lower blepharoplasty and discussed an unpublished retrospective review of

4460 transcutaneous blepharoplasty cases and 3438 transconjunctival blepharoplasties. Malposition of the eyelid was the most frequently reported complication associated with the transcutaneous approach, which occurred in 1.4% of patients vs. 0.7% with the transconjunctival technique (3b) [25].

Interestingly, with incorporation of concomitant canthal suspension and eyelid-shortening techniques, eyelid malposition complications have become less frequent. In a retrospective chart review of primary lower transcutaneous blepharoplasty series over a 10-year period by Codner et al., 264 patients were followed up for a median of 264 days. Eyelid malposition requiring operative correction occurred in nine patients (3.5%). It was concluded by the authors that lateral canthal support should be considered a routine component of lower transcutaneous blepharoplasty to obtain a natural eyelid shape (3b) [57]. The percentage of malposition reported by Codner et al. is substantially less than that reported by Kim and Bucky, where its incidence after conventional transcutaneous blepharoplasty was reported to be as high as 15–20% [58]. Castro conducted a similar prospective study of 100 lower eyelid blepharoplasty cases. The transcutaneous approach (with and without canthopexy) was compared to the transconjunctival approach (with and without fat removal and canthopexy). The author found that each patient's treatment must be individually tailored (5) [59].

In a recent retrospective study, Sultan et al. found in 100 patients undergoing transcutaneous bilateral skin–muscle flap lower eyelid blepharoplasty that the mean distance of malposition was 0.33 mm from the pupil to the lower eyelid margin and 0.32 mm from the lateral limbus to the lower eyelid margin. For patients undergoing concurrent canthopexy, there was a significantly greater change in the eyelid position ($p < 0.001$). Therefore, the authors concluded that transcutaneous skin–muscle lower eyelid blepharoplasty with selective performance of canthoplasty or canthopexy causes a small, predictable eyelid position change in this population with a low rate of revision procedures (3b) [60].

Over the past few decades, attempts to reduce rates of lower lid malposition led to popularization of the transconjunctival approach. With lower eyelid transconjunctival blepharoplasty techniques, herniated fat compartments were debulked. Excess skin resulting from this approach was corrected by skin pinching, ablative laser, or chemical peels.

In their article, Zarem and Resnick described their experience with 104 patients over 2 years and reported no observation in lower eyelid retraction problems, presumed to be due to avoiding the middle lamella (5) [61]. Baylis et al. reviewed 122 patients who underwent transconjunctival blepharoplasty over a 24-month period. The main complication was underexcision of fat (7.4%). The authors had no cases of lower eyelid retraction, which is the most common complication of the transcutaneous technique that has been previously noted (4) [62]. A more recent review of the literature by Baylis et al. also reports inadequate removal of fat as the most common complication after transconjunctival blepharoplasty, occurring in as many as 20% of cases (4). The author advises patients that the goal of lower blepharoplasty is to remove 90% of the excess fat (5) [63]. Taban et al. found no difference in the lower eyelid position after the transconjunctival approach for fat removal with and without skin removal by the pinch technique in their retrospective analysis on patients undergoing bilateral lower blepharoplasty (3b). The authors postulated that the position of the eyelid is not affected either way because the middle lamella was not violated [64].

Rizk and Matarasso reported that the transconjunctival approach for lower eyelid blepharoplasty avoids damage to the orbital septum as compared to the transcutaneous approach [11]. In addition to trauma to the septum, the transcutaneous technique may lead to denervation with consequent retraction, scarring, and rounding of the eye and scleral show, even with conservative technique. However, the transconjunctival approach limits the surgeon's ability to correct redundant skin (5).

Griffin et al. performed a randomized controlled trial of 36 patients to compare transcutaneous

blepharoplasty without resurfacing to transconjunctival blepharoplasty with resurfacing. The study found no statistically significant difference in lower eyelid bulging and wrinkles between the two groups. Lateral eyelid rounding with scleral show and ectropion developed in 3.2% of the transcutaneous blepharoplasty patients. The authors point out that the main advantages of the transconjunctival technique, namely, lack of eyelid malposition and visible scar formation, can become a concern when transconjunctival surgery is combined with adjuvant CO_2 laser resurfacing or chemical peels (2b) [65].

Managing Excess Skin

There are multiple ways to manage excess skin after lower eyelid blepharoplasty, including skin pinching, ablative laser, or chemical peels. The difficulty lies in deciding if the excess skin needs to be removed and how much should be removed to optimize the patient's results.

If severe skin excess is present after volume preservation lower eyelid blepharoplasty, skin flap elevation and excision should be performed to correct excess skin excess that extends along the entire length of the lower eyelid.

For moderate excess, a skin pinch can be performed. Kim and Bucky published a retrospective review of 71 patients who underwent pinch blepharoplasty of the lower eyelid, a technique that does not involve skin undermining [58]. The authors believe that avoiding skin undermining allows for a decreased risk of contraction and hence less postoperative lower eyelid malposition. Their study also found that the pinch method allows resection of more skin and allows the addition of simultaneous laser resurfacing (5). Rosenfield published a case series of 77 patients who underwent pinch blepharoplasty [54]. Of these patients, none had postoperative lower eyelid malposition. Additionally, these patients did not require taping, had no scleral show, and did not develop ectropion. This series suggest that pinch blepharoplasty can reliably remove crepe-like skin with less chance of scleral show and eyelid malposition (4) [54].

For mild skin excess (<2 mm) and rhytides following lower eyelid blepharoplasty, ablative skin resurfacing techniques—such as ablative laser or chemical peels—can be employed. These procedures should generally be reserved for patients with Fitzpatrick skin type III or lower. Because of the risks of pigmentary alterations in patients with type IV skin or higher, caution should be taken when considering these procedures. Pretreatment with a 4- to 6-week nightly regimen of topical retinoic acid (0.05% or 0.10%), hydroquinone (4–8%), and alpha hydroxy acid (4%–10%) up until 1 week before treatment is recommended [27]. In a retrospective chart evaluation by Herbig et al., a combination of Jessner's and 35% trichloroacetic acid chemical peel was applied on 115 female patients. The author concluded that this method was an effective, safe resurfacing tool that treats superficial to moderate rhytides (3b) [66]. Laser facial ablative resurfacing is also an option to correct excess skin as summarized by Roy et al. in a review article; commonly used lasers are CO_2 and erbium:yttrium–aluminum–garnet lasers. While these platforms are effective, they can also lead to risk for prolonged healing time, erythema, edema, and hypopigmentation (5) [67]. For this reason, fractional laser resurfacing has nearly supplanted the traditional full-field laser resurfacing. In Yates' review article, he discussed that fractionated ablative platforms can help lead to faster re-epithelialization and therefore quicker healing times (5) [68].

Closure

Subtleties in surgical technique—such as sutures used for incision closure—can drastically affect cosmetic outcomes. Suture materials commonly used include polypropylene, monofilament nylon, fast-absorbing gut, and ethylcyanoacrylate.

A randomized controlled trial by Greene et al. assessed the efficacy of octyl-2-cyanoacrylate tissue glue in blepharoplasty against traditional

running suture closure [69].Twenty upper blepharoplasty patients were studied. One surgical site was closed with tissue glue; the opposite incision was closed with a running suture. Five blinded observers did not find any statistically significant difference in wound quality using a visual analog scale and a modified Hollander scale. No significant difference was found in the duration of healing, inflammation, and wound complications. The authors concluded that octyl-2-cyanoacrylate glue is an excellent alternative to suture closure. Tissue glue did not result in any inflammatory complications and withstood the forces of closure (2a) [69]. Scaccia et al. conducted a prospective study of 30 patients to compare subcuticular closure using 5–0 polypropylene suture with running 6–0 fast-absorbing catgut suture for approximation after blepharoplasty. Both materials resulted in comparable morbidity and postoperative discomfort levels (5) [70].

In a randomized, split-eyelid, single-blind, prospective study by Kouba DJ (2011) et al. on upper eyelid blepharoplasty, three subgroups were tested (ECA versus fast-absorbing gut, ECA versus polypropylene, and fast-absorbing gut versus polypropylene). Although sutured epidermal closure and tissue adhesive are highly efficacious for upper eyelid blepharoplasty, physicians and participants felt that cosmesis with ECA was superior to that with fast-absorbing gut (2b) [71].

Asian Eyelid

Upper eyelid blepharoplasty is the most popular cosmetic procedure in Asia. To perform surgery on the Asian eyelid requires understanding of the ethnic differences in anatomy. A review by Lee CK et al. analyzed the ethnic anatomical differences, e.g., the increased amount of preseptal fat, high variability in the superior palpebral fold, and presence of a medial epicanthal fold (5) [72]. In a separate review article, Chen et al. discussed many differences between the Asian and Caucasian eyelids and the supraorbital bones surrounding the eyelid. The different standards and public preferences for aesthetic double eyelids are due to these anatomical differences (5) [73]. An overview article by Chee and Choo discussed that the aim of Asian upper blepharoplasty is to create a pleasing and permanent upper eyelid crease (5) [74].

In a level V evidence study by Gao et al., 65 articles describing objective criteria in Caucasian and East Asian populations found that there lack objective and scientific studies regarding Asian aesthetic criteria. These objective criteria are needed to ensure successful aesthetic surgeries (5) [75].

Recent Trends

The current trend in lower eyelid blepharoplasty is toward greater preservation and even augmentation of volume during lower eyelid blepharoplasty. While debulking fat compartments still plays an important role in this procedure, recent studies theorize the importance of fat preservation for facial rejuvenation. In an article by Mendelson et al., the surgical anatomy of the midcheek is defined. This is further supported by Rohrich et al. who published a cadaveric study in which eight hemifacial fresh cadaver dissections were performed to study the anatomy of the midface adipose tissue. It was concluded that loss of deep fat compartments leads to a change in shape and contour, leading to the perception of aging. These anatomical observations defined targets for future augmentation and rejuvenation (5) [76].

The importance of midface fat preservation is discussed in recent literature. In a separate study in 2011, Rohrich et al. reviewed 50 lower eyelid blepharoplasties (a total of 100 operated lids) and used software to define aesthetics (e.g., positioning of the tear trough, lower eyelid relative to the pupil, and intercanthal angle). Through this review, the investigators defined five steps to improve blepharoplasty: (1) augmentation of malar fat compartment, (2)preservation of lower eyelid orbicularis muscle and minimal fat removal, (3) release of the orbicularis retaining

ligament, (4) strengthening of the lateral canthal support, and (5) minimal skin removal (5) [77]. Einan-Lifshitz et al. published a study on volumetric rejuvenation. In their study, they reviewed 57 patients who underwent lower eyelid blepharoplasty (a total of 114 eyes) with fat reposition and/or fat transfer. They found that volumizing the tear through fat reposition and/or transfer can improve outcomes (3b) [78].

In situations where fat repositioning is inadequate to correct infraorbital hollowing, autologous fat grafting to the deep malar cheek pads and the remaining periorbital areas should be considered. Periorbital and midface volume loss arise as a patient ages. Fat grafting allows for comprehensive augmentation of facial fat compartments.

Complications

While blepharoplasty has a tolerable risk profile, complications with blepharoplasty should be thoroughly understood by the surgeon. Lelli and Lisman reviewed complications and categorized them into early, intermediate, and late phases [79]. Figure 27.1 summarizes these complications.

Early Postoperative Period (Within the First Week)

Vision Loss

In the early postoperative period (first week), the most feared complication is permanent vision loss. The most common cause of this complication is retrobulbar hemorrhage, although other causes such as globe perforation, ischemic optic neuropathy, and angle closure glaucoma have been reported.

DeMere et al. reported the incidence of retrobulbar hemorrhage as 0.04% [80]. Hass et al. conducted an analysis of 237 questionnaires completed by the members of the ASOPRS. They found that the incidence of orbital hemorrhage after cosmetic eyelid surgery is 0.055% (1:2000). The incidence of hemorrhage with permanent visual loss is 0.0045% (1:22000). The authors recommend that physicians remain available for at least 24 h after surgery as the majority of cases occur in the immediate postoperative period (5) [81].

A suspicion of orbital hemorrhage and/or vision loss should not be taken lightly. Total vascular insufficiency of 60–120 min can produce permanent visual loss. Presenting signs include eye pain, pressure, loss of vision, diplopia, nausea, vomiting, proptosis, dilated or unresponsive

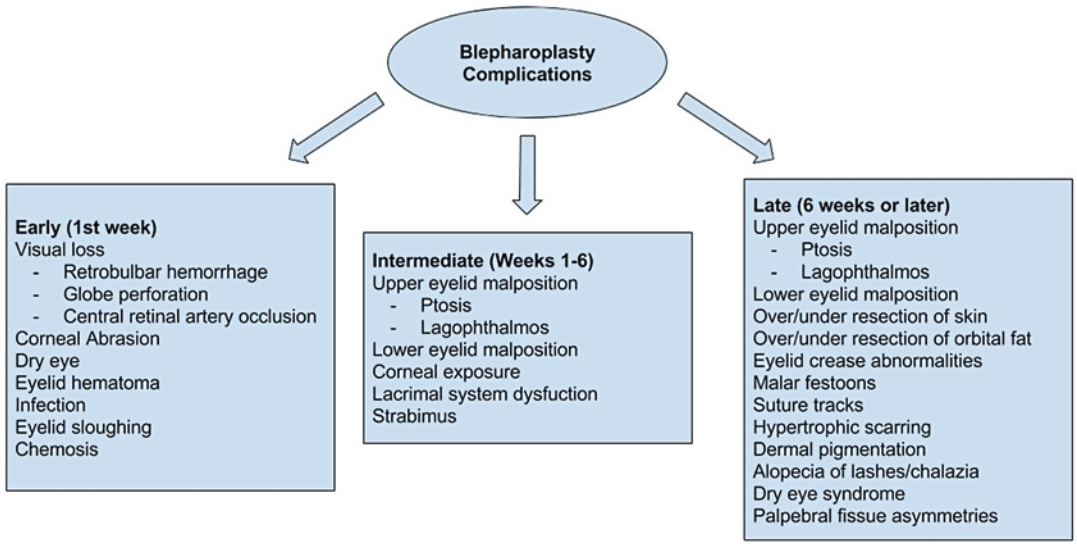

Fig. 27.1 Blepharoplasty complications. (Adapted from Lelli and Lisman)

pupils, limited extraocular movement, and lid ecchymosis. If vision is threatened, immediate ophthalmologic consultation and medical and/or surgical treatment should be obtained. Medical treatment may include intraocular pressure-reducing medications such as mannitol, acetazolamide, steroids, and beta-blocker eye drops.

Surgical treatment includes wound exploration, hemostasis, and hematoma evacuation (5). In an experimental study by Zoumalan et al., ten human cadaver orbits were injected to simulate retrobulbar hemorrhage [82]. The effectiveness of various surgical techniques such as canthotomy, cantholysis, and septolysis was studied. Orbital pressure and intraocular pressure decreased with these techniques; however, the effect was short-lived in the setting of continued simulated hemorrhage (5).

Infection

Another complication that may occur within the first operative week is infection. While rare due to extensive vascularization of the region, infections do occur and need early appropriate antibiotic treatment. The infection rate after blepharoplasty has been estimated to be 0.2% [83]. Case reports of postoperative infection with Group A Beta-hemolytic Streptococcus have been described. Suner et al. presented a case of necrotizing fasciitis after bilateral upper blepharoplasty in a patient with diabetes mellitus (5) [84]. Jordan et al. reported a similar case of necrotizing fasciitis after blepharoplasty. In this case, the patient's son was found to have had impetigo before the procedure (5) [85]. Goldberg and Li described a comparable case in a healthy patient who presented for 30 hours postoperatively, demonstrating that necrotizing fasciitis is initially indistinguishable from cellulitis (5) [86].

While orbital abscess is rare, diagnosis by physical signs is not sufficient; a case of orbital abscess diagnosed with ultrasonography has been described by Rees et al. and the authors recommend utilizing ultrasonography to aid diagnosis [87]. In a case report by Juthani et al., a patient with postoperative orbital cellulitis caused by methicillin-resistant *Staphylococcus aureus* was promptly identified and treated with IV antibiotics. While the Centers for Disease Control and Prevention recommends early antimicrobial prophylaxis and routine surveillance of MRSA, the authors suggest that antimicrobial prophylaxis should be considered in immunocompromised hosts or patients colonized with methicillin-resistant *S. aureus* (5) [88].

To summarize, early postoperative pain and edema should not be taken lightly as these may be early signs of infection. Immediate treatment with intravenous antibiotics, debridement, drainage, and possible hyperbaric oxygen is recommended (5) [79].

Corneal Abrasion

Corneal abrasion is a generally reversible cause of vision changes and is caused by inadvertent damage to the surface corneal epithelial layer. The diagnosis is made by patient symptoms (pain, foreign body sensation, light sensitivity) and is usually apparent immediately after surgery. The diagnosis is confirmed by evaluating the cornea under a cobalt blue light after instillation of fluorescein. Abrasions are treated with ophthalmic antibiotic ointment four times daily and should resolve within 24 hours. Persistent signs and symptoms should prompt ophthalmologic evaluation.

Intermediate Postoperative Period (Weeks 1–6)

Multiple complications can arise during the intermediary time after operation: these include upper eyelid malposition, lower eyelid malposition, corneal exposure, and lacrimal system dysfunction.

Upper Eyelid Malposition

Upper eyelid malposition complications include ptosis and lagophthalmos. For ptosis, no data exists on frequency. Mechanical ptosis is believed to be caused by postoperative edema or ecchymosis, which can resolve with conservative treatment with cool compresses (5). In the observational case series of six patients with postoperative ptosis by Rainin et al., it was hypothesized that myotoxic effects of local anesthetics may lead to

degeneration and subsequent regeneration of muscle fibers of the levator or extraocular muscles, resulting in temporary or permanent muscle weakness (4) [89].

Lagophthalmos is the inability to completely close the eyelids and is usually a transient postoperative complication. Reasons for lagophthalmos include excessive skin removal, trauma to the orbicularis muscle or peripheral seventh cranial nerve, tethering of the eyelids by sutures or Steri-Strips (3 M, St. Paul, MN), and postoperative pain, leading to guarding and incomplete closure. In a study by Kornet al., a retrospective chart review of six patients who had both LASIK and blepharoplasty demonstrates that these patients had increased frequency of dry eye syndrome [90]. The authors warn that patients who have a history of LASIK are at a higher risk of exposure keratopathy, and hence, a thorough preoperative assessment should be performed to minimize complications (4). Lagophthalmos is usually temporary, and lubrication and eyelid massage are advisable in the intermediate postoperative period (5).

Lower Eyelid Malposition

The most commonly reported complication after lower eyelid blepharoplasty is lower eyelid malposition, which may range from mild inferior scleral show as reported by Baylis et al. [91] to severe cicatricial ectropion in 1% of patients as reported by McGraw et al. [92] Predisposing factors include globe proptosis, high myopia, hypoplasia of the malar eminence, and thyroid ophthalmopathy. Treatment options include wound gapping, which allows for granulation of a portion of the eyelid. Topical steroid ointment and massage are employed during granulation to stretch and counter the forces of contraction. Further surgical management is delayed until late postoperative period (5).

Lacrimal System Dysfunction

Epiphora (excessive watering of the eye) can result secondary to dry eye, exposure keratopathy, or an impaired lacrimal pump. Data does not exist on the frequency of this postoperative complication. However, dysfunction often returns to normal. If tearing persists, punctal malposition or canalicular damage should be evaluated further (5) [79].

Strabismus and Extraocular Muscle Disorder

Diplopia is a rare but potentially disabling complication of blepharoplasty. Signs that make diplopia less worrisome are preoperative history of strabismus, monocular diplopia that clears with blinking (suggestive of precorneal tear film abnormality), and intermittent occurrence.

Persistent binocular diplopia requires additional consideration. In a case series, Syniuta LA et al. reported 12 patients who developed acquired strabismus after cosmetic blepharoplasty. This was believed to be from superior oblique muscle palsy or inferior rectus paresis (4) [93]. In a review of 920 blepharoplasties performed in Manhattan, the risk of persistent strabismus was approximately 0.2% (4). The explanation offered for this phenomenon is a Volkmann-type contracture of the extraocular muscles following edema and hemorrhage into the muscle sheath [94].

Late Postoperative Period (After 6 Weeks)

Late postoperative complications include similar complications to the intermediate postoperative period, e.g., ptosis, lagophthalmos, and lower eyelid malposition. Additionally, patients are also at risk for malar Festoons and dry eye syndrome.

Lower Eyelid Malposition

The late lower eyelid malposition has some additional complications when compared to the intermediate postoperative period. Identifying the affected lamella (anterior, middle, or posterior)—usually caused by a deficient tissue or cicatrization—is important in rectifying the issues.

An anterior lamellar deficiency is often the result of transcutaneous blepharoplasty. It is diagnosed by noting lower eyelid movement with opening of the mouth. Surgical repair involves skin grafting. Tarsal suspension may be performed

alone as an indirect secondary procedure in those patients who are unhappy with the thought of skin grafting VI.

Middle lamellar deficiency is a result of adhesions at the level of capsulopalpebral fascia and orbital septum. This may lead to eyelid retraction ("scleral show") of the lateral one-third of the lower eyelid, with associated rounding and inferior displacement of the lateral canthus. Repair involves lysis of adhesions if conservative stretching fails. Shorret et al. describes the "Madame Butterfly" procedure, which addresses the triad of lysis of the middle lamellar cicatrix, lateral canthus reconstruction, and cheek elevation as a successful way of addressing cicatricial lower eyelid retraction [95]. The authors showed in their study that this new procedure can be used to elevate the lower eyelid rather than lower the upper eyelid in cases of postblepharoplasty lagophthalmos with exposure keratopathy, thus allowing for cosmetic and functional repair (5).

Posterior lamellar deficiency usually presents as entropion (an inward folding of the lower eyelid). The repair often involves the addition of posterior lamella. A retrospective study by Li et al. compared 35 patients undergoing grafting of the alloplastic material AlloDerm (LifeCell Corporation, Branchburg, NJ) to 25 patients undergoing hard palate grafting. They did not notice any statistically significant differences between the two materials. They recommended that surgeons weight advantages and disadvantages when choosing the material for lower eyelid spacer graft to prevent contraction of the posterior lamellae (4) [96].

Malar Festoons

Malar festoons occur in patients predisposed to fluid accumulation, e.g., those with a history of thyroid disease, renal failure, sinusitis, and allergies. According to the review article by Lisman, the best method to prevent this complication is early preoperative diagnosis and intraoperative intravenous steroids or postoperative oral steroids for those at the highest risk [97]. Other treatments include diuretics such as furosemide (20–40 mg daily) or hydrochlorothiazide (25–50 mg daily). Although persistent malar festoons can be excised, the success rate is low. If the underlying condition is systemic, eyelid surgery cannot locally correct the problem.

Dry Eye Syndrome

If dry eyes persist even after resolution of early and intermediate sicca symptoms, then this is considered a late postblepharoplasty complication. Dry eyes postblepharoplasty can result from widened palpebral fissures or dermatochalasis.

Initial treatment of dry eye consists of ocular lubrication. Treatment failure should prompt ophthalmologic examination. In a randomized, multicenter, controlled trial, Stevenson et al. described the importance of using antiinflammatory eye drops (such as topical cyclosporine) to improve moderate-to-severe dry eye syndrome (2b) [98]. Punctal occlusion can also be considered.

Vold SD et al. suggested that upper eyelid blepharoplasty should be considered if dry eyes is a result of dermatochalasis. In his retrospective chart review on 141 patients with dermatochalasia, 33 out of 38 patients who underwent upper eyelid blepharoplasty (86.8%) reported subjective improvement in dry eye symptoms (4) [99].

In summary, although blepharoplasty surgery appears straightforward, all surgeons encounter complications. These complications can be minimized by a thorough preoperative evaluation, adequate expectations, meticulous and individualized surgical judgment, and early recognition of adverse events with immediate appropriate interventions.

Alternative and Complementary Procedures

Although there are no options with outcomes comparable to those of blepharoplasty, there are alternative and complementary procedures to correct eyelid cosmesis.

Upper Eyelid

For the upper eyelids, alternatives include surgical brow lift, nonsurgical brow lift (e.g., Botox

injection or hyaluronic acid gel (HAG) injection), or noninvasive brow lift (e.g., Ultherapy). In a retrospective chart review by McElhinny et al. on 16 patients with pseudoptosis, administration of botulinum toxin A injection at low doses (an average of two injection sites with 2 units per site) into the pretarsal orbicularis muscle demonstrated that the drug can raise a relatively ptotic eyelid by weakening the orbicularis oculi muscle, thus shifting the balance toward the eyelid elevators (4) [100]. The average lift is approximately 1 mm. The injection is subcutaneous, as deeper injection raises the risk of inadvertently worsening the ptosis due to levator weakening.

In a pilot study conducted by Mancini et al., eight patients with upper eyelid margin asymmetry relating to relative upper eyelid retraction were injected with hyaluronic acid gel in the upper eyelid. At follow-up, 8 of 8 demonstrated persistent improvement in asymmetry when compared with pretreatment ($p = 0.018$). The authors concluded that hyaluronic acid gel filler may be an effective nonsurgical alternative to improve upper eyelid margin asymmetry in cases of relative upper eyelid retraction (4) [101]. HAG injections administered into the central and lateral subbrow regions can also address postsurgical and/or age-related superior sulcus volume loss [102].

Lower Eyelid

For the lower eyelid, options include injectable fills and resurfacing (laser or chemical peel). Lower eyelid retraction, scleral show, and volume loss of the orbital rim can all be improved nonsurgically using HAG fillers [101, 103].

Complications

Botulinum toxin A and HAG injections also have complications. Complications occurring after administering botulinum toxin injection include injection-related ecchymosis, inadvertent eyelid or eyebrow ptosis, lower eyelid retraction, diplopia, dry eye, and lagophthalmos (5) [104–106].

The literature of complications with HAG injections continues to grow. HAG injection complications include periocular injections are minor and include temporary erythema, edema, and ecchymosis at the injection site; contour irregularities; fluid accumulation; and bluish discoloration secondary to light scattering. If the complications are severe, enzymatic dissolution with hyaluronidase may be necessitated. Some rare, albeit severe complications can also occur, including cutaneous hypersensitivity reactions, vascular occlusions including branch retinal artery occlusion and vision loss, and infections including biofilm-type processes (5) [107].

Postoperative Care

Postoperative management varies greatly according to the surgeon's preference. A recent review by Zoumalan et al. recommended multiple steps, which have been echoed by other review articles [27, 100]. From the immediate postoperative period to 72 hours, patients should use ice-water-soaked gauze or cool packs. Head position should be above the heart level to reduce edema. Patients who develop severe pain should be immediately evaluated to rule out retrobulbar hematomas and infection. Suture removal can be done on postoperative days 5–7.

During the first 1–2 weeks, antibiotic eye drops (i.e., erythromycin) should be prophylactically applied two times per day. If a conjunctival incision is made, antibiotic with or without a steroid component should be applied four times per day. Consistent use of eye drops and lubricating eye ointments are necessary to prevent corneal abrasions during this time (5) [108]. In the first 2 weeks, the patient should also be advised to avoid strenuous activity. Edema may persist 2 weeks postoperatively, and asymmetric residual swelling can continue for 3–6 months.

In conclusion, blepharoplasty is a functional and cosmetic surgical procedure with high patient satisfaction. Preoperative evaluation and setting expectations are crucial. There are various instruments and operative techniques that can be employed during blepharoplasty.

Complications can arise at any time postoperatively. Successful blepharoplasty depends on the surgeon's understanding of facial anatomy and the aesthetic interplay of the eyes and periorbital structures.

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Self-Assessment Questions

1. Patients who underwent refractive surgery within the past 6 months are not suitable candidates for blepharoplasty because of the increased risk of dry eyes and keratopathy. Which of the following is NOT a reason for this increased risk?
   (a) Alteration in corneal sensation
   (b) Alteration in tear production
   (c) Alteration in vision
   (d) Alteration in film formation
   (e) None of the above
2. Which is not a predisposing condition for malar festoons?
   (a) Thyroid disease
   (b) Renal Failure
   (c) Sinusitis
   (d) Allergies
   (e) Angina
3. What are the two methods for lower eyelid blepharoplasty?
   (a) Transconjunctival
   (b) Transcutaneous
   (c) Transcilliary
   (d) a & b
   (e) None of the above
4. Within the first few days postoperatively, what recommendations should a surgeon give to a patient who just underwent blepharoplasty?
   (a) Do not use antibiotic eye drops as these drops can cause inflammation and impede healing
   (b) Light and strenuous activities are tolerated and encouraged
   (c) Use cool packs on eyes and position the head above the heart level to reduce edema
   (d) If severe pain develops, please return immediately to get sutures removed
   (e) All of the above
5. Which choice provides a list of ways to manage excess skin after lower eyelid blepharoplasty?
   (a) Skin pinching, ablative laser, chemical peels, and excision
   (b) Botox, hyaluronic acid fillers, ablative laser, and excision
   (c) Skin pinching, ablative laser, Botox, and hyaluronic acid injection
   (d) Chemical peel, skin pinching, ablative laser, and Botox
   (e) None of the above

Correct Answers

1. c: Patients who underwent refractive surgery within the past 6 months are not suitable candidates for blepharoplasty (2B) [20–22]. This patient population is at risk for development of dry eyes and keratopathy because of the alteration in corneal sensation, tear production, and tear film formation. The goal of LASIK is to improve vision; improved vision does not lead to increased risk of dry eyes or keratopathy.
2. e: Patients who are predisposed to fluid accumulation may develop malar festoons. Conditions that can predispose patients include thyroid disease, renal failure, sinusitis, and allergies. Angina (chest pain) in isolation is not a usual condition that can lead to fluid accumulation in eyelids. Of note, congestive heart failure may cause fluid retention. The best method to prevent fluid buildup is early preoperative diagnosis and intraoperative intravenous steroids or postoperative oral steroids for those at the highest risk. Other treatments include diuretics such as furosemide (20–40 mg daily) or hydrochlorothiazide (25–50 mg daily); however, these medications should be used with caution as they require vigilant monitoring of renal function. The success of malar festoon excision is low.
3. d: Lower eyelid blepharoplasty is based on the more conservative removal of a pinch of skin, as excessive skin removal leads to scleral show (4) [54]. The ideal approach for lower eyelid blepharoplasty is under debate. There exist two distinct methodologies: (1) external transcutaneous incision and (2) internal transconjunctival incision. Transcilliary is not one of the methods for lower eyelid blepharoplasty.
4. c: From the immediate postoperative period to 72 hours, patients should use ice-water-soaked gauze or cool packs. The head position should be above the heart level to reduce edema. Antibiotic eye drops are recommended twice a day for prophylaxis. Consistent use of lubricating eye drops and ointment is necessary to prevent corneal abrasions during this period. Strenuous activities are discouraged. If the patient develops severe pain, then they should be evaluated for possible retrobulbar hematomas or infection, not to get their sutures removed.
5. a: There are multiple ways to manage excess skin after lower eyelid blepharoplasty; this includes skin pinching, ablative laser, chemical peels, and skin excision in severe cases. The difficulty lies in deciding if the excess skin needs to be removed and how much should be excised to optimize the patient's results. Botox and hyaluronic acid fillers are not ways to manage excess skin.

Rhytidectomy

28

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Abstract

The goal of the facelift, or rhytidectomy, is to restore the anatomical changes which occur through the natural process of aging. There are a variety of surgical techniques the cosmetic surgeon can utilize to accomplish this restoration. These rejuvenating procedures can be performed in the ambulatory, office-based setting with local anesthesia and optional sedation.

Keywords

Rhytidectomy · Facelift · Suspension suture SMAS · Indications · Technique · Safety Efficacy

Introduction

The goal of the facelift, or rhytidectomy, is to restore the anatomical changes which occur through the natural process of aging. There are a variety of surgical techniques the cosmetic surgeon can utilize to accomplish this restoration. These rejuvenating procedures can be performed in the ambulatory, office-based setting with local anesthesia and optional sedation.

There are numerous rhytidectomy techniques that produce excellent results. Each surgeon must adopt a technique which is best suited for his or her patient. Ideally, the technique should be safe, consistent, reproducible, and applicable to a range of anatomic defects. The surgeon must also have the versatility to modify his or her technique to the needs and desires of each patient.

It is important for both practicing physicians and patients to understand the benefits of the various procedures and techniques as well as how they compare in both safety and efficacy.

Indications and Technique

The changes that occur in the aging face are multifactorial. This process is characterized by loss of skin elasticity, fat and bone resorption, and loss of muscle tone and volume. Although the facial skeleton is responsible for the morphologic basis of aging, boney augmentation is limited, which leaves the soft tissue as a target for facial rejuvenation. Soft tissue ptosis leads to deep creases of the aging face and represents the target of surgical correction. As facial soft tissue ptosis develops with aging, the vector of descent is primarily downward.

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Current surgical management seeks to reverse this descent often through elevation of the superficial musculoaponeurotic system (SMAS), which underlies the skin and subcutis and overlies the muscle and deep neurovascular structures. There have been a large number of surgical facelift techniques described ranging from the skin-only facelift to a variety of procedures that address the SMAS and various other deep-plane techniques. Absorbable and nonabsorbable suspension sutures have also been used to achieve tissue lifting via a minimally invasive approach.

A number of techniques are employed to specifically address the particular patient's needs; these are summarized in Table 28.1. The classic subcutaneous lift involves subcutaneous undermining of the face with advancement and excision of excess skin to achieve the effective lift [1]. This procedure requires minimal operative time with few complications and a hastened recovery; however, the lift may not be as durable as it does not address the underlying issues of the aging face.

The basic approach to lifting the SMAS is achieved via SMAS plication or imbrication [2]. Using this technique, the SMAS is folded upon itself and secured without additional undermining. A primary advantage to this approach is that there are minimal complications as the sub-SMAS structures including the facial nerve are left undisturbed and intact. The lateral SMASectomy approach popularized by Baker [3] is similar to plication in that no undermining of the SMAS is performed. For the lateral SMASectomy, a strip of the SMAS overlying the parotid gland is first resected. Using absorbable sutures, the resected edges of the SMAS are joined which elevates the lower portions of the SMAS. With Baker's technique, the facial nerve is protected by the parotid gland at the site of SMAS resection. More extensive rhytidectomies are performed by creating a limited SMAS flap (conventional SMAS facelift) or an extended SMAS flap. The creation of the SMAS flap is in addition to the skin flap and is separately repositioned, potentially in multiple vectors. This procedure may be referred to as a "deep-plane" rhytidectomy and requires careful localization and avoidance of deep neurovascular structures, including the facial nerve and its branches. Barton also described the "high SMAS" technique [4], which is characterized by suspending the SMAS more superiorly above the zygomatic arch. Dissection of a composite flap transitions from sub-SMAS to a subcutaneous plane above the zygomatic major, helping to efface the nasolabial fold. This procedure ensures release of the zygomatic ligaments allowing a true superior pull of the malar and zygomatic soft tissues.

The continued desire for a less invasive facelift prompted the development of an even more minimally invasive approach than the standard SMAS plication facelift. These so-called short-scars or mini-lifts include procedures such

Table 28.1 Facelift techniques

Facelift technique	Essential features	Comments
SMAS plication	Skin flap created. SMAS is folded on itself with no undermining	Straightforward. Limited anesthetic requirement. Minimal risk of nerve injury
Lateral SMASectomy	Skin flap created. SMAS overlying parotid is resected and tightened. No SMAS undermining	Possibly more effective contour change. Minimal risk of nerve injury
SMAS lift (extended/conventional)	Skin flap created. Separate SMAS flap created. Flaps independently advanced	Benefit is uncertain. Extended SMAS lift enables greater flap mobility
S-lift and variants	Skin flap created. No SMAS undermining. SMAS is plicated with purse-string-type suture	Similar to SMAS plication. Limited anesthetic requirement
High SMAS	Skin flap created. Composite flap from sub-SMAS to subcutaneous plane with superior vector advancement	Release of zygomatic ligaments allowing superior pull
Subcutaneous lift	Skin flap created only. Advancement and excision of excess	Straightforward. Minimal complication. Less durability

as Saylan's "S-lift" [5] and Tonnard's "minimal-access cranial suspension" [6]. The common features of these approaches are a limited facelift incision, conservative skin flap creation, and the use of sutures in a loop configuration to plicate the deeper tissues. When compared to the traditional rhytidectomy procedure, two clear advantages of the short-scar rhytidectomy procedure are the quicker recovery time and the potentially decreased expense to the patient.

Preoperative Evaluation

Preoperative assessment of patients undergoing facelift involves a thorough review of particular aspects of the history and physical exam. Specific preoperative medical evaluation and associated data are summarized in Table 28.2.

Age

Many facelift patients are elderly but may not have apparent or concerning comorbidities. In a multicenter, prospective cohort study of 11,300 patients, Gupta et al. [7] (1b) did not find a significant difference in complication rates for older patients who were 70 years of age and older. In a retrospective review of 216 patients, those older than 65 years were compared with a group younger than 65 years [8] (3b) which also demonstrated no difference in major complications (2.9% vs. 2.0%, $p = 0.65$) or minor complication rates (5.9% vs. 6.1%, $p = 0.99$). The study may have been underpowered, but the age differential was significant (average age of 70.0 years vs. 57.6 years). Becker et al. also demonstrated the safety of facelifts in patients older than 75 with similar complication rates to matched controlled younger patients [9] (3b).

Table 28.2 Preoperative evaluation

Evaluation	Evidence	Quality of evidence
Age	Equal safety in older (>65 and >70) vs. younger age groups	B
Body mass index	Body mass index >25 had increased risk of hematoma and infection	C
Smoking	Smoking associated with complications, more likely minor	B
Hypertension	Hypertension may increase risk of hematoma	C
Diabetes	Diabetes is a risk factor for complications in other surgical procedures, but may not affect facelifts	C
Aspirin	Aspirin use is associated with hematoma risk	C
Infection risk	Infections in facelifts are very rare	D

Body Mass Index

Increased body mass index not only places a patient at greater risk of developing comorbidities but also increases surgical morbidity. A 2012 retrospective review of 620 patients revealed that a body mass index greater than 25 resulted in an increased complication rate (9.5% vs. 4.7%) [10] (3b). A larger 2016 prospective cohort study reported a body mass index greater than 25 as a significant risk factor for infection with a relative risk of 2.78 [7]. However, this study only had a minority of patients having a body mass index greater than 25 (38.5% vs. 71.1% in the previous mentioned study [10]).

Smoking

While preoperative smoking cessation is recommended for all cosmetic procedures, there are no established guidelines. Smoking creates an environment of relative tissue hypoxia and delayed wound healing. The incidence of facelift skin flap necrosis was found to be 12.5 times greater in smokers than in nonsmokers [11] (4). Another prospective study confirmed a strong association between active smoking and skin slough in facelift patients [12] (2b). Nonsmokers had a 5% incidence of superficial skin slough compared with active smokers who experienced a 19.4% incidence of skin slough. Another large retrospective study in 2001 found an increased hematoma rate

in smokers undergoing facelift [13] (2b). Conversely, a larger prospective cohort study did not demonstrate smoking to be a significant risk factor for major complications (2.0% vs. 1.8%, $p = 0.4$) [7]. The authors attribute this to caution exerted by surgeons when deciding to operate on patients who smoke. Additionally, many of the complications attributed to smoking such as wound healing and infections were not as easily evaluable in their database.

Hypertension

Multiple studies have reported a higher incidence of hematoma in facelift patients with perioperative hypertension. In a retrospective study of 985 patients undergoing facelift by a single surgeon, the incidence of hematoma decreased from 8.7% to 4.6% after a strict perioperative antihypertensive regimen was initiated [14] (4). Another retrospective review of 1078 patients demonstrated that preoperative systolic blood pressure above 150 mm Hg increased the risk of hematoma 3.6 times ($p = 0.02$) [13]. Hypertension again showed a strong tendency to develop hematoma (8.2% vs. 3.5%, $p = 0.017$) [15] (4). However, hypertension was not found to be an independent predictor of hematoma on multivariate analysis ($p = 0.19$).

Diabetes

Previous studies suggest that diabetes mellitus in patients undergoing other surgical procedures may increase the risk of infection and decrease the healing capacity. In their prospective cohort study, Gupta et al. [7] did not show diabetes to be a significant risk factor for complications for patients undergoing a facelift. Of the 303 diabetic patients, 3.3% had a complication compared to 1.8% among nondiabetics ($p = 0.07$).

Aspirin

Grover et al. found that aspirin use held a 2.3-fold increase in risk ($p = 0.04$) for hematoma in their retrospective review of 1078 patients [13]. Aspirin use was also associated with postoperative hematoma formation in a single-center study of 620 patients [15].

Infection Risk

Infections in facelift surgery are rare, and thus the studies evaluating their prevention and treatment are poorly powered. A 2015 systematic review performed by Dauwe et al. [16] (3a) evaluated topics of bacterial decolonization, prophylactic antibiotics, and body temperature regulation. However, recommendations were based on expanded criteria to studies evaluating surgical site infection in clean cosmetic procedures as well as expert opinion rather than facelift-specific data-driven studies.

Safety

Studies evaluating the safety of facelifts are summarized in Table 28.3.

A large prospective cohort study of 11,300 patients undergoing facelift between 2008 and 2013 assessed the safety and preoperative risk factors for complication [7]. Gupta et al. found that facelifts had a 1.8% complication rate, similar to the 2% rate associated with other cosmetic surgeries. The most common complications encountered were hematoma (1.1%) and infection (0.3%). As a result, the authors concluded that rhytidectomy is a very safe procedure.

A meta-analysis of 41 studies published between 2001 and 2013 found a 1.8% incidence of hematoma following facelift [17] (2a). The authors performed meta-analyses for subsets of the three most popular facelift techniques (SMAS flap, SMAS plication, and deep-plane) and found no significant difference in hematoma rates. However, the study demonstrated significantly less hematoma formation following limited incision facelift compared with non-limited techniques. The authors note that this reduction is not surprising given the reduced dissection, but note that there are many other considerations when choosing a specific facelift technique.

Table 28.3 Summary of studies evaluating rhytidectomy safety

Study	Type	Evidence	Quality of evidence
Mustoe et al. [17]	Meta-analysis, 41 studies	1.8% incidence of hematoma	B
Gupta et al. [7]	Prospective cohort, 11,300 patients	1.8% complication rate; hematoma (1.1%), infection (0.3%)	B
Tanna et al. [18]	Retrospective review, 1000 short-scar facelifts	<1% risk of poor scarring	C
Grover et al. [13]	Retrospective cohort, 1078 consecutive facelifts	4.2% incidence of hematoma	C
LeRoy et al. [19]	Retrospective cohort, 6166 consecutive facelift	Infection requiring admit was 0.18%, no identifiable risk factors	C
Rees et al. [20]	Retrospective cohort, 1236 consecutive facelifts	1.86% incidence of hematoma	C

Several other retrospective cohort studies and case series assessing safety and efficacy have also been published. Tanna and Lindsey [18] (2b) have published one of the largest series of short-scar rhytidectomies in which they assessed their experience of 1000 short-scar rhytidectomies. In this study, all patients safely underwent the procedure with local anesthesia. An additional one third of patients also required oral sedation but none required general or intravenous anesthesia. Postoperative suture extrusion was the most frequently observed complication occurring in 148 patients, followed by hematomas in 10 patients. Hyperpigmentation and hypertrophic scarring occurred with an incidence of less than 1%, and there were no episodes of nerve injury, skin flap necrosis, alopecia, or parotid injury. Although the cosmetic results from this series were not systematically analyzed, the authors assert that their patients were pleased with their results. They concluded that the short-scar rhytidectomy is an excellent option for patients with mild to moderate aging of the face.

Grover et al. published a retrospective study of 1078 consecutive facelifts by two surgeons to determine associations with hematoma formation [13]. The multivariate analysis found a 4.2% hematoma rate. They found many significantly associated factors (hypertension, sex, aspirin use, smoking) that are discussed previously in the preoperative section of this chapter. A factor that was not significant was the type of facelift technique performed.

Another retrospective study evaluated infection rate in 6166 consecutive facelifts performed by 35 surgeons at one institution [19] (2b). The authors found no associations regarding medical history, use of perioperative antibiotics, drains, technique, or surgical equipment. The incidence of infections requiring hospital readmission was 0.18%. Although the study is limited by bias, the study included a relatively large sample size.

Rees et al. published a retrospective review of 1236 consecutive facelifts performed by 50 surgeons at one institution [20] (2b). This study found an overall hematoma incidence of 1.86%. SMAS plication had a higher hematoma rate than moderate or extensive SMAS dissection ($p = 0.002$) but became nonsignificant when controlled for the performing surgeon. Age, preoperative tests, medical history, gender, perioperative medications, blood pressure, type of anesthesia, or number and combination of procedures did not independently affect the incidence of hematomas.

In addition to larger retrospective series assessing facelifts for overall safety and efficacy recently, there have been multiple case series and cohort studies that have examined more specific features of facelifts. These include studies that describe and test novel techniques, improvements upon existing methods, and methods to avoid potential complications.

Technique and Effectiveness

Due to the large variety of procedures and surgeon variations, it is not surprising that the literature is inconclusive regarding outcomes as

determined by the technique. Due to the elective nature of the facelift procedure, patients are reluctant to be randomized to a given treatment modality. The private practice settings in which many of these procedures are performed and differences in operative technique across surgeons have impeded the completion of multiple large studies and meta-analyses.

A systematic review performed by Chang et al. [21] (2a) conducted a literature search from 1950 to 2009 and found ten articles in which comparisons of techniques were performed. No conclusions demonstrating superiority of one technique over another were made. Overall, the authors concluded that there exist no quality data that have shown better efficacy of one facelift technique over another and noted a need for higher-quality studies in the future.

One study published nearly 20 years ago randomized 21 patients to undergo limited/conventional SMAS facelift on one side of their face and extended SMAS/composite rhytidectomy on the other [22] (3b). Patients were then followed for 1 year postoperatively. The results were photographed and assessed by three independent facelift surgeons, the operating surgeons, and the patients. At 24 h, 6 months, and 1-year follow-up, neither the independent surgeon evaluator nor the operating surgeon nor the patient could detect a difference in the facelift result between the two sides. The results of this study support the use of less invasive techniques. However, differences could become evident with longer postoperative follow-up.

In a similar although nonrandomized study, Prado et al. [23] (4) compared the outcomes of minimal access cranial suspension to lateral SMASectomy. There was no difference in cosmetic results between the two techniques at 1-month and 2-year follow-up. However, it was noted that SMASectomy required a longer surgery time, but the patients experienced less pain. More than half of the cases needed a revisionary tuck procedure in both groups, and the long-term persistence of efficacy was not compared.

The largest study was a retrospective analysis by Kamer and Frankel of 634 patients comparing a deep-plane technique to a conventional SMAS technique performed by a single surgeon [24] (3b). They evaluated the need for a secondary tuck procedure as a marker for a less efficacious and less optimal facelift. The revision rate was significantly lower with the deep-plane technique (11.4% vs. 3.3%; $p = 0.0001$) than the conventional SMAS technique.

Perioperative Treatment, Additional Complications, and Avoidance Strategies

A variety of complications are seen in association with rhytidectomy. These include hematoma formation, infection, neuropraxia, paralysis, skin necrosis, disfiguring scar, and alopecia. There are few studies evaluating peri- and postoperative treatments of complications which are summarized in Table 28.4.

Alopecia

Temporal alopecia resulting from traumatized hair follicles is an unpleasant complication that detracts from the final appearance post-rhytidectomy. In an attempt to prevent temporal hair loss, Eremia et al. [25] (3b) studied the use

Table 28.4 Complications and treatment

Complication	Therapy	Quality of evidence
Alopecia	Post-rhytidectomy temporal alopecia can be avoided with the use of minoxidil	C
Facial edema	Perioperative steroid administration does not reduce facial edema following rhytidectomy	C
Hematoma	Fibrin glue may decrease hematoma formation; however, its clinical relevance is not proven Surgical drains do not decrease hematoma incidence	C
Nerve injury	Nerve injury is uncommon and the majority of injuries resolve spontaneously within 6 months	C

of minoxidil. In their series, 60 women underwent either standard SMAS/flap technique or plication and were treated with either 2% or 5% topical minoxidil for 2 weeks prior to surgery and 4 weeks postoperatively. Subjects were followed for 3–6 months. The use of minoxidil resulted in a 0% incidence of permanent alopecia and a 1.7% incidence of temporary alopecia (one patient developed alopecia that resolved upon resuming 5% minoxidil). In comparison, historical controls [26] reported the incidence of temporary alopecia at 8.4%. Therefore, minoxidil appeared to provide a protective benefit when used before and after facelift. However, since the historical controls were from 1977, it is uncertain to what extent the two groups of patients were comparable.

Tissue Sealants

Postoperative hematomas can cause facial edema, tissue ischemia, and hyperpigmentation which may necessitate placement of drains. Drain placement is not without risk as drains can serve as a portal of entry for bacteria into the wound leading to infection and the potential for scarring. It is therefore desirable to prevent hematomas intraoperatively. Fibrin glue has been widely studied in the plastic surgery community for this purpose. Zoumalan and Rizk [27] (3b) studied whether spraying fibrin glue underneath the flap prior to closure reduced hematoma formation. In this nonrandomized study of 600 patients, a significant difference ($p = 0.01$) in hematoma formation was detected among patients who did and did not receive fibrin glue. Patients who did not receive fibrin glue developed hematomas at a rate of 3.4% compared to 0.4% in those who did receive the fibrin glue. In this study, all the hematomas from both groups were minor, managed with needle aspiration, and did not require repeat operation.

A recent meta-analysis evaluating the use of tissue sealants in facelifts analyzed ten randomized trials of which three were found to be suitable for analysis as randomized, prospective, blinded trials [28] (2a). Although not statistically significant, the use of tissue sealants demonstrated a strong trend toward reduction of drainage at 24 h postoperatively and ecchymosis at 1 week. Conversely, tissue sealants did not decrease postoperative edema. These data combined with the series published by Zoumalan and Rizk [27] strengthen the argument for routinely using tissue sealants intraoperatively during facelift procedures.

Surgical Drains

In a prospective, randomized, controlled study involving 50 patients in which drains were used on one side but not on the other, there was no significant difference in hematoma formation, but there was a reduction in ecchymosis ($p = 0.005$) [29] (3b).

Edema

A prospective, randomized study by Owsley et al. [30] (3b) sought to ascertain whether the use of a steroid medication could reduce facial edema following facelift surgery. Fifteen patients were treated with methylprednisolone 500 mg preoperatively followed by a 6-day tapering course. When compared to 15 patients who did not receive steroids, there was no difference in facial edema. There is potential risk for decreased wound healing encountered in patients on steroids. Based upon equivocal results, steroids may not be routinely recommended as prophylaxis for facial edema reduction.

Nerve Injury

Historically, one of the more concerning complications of rhytidectomy has been nerve injury. The great auricular nerve is the most commonly injured nerve, occurring in 1–7% of procedures [31] (3b). Other nerves at risk include the lesser occipital nerve, branches of the facial nerve (marginal mandibular and temporal branch with incidence of 0.3–2.6%), and spinal accessory nerve.

The distinction between marginal mandibular nerve pseudoparalysis and true nerve injury should be made with the appropriate physical exam, as cervical nerve injury may masquerade as pseudoparalysis of the marginal mandibular nerve in 1.7% of surgeries [32] (4). Fortunately, more than 80% of facial nerve injuries (and the majority of sensory nerve injuries) from rhytidectomy are expected to spontaneously resolve within 6 months [31].

Alternative Procedures and Modifications

Suspension Suture Techniques

One variant of the limited facelift uses suspension sutures to achieve tissue lifting via a minimally invasive approach. Placement of these sutures without the need to make an incision is thought to be less time intensive and also potentially safer than more conventional facelift procedures. However, there are sparse data confirming the safety, efficacy, and longevity of suspension suture lifts. Table 28.5 summarizes publications that evaluated suspension sutures.

Villa et al. [33] (3a) recently reviewed the literature to evaluate the clinical efficacy and longevity of various types of barbed sutures, overall safety, and the risk of serious adverse events including injury to the facial nerve. Only six studies met their inclusion criteria for analysis. The authors concluded that the clinical efficacy, peak correction, and longevity of effect were inconclusive. Adverse events did occur although they were noted to be mostly minor and self-limited. They concluded that objective outcome measures and long-term follow-up data are not available in a systematic manner in the currently published literature.

A retrospective study by Kaminer et al. [34] (4) assessed the long-term patient satisfaction

Table 28.5 Recent studies on suspension suturing techniques

Type of suture	Reference	Quality of evidence	Results/conclusion
Contour lift—barbed, anchored, unidirectional, nonabsorbable	Kaminer et al. [34]	C	The barbed suture lift provides moderate long-term improvement for facial laxity up to 16 months post-procedure
	Garvey et al. [38]	C	42% underwent secondary procedure at 8 months, 31% required revision at 9 months, and 11% required removal of threads. Suspension suture technique is limited
Silhouette suture—a 3-0 polypropylene suture with ten absorbable hollow cones equally interspersed with knots	Bisaccia et al. [36]	C	In appropriately selected patients, excellent correction of ptotic facial and neck tissues was achieved
Monogram suture—2-0 absorbable monofilament with five to nine equally spaced knots through which 7–9-mm bits of similar suture material with 0 thickness are secured	Eremia and Willoughby [37]	C	In conjunction with open facelifts, excellent results are achieved at 1 year. Results from pure suspension lift were lost in 80–100% of patients after 1 year
2-0 Polypropylene— using a Khawaja-Hernandez or Keith needle	Khawaja and Hernandez-Perez [39]	C	Nearly 80% of patients were satisfied with their results at 1 year
Various barbed sutures	Villa et al. [33]	C	Clinical efficacy, peak correction, and longevity of effect were inconclusive. Adverse events are minor and self-limiting
Aptos Thread and 2G	Sulamanidze et al. [35]	C	All complication incidence was < 3%. Results were inconsistent and had early relapse of deformity

and longevity of improvement following a lifting procedure utilizing barbed, anchored, unidirectional, and nonabsorbable sutures. In this series, both patients and independent dermatologists assessed the results after 6 months. Interestingly, patients rated their average satisfaction as 6.9 on a scale of 1–10, while independent scorers rated the average improvement as 4.6 out of 10. This discrepancy prompted the authors to question what defines a successful operation. However, based upon patient satisfaction scores, they advocated the continued use of suspension sutures.

Sulamanidze et al. [35] (3a) performed a large retrospective review of 12,788 face and neck thread lift procedures from 1998 to 2010. The study of 6098 patients showed inconsistent results and early relapse of deformity with the Aptos Thread and Aptos Thread 2G methods. All complications were less than 3% and included thread visibility or migration, skin dimpling, hypo- and hypercorrection, transient paresthesias, and a small number of cases of injury to underlying structures. The incidence of complications correspondingly decreased in the latter part of the series as new devices were developed, and the technique was refined. Of note, the authors of this study are also the co-owners of all patents held on Aptos products.

In a case series by Bisaccia et al. [36] (4), the Silhouette suture (a 3-0 polypropylene suture with ten absorbable hollow cones equally interspersed with knots) is described for the elevation of sagging tissues of the face and neck. Patients who underwent rhytidectomy with this procedure experienced improvement leading the authors to conclude that the Silhouette suture will become a useful addition to the field of facial rejuvenation. However, this data was obtained using nonrandom selection techniques and further validation is warranted. A similar product now available in the United States is the Silhouette InstaLift suture (Sinclair Pharmaceuticals, Irvine, CA) which is entirely absorbable, made of polyglycolide/L-lactide.

Eremia and Willoughby [37] (3b) published a controlled study evaluating the use of the Monogram suture technique. The Monogram suture is a 2-0 absorbable monofilament; in the procedure, five to nine equally spaced knots are placed to secure 7–9-mm portions of similar suture material of 0 thickness. In this comparative study, one group of patients had suspension suture elevation with no skin excision, and the other group had suspension suture elevation in combination with conservative open surgical facelifts. Patients for whom the Monogram suture was used in conjunction with open facelifts experienced excellent results that persisted for up to 1 year. Conversely, the benefits from the pure suspension lift were lost in 80–100% of patients after the 1-year mark.

In another case series by Garvey et al. [38] (4), a single surgeon's experience with 72 patients undergoing thread lifts was retrospectively reviewed. Minor complications were common and usually self-limited. Ultimately, 42% of patients underwent a secondary procedure following primary threadlift after an average of 8.4 months, while 31% required revision surgery for cosmetic reasons after an average of 8.7 months. Finally, 11% of patients required removal of palpable threads. This study highlights the limitations of this technique and its high rates of revision surgery.

Khawaja and Hernandez-Perez [39] (4) published a series of 19 patients who underwent a transcutaneous facelift. In their procedure, a 2-0 polypropylene suture was anchored to the periosteum of the temporal bone which was then utilized to pull up the SMAS. The follow-up ranged from 6 months to 1 year postoperatively. Based upon a patient satisfaction survey, nearly 80% of patients were pleased with their results.

Minimally Invasive Techniques for Particular Facial Subunits

Traditional facelift procedures address aging associated with the entire face. However, such invasive procedures may not be appropriate for younger patients with specific concerns. Furthermore, avoiding the possible morbidity of an invasive operation is extremely desirable. Limited facelift procedures aimed at addressing

specific facial subunits have been developed to provide patients with tailored results while decreasing overall complications.

In 2004, authors from Columbia University published their 2-year experience [40] (4) with 30 patients who underwent a minimally invasive facelift procedure to correct mid-facial aging. Although the results were not systematically analyzed, the authors asserted that most patients were pleased with the results, and maintenance of correction achieved with this technique persisted for up to 2 years. Similarly, Fulton et al. [5] (4) published a series of 23 patients who underwent an S-lift facelift utilizing purse-string sutures placed in the SMAS from the zygoma to the jawline. They concluded that after a follow-up period of 6 months, there were no episodes of skin necrosis or patients requiring repeat correction.

For patients with specific desires pertaining to upper facial rejuvenation, a subcutaneous brow and forehead lift may be preferable. Niamtu [41] (4) recently published a series of 50 female patients who underwent such a procedure. After 30 months, there were no reported cases of relapse, and only two patients experienced flap necrosis. However, it is worth noting that the results were not well categorized or systematized.

Combined Procedures

In a multicenter, prospective cohort study of 11,300 patients, Gupta et al. [7] found that the majority of facelifts (57.4%) were performed in combination with other aesthetic surgery procedures. The most often combined procedures included blepharoplasty, brow lift, and liposuction. Combined procedures were found to be a significant risk factor for overall complications with a relative risk of 1.44. The overall major complication rate increased from 1.5% with facelift alone to 2.0% with one additional procedure and 2.5% with additional procedures on more than two body regions. An additional procedure was also an independent risk factor for postoperative infection with a relative risk of 3.52. The increase in complication rate in combined procedures remained less than the sum of the complication rate of each procedure separately. However, careful consideration should be taken given the increase in major complications following elective surgery.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE). See Tables 28.1, 28.2, 28.3, 28.4 and 28.5.

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Self-Assessment Questions

1. Which of the following is true of the SMAS plication?
   (a) It must be performed under general anesthesia.
   (b) It involves extensive dissection and mobilization of the sub-superficial musculoaponeurotic system structures, such as the facial nerve.
   (c) It is a complicated and difficult to learn procedure.
   (d) The procedure relies upon folding the SMAS upon itself and securing it without additional undermining.
2. What distinguishes the SMAS plication from the lateral SMASectomy?
   (a) In the lateral SMASectomy, there is undermining of the SMAS.
   (b) In the lateral SMASectomy, a strip of the SMAS overlying the parotid gland is resected.
   (c) In the lateral SMASectomy, the facial nerve is divided.
   (d) In the lateral SMASectomy, no effort is made to elevate the lower portions of the SMAS.
3. Which of the following is the most likely to occur after rhytidectomy?
   (a) Infection
   (b) Hematomas
   (c) Hyperpigmentation and hypertrophic scarring
   (d) Alopecia
4. Which of the following is the most significant for increasing a patient's risk for post-rhytidectomy hematoma?
   (a) Increasing age
   (b) Diabetes
   (c) Hypertension
   (d) Type of facelift technique
5. What methods have been described to prevent temporal alopecia resulting from traumatized hair follicles following rhytidectomy?
   (a) Either 2% or 5% of topical minoxidil for 2 weeks prior to surgery and 4 weeks postoperatively
   (b) Phototherapy
   (c) Ethanol injection
   (d) Topical steroids

Correct Answers

1. d: The procedure relies upon folding the SMAS upon itself and securing it without additional undermining. When performing the SMAS plication, the SMAS is folded upon itself and secured, without additional undermining. A primary advantage to this approach is that there are minimal complications as the sub-SMAS structures, including the facial nerve, are left undisturbed and intact. This is a straightforward procedure with limited anesthetic requirements.
2. b: In the lateral SMASectomy, a strip of the SMAS overlying the parotid gland is resected. The lateral SMASectomy approach is similar to plication in that there is no undermining of the SMAS. With the lateral SMASectomy, a strip of the SMAS overlying the parotid gland is resected. Effort is made to elevate the lower portions of the SMAS. The facial nerve is protected by the parotid gland in the area of SMAS resection.
3. b: Hematoma. Postoperatively after rhytidectomies, hyperpigmentation, hypertrophic scarring, infection, and alopecia are all relatively rare complications.
4. c: Hypertension. Multiple studies have reported a higher incidence of hematoma in facelift patients with perioperative hypertension. Studies include those by Grover et al., Baker et al., and Abboushi et al.
5. a: Either 2% or 5% of topical minoxidil for 2 weeks prior to surgery and 4 weeks postoperatively. Eremia and colleagues studied the use of minoxidil. Subjects were followed for 3–6 months. The use of minoxidil resulted in a 0% incidence of permanent alopecia and a 1.7% incidence of temporary alopecia. In comparison, historical controls reported the incidence of temporary alopecia at 8.4%. Therefore, minoxidil appeared to provide a protective benefit when used before and after facelift.

Genital Rejuvenation

29

Min-Wei Christine Lee

Abstract

Female rejuvenation includes a range of functional and aesthetic procedures in the female genital region. More than half of the female population over age 50 suffers from stress urinary incontinence or some degree of uterine or pelvic organ prolapse. Almost all postmenopausal women have vaginal atrophy, dryness, dyspareunia, and other symptoms associated with menopause. Many of the symptoms associated with these common gynecologic disorders can be effectively and safely treated with lasers and other noninvasive devices. This is a comprehensive review and assessment of the scientific evidence regarding procedure selection, effectiveness, and safety of the available procedures in the area of female genital rejuvenation.

Keywords

Female rejuvenation · Genital rejuvenation Vaginal rejuvenation · Women's health Feminine health · Feminine wellness · Female health · Female wellness · Lasers · Erbium:YAG Carbon dioxide · CO_2 · Fractional erbium:YAG Fractional CO_2 · Radiofrequency · Nonablative Noninvasive

The aging of tissue generates laxity, and the vaginal mucosa is no exception. Age, vaginal deliveries, weight fluctuations, hormonal changes, instrumentation, and surgeries in the vaginal canal can cause disorders in the vaginal mucosa, producing a sensation of permanent dilation. This can also lead to damage to the pelvic floor which can result in uterine or pelvic organ prolapse and stress urinary incontinence (SUI).

Vaginal relaxation syndrome (VRS) is a quite common medical condition described as a loss of the optimal vaginal structure and is usually associated with vaginal child delivery and natural aging. Multiple pregnancies and deliveries contribute to a worsening of VRS, as well as the onset of menopause, which causes a decline in hormone levels and vaginal atrophy. VRS results in a decrease or loss of sexual gratification [1].

The genitourinary syndrome of menopause (GSM) is the new definition for the variety of menopausal symptoms associated with physical

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changes of the vulva, vagina, and lower urinary tract and is caused by estrogen deficiency. The genitourinary syndrome of menopause (GSM), caused by estrogen deficiency, is responsible for the appearance of symptoms affecting qualify of life, such as vaginal dryness and/or dyspareunia or urinary symptoms, and affects at least 50% of postmenopausal women [2].

Female stress urinary incontinence (SUI) is a highly prevalent lower urinary tract dysfunction, most commonly affecting middle-aged and elderly women [3]. Although the etiology of SUI is not fully understood, the risk factors for the condition include congenital factors, pregnancy, childbirth, hypoestrogenism, cognitive impairment, obesity, and advanced age. Its prevalence has been estimated to be as high as 40% in European countries [4–6] and 50% in the USA [7].

There are many possible nonsurgical and surgical therapies for SUI; however, TVT (tension-free vaginal tape) has been considered the gold standard in SUI [8, 9]. Initial therapy involves nonsurgical options such as behavioral changes in terms of diet reduction for overweight patients, smoking cessation, bladder training, and pelvic floor muscle training (PFMT). Although good results can be achieved with PFMT, long-term improvement is hard to maintain due to lack of training and poor patient persistence. Mechanical devices such as pessaries, vaginal cones, and urethral obturators and electrical stimulation play an integral part in the management of these patients. Drug therapy also may reduce SUI.

Surgical procedures are more effective for SUI than nonsurgical therapies, but are sometimes associated with adverse effects and complications, such as bleeding, bladder perforation, urethral injury, infection, groin pain, and a sexual abstinence period of 6 weeks after surgery. It also has risk of complications of failure of sexual function, discomfort during intercourse, creating excessive obstruction of the lower urinary tract, neuritis of the obturator nerve, and postoperative restrictions. In addition, the recurrence rate for urinary incontinence after surgery ranges from 5.7% to 30–40% [10].

Noninvasive therapies such as electrical stimulation, radiofrequency, and laser photothermal therapy have been replacing surgical treatment as safer treatment options. Studies have demonstrated collagen remodeling effects of laser irradiation to help strengthen the pelvic floor supportive structures by heating pelvic floor tissue. Many studies have shown erbium:YAG laser therapy to be an effective and safe option for different gynecological applications, such as SUI, vaginal relaxation syndrome, and vaginal atrophy (A) [11–14].

In terms of evaluating effectiveness of laser procedures, the areas of genital rejuvenation can be broken down into three distinct areas: [15] vaginal atrophy and laxity, [16] stress urinary incontinence, and [1] uterine/pelvic organ prolapse. The laser procedures can further be categorized as follows: noninvasive vs. invasive. The only noninvasive laser procedure on the market is a nonablative fractional erbium:YAG laser (Intimalase and Incontilase, Fotona). All the other laser wavelengths are invasive and include fractional carbon dioxide (CO_2), fractional ablative erbium:YAG, and fractional ablative erbium:YAG combined with nonablative 1470 diode laser. Devices using radiofrequency are also noninvasive (Table 29.1).

Table 29.1 Summary of vaginal lasers on the market grouped by mechanism of action

Nonablative fractional erbium:YAG (250-msec long pulse duration)
Intimalase and Incontilase (Fotona, Dallas, TX) (the only laser with this unique wavelength)
Erbium:YAG (fractional ablative erbium:YAG)
Petit Lady (Lutronic, Korea)
Juliet (Asclepion, Germany) (distributed by Cutera)
DiVa (Sciton, Palo Alto, CA) (fractional ablative Er:YAG + fractional nonablative 1470 diode)
CO_2
MonaLisa Touch (Deka, Italy) (distributed by Cynosure)
FemiLift (Alma, Israel)
CO_2RE Intima (Syneron, Israel-USA)
FemTouch (Lumenis, Israel)
EdgeOne (Jeisys, Korea)
Beladona (Won Tech, Korea).
Radiofrequency
ThermiVa (ThermiAesthetics, Irving, TX)
Ultra Femme (BTL, Boston, MA)
Geneveve (Viveve, Sunnyvale, CA)
Revive (Viora, Manhattan, NY)
Pelleve (Ellman, Phoenix, AZ)
Votiva Forma V (Inmode, Lake Forest, CA)

One of the first reports on the use of erbium:YAG (Er:YAG) laser technology for gynecological treatments dates back to 2000 when Dr. Claudia Pidal and colleagues reported on the use of a Fotona Fidelis erbium:YAG laser (now known as the Intimalase and Incontilase, Fotona) for treating vaginal tissue [15, 16]. The results were impressive. The treatment was effective and painless and led to the rapid development of various erbium ablative procedures, including the treatment of human papilloma virus infections, cervical ectropion, vulvar intraepithelial neoplasia, dystrophic lesions, melanosis, and many other conditions. These treatments have also obtained US FDA clearance, and since then thousands of such procedures have been performed in many countries. A high rate of success, with only minor complications, was reported when performing ablation of the lower genital tract, treatment of multifocal and multicentric lesions, excisions, and tissue coagulation [16].

As an interesting and unexpected side effect, many patients reported that they felt a vaginal tightening effect following these erbium:YAG treatments, which resulted also in their enhanced sexual experience. This discovery initiated further research in the direction of developing a minimally invasive, nonsurgical, and nonablative erbium treatment for vaginal relaxation syndrome (VRS) [16].

There is a large spectrum of various VRS treatment options on the market ranging from behavioral (Kegel exercises) through pharmacological therapies (hormonal, tightening creams and sprays) to various more or less invasive surgical procedures. While behavioral and pharmacological therapies are noninvasive and safe, they have limited efficacy. On the other hand, various surgical procedures promise a much better final result at the price of higher associated risks [1].

Surgical procedures require the cutting and rearrangement of vaginal and peripheral tissue in order to reduce the size of the vaginal canal. Operating on or near sensitive vaginal tissue is inherently risky and causes scarring, nerve damage, and decreased sensation. Furthermore, patients require an extended recovery period, and the procedure involves considerable pain, discomfort, and risk of infection and serious complications associated with surgery and general anesthesia, including mortality [1].

Vaginal relaxation syndrome (VRS) is a quite common medical condition described as a loss of the optimal vaginal structure and is usually associated with vaginal child delivery and natural aging. Multiple pregnancies and deliveries contribute to a worsening of VRS, as well as the onset of menopause, which causes a decline in hormone levels and vaginal atrophy. VRS results in a decrease or loss of sexual gratification [1].

The first studies of the thermal effects of a nonablative erbium:YAG on human soft tissue using Fotona Intimalase with SMOOTH mode were performed by Majaron and colleagues in 2000 [17] and Drnovsek and colleagues in 2004 [18]. Based on these findings, the nonablative SMOOTH-mode erbium also began to be used on mucosal tissue. The first experiences in targeting mucosal tissue were intraorally. Application of the SMOOTH mode on the soft palate produces tissue contraction, which is an ideal noninvasive method for treating snoring and sleep apnea complications [16]. The first trials with SMOOTH-mode erbium tightening of the vaginal canal had already begun in 2008/2009 [13]. Tightening of the vaginal canal and consequently the improvement of sexual gratification were observed [13].

These trials also revealed that the SMOOTH-mode erbium results in improvement of stress urinary incontinence (SUI) in women. This resulted in the development of two protocols for two new minimally invasive, nonsurgical, and nonablative procedures: Intimalase (for VRS) and Incontilase (for SUI) [13, 19, 20]. These protocols are based on heating the vaginal wall mucosa up to approximately 65° C and include two treatment sessions with a 4–6-week interval. The time needed to execute the Intimalase protocol is approximately 8 min and for Incontilase around 15 min [16].

The wide use of erbium SMOOTH-mode technology brought further discoveries—in 2013 Bizjack-Ogrinc and Sencar reported excellent results achieved in the reduction of pelvic organ prolapse, [21] and in the same year Gaspar presented his pioneering work on vaginal atrophy [22]. The protocol for treatment of pelvic organ prolapse is based on the sample principle of

collagen hyperthermia as are the protocols for vaginal tightening and SUI, although with a difference in the treatment intensity (increased) and the location of the major area treated (the prolapsed part of the vaginal wall). This protocol requires three to five sessions at 4–6-week intervals. The number of sessions is dependent on the severity (grade) of the prolapse [16].

The vaginal atrophy protocol is based on a slightly different concept of milder hyperthermia, whereby the mucosa is warmed up to 45° C, thus causing the stimulation of cell proliferation via heat shock protein activation, an increase of collagen production as well as anti-inflammatory action. This protocol consists of three sessions at intervals of 3 weeks. After immediate tissue shrinkage, the process of neocollagenesis could take up to 6 months to complete [16].

Table 29.2 from the Palacios article shows the level of evidence of treatments for GSM. The vaginal laser received grade I-A level of evidence for improvement of symptoms and tropism for treatment of genitourinary syndrome of menopause (GSM) [23].

GSM, caused by estrogen deficiency, is responsible for the appearance of symptoms affecting qualify of life, such as vaginal dryness and/or dyspareunia or urinary symptoms, and affects at least 50% of postmenopausal women [2].

Treatment for GSM is aimed to restore the urogenital epithelium and relieve symptoms. For symptoms such as vaginal dryness, dyspareunia, or other symptoms associated with this syndrome, the first line of treatment is moisturizers (Evidence I-A) and vaginal lubricants (Evidence II-B) (Table 29.2). If they do not provide adequate improvement of symptoms or if moderate to severe symptoms continue, estrogens are used. Estrogens are the most effective treatments. In cases of vaginal atrophy, the choice is local estrogen therapy (Evidence I-A). Local estrogenic or systemic treatments can be combined with moisturizers and lubricants (Table 29.2) [23].

New therapeutic alternatives such as ospemifene (Evidence I-A) have recently appeared. Ospemifene is a selective estrogen receptor modulator (SERM) that selectively exerts agonist effects on the vaginal tissue. It is the first nonhormonal oral alternative for vulvovaginal atrophy or the genitourinary syndrome of menopause. Vaginal laser has also emerged as a possible option for noninvasive treatment of GSM (Evidence I-A) (Table 29.2) [23].

Table 29.2 Level of evidence of treatments for genitourinary syndrome of menopause [23]

Treatments	Level of evidence
Lifestyle	
Sexual activity	II-2B
Obesity	III-C
Exercise	III-C
Smoking	II-3B
Vaginal moisturizers 2–3 times/week for improvement of symptom	I-A
Vaginal lubricants for sexual activity	II-2B
Other treatments	
Homeopathy	III-D
Phytotherapy	III-D
Phytoestrogens	II-3D
Systemic and local hormonal therapy	
Improvement of symptoms	I-A
Tropism	I-A
Vaginal laser for improvement of symptoms and tropism	I-A

Effectiveness of Procedures

Nonablative Erbium for GSM and VSR

Gambacciani et al. conducted a pilot prospective longitudinal study performed in 45 postmenopausal women suffering from GSM. Nineteen of these women also suffered from SUI. They were treated with nonablative erbium laser (Fotona), receiving three laser applications every 30 days with follow-up visits up to 24 weeks after the last laser treatment. A control group of 25 postmenopausal women were treated with an established treatment for GSM of topical estriol vaginal gel twice weekly for 3 months. Results showed significant improvement of both vaginal dryness and dyspareunia. In postmenopausal women suffering from mild to moderate SUI, there was also significant improvement of SUI scores (A)(1b) [12].

In another prospective study by Gambacciani, 65 postmenopausal women suffering from GSM

were treated with 3 laser applications of nonablative erbium laser (Fotona) every 30 days and followed up to 1 month. In addition, 21 of the patients suffering from mild to moderate SUI were also evaluated for changes in these measurements. Results showed statistically significant improvement in vaginal dryness and dyspareunia in all patients at 4 weeks posttreatment. In the 21 patients with SUI, the laser treatment induced a significant decrease in the SUI scores. The nonablative nature of the erbium laser allows several passes on the vaginal canal that are necessary for the treatment of the anterior vaginal wall in women suffering from SUI. This is not possible with ablative lasers such as fractional CO or ablative erbium due to tissue necrosis and pain limiting the number of passes that can be performed or tolerated (A)(1b) [11].

In a prospective study, 43 postmenopausal breast cancer survivors were treated by Gambacciani et al. with 3 laser applications of Fotona erbium laser every 30 days. It was found to be effective and safe for the treatment of genitourinary syndrome of menopause (GSM). Effect of the laser treatment on dryness and dyspareunia was measured up to 18 months from the last laser treatment. At each visit, the Vaginal Health Index Score (VHIS) was calculated. The VHIS evaluates the appearance of the vaginal mucosa and consists of five parameters: elasticity, pH, vaginal discharge, mucosal integrity, and moisture. Results showed improvement in both dryness and dyspareunia and subsequent VHIS calculations, inducing a rapid and long-lasting positive effect on vaginal tissues, up to 12 months after the last laser treatment. There was still improvement at 18 months compared to baseline, but there was a diminishing effect by this timepoint. This study had the limitation of the lack of randomization with a sham treatment and/or standard treatment (A)(1b) [24]. In a previous study performed by the same authors, they compared the vaginal erbium laser with low-dose vaginal estriol administration, a standard GSM treatment, and showed that the estrogen effects fade away 12 weeks after the end of treatment, whereas the laser treatment group maintained the results for 6 months (up to the end of the follow-up period) [12]. This study had a shorter follow-up period (6 months) than the previous study (18 months). Thus, as expected, laser therapy cannot be considered a definitive cure for GSM, but the vaginal erbium laser inducing no tissue ablation or injury could be repeated on an annual basis when the beneficial effects seem to decrease [24].

A prospective study with control group was conducted by Gaspar et al. Fifty patients with GSM were divided into 2 groups: 1 group received topical estriol treatment for 8 weeks and the other group received laser treatment with the Fotona erbium laser in nonablative mode. The laser group received three sessions over an 8-week period. Patients were followed up to 18 months posttreatment. Results showed that the erbium laser treatment successfully relieved symptoms of GSM and that the results were more pronounced and longer lasting compared to topical estriol treatment. The major benefit of the laser treatment in comparison to the 8-week local estriol treatment is that the laser treatment produces a long-lasting effect characterized by an improved vascularization and increased extracellular matrix component, while estriol-only treatment increases the glycogen level in the vaginal epithelium and its turnover, with less effect and only transient effect on vascularization and changes in the lamina propria, requiring maintenance treatment for the effects to be sustained. Due to these enhanced effects, the laser treatment provides great improvement in GSM which remains evident for a longer sustained period up to 12 months. There was diminishing effect at the 18-month follow-up, although the improvement was still highly significant compared to baseline. The authors emphasized that since the treatment is safe and noninvasive, it could be repeated once the patients feel the return of symptoms and in that way sustain the beneficial mucosal state (A)(1b) [25].

Gaspar et al. performed previous studies using a fractional CO_2 laser for vaginal rejuvenation [26]. Salvatore et al. also performed a 3-month follow-up study showing that treatment with a fractional CO_2 laser improves symptoms of GSM [27]. Gaspar pointed out in the latter erbium laser study article that the major difference between

CO_2 and the erbium laser method used in the latter study was in the ablative characteristics of the CO_2 laser, which works by vaporizing columns of tissue. Tissue vaporization of epithelial layer surface is necessary to expose deeper, underlying connective tissue, which is more abundant in water, to the thermal effects of the CO_2 laser pulse for achieving the desired photobiomodulatory effect [28]. In contrast, erbium laser with nonablative SMOOTH mode (unique only to the Fotona laser) creates heat pulses without damaging the mucosa. The temporal distribution of energy delivered with the special nonablative SMOOTH mode allows the heat to slowly dissipate to depths of approximately 200–500 μm, thus achieving the same biological effects and the thermal effects of a CO_2 laser pulse, with the additional benefit of avoiding mucosal damage. Consequently, the risk of infection, necrosis, scarring, and other side effects is minimized compared to CO_2 laser [25]. Gaspar used the first generation of Deka's CO_2 laser (SmartXide2) (which was much more robust and aggressive than today's MonaLisa Touch) when he did his comparison of CO_2 and erbium:YAG in 2012. After seeing the high incidence of adverse side effects, they reduced the depth of drilling in the current fractional CO_2 MonaLisa Touch (Deka, Cynosure) to about 200 μm (earlier it was much more) and produced new much gentler accessories (almost exact copies of Fotona's G-set adapters).

In this prospective study examining the effects of laser treatment on vaginal atrophy, Bojanini et al. had 40 patients who were split into 2 groups: 20 patients in postmenopausal group with no history of gynecologic cancer (group A) and 20 menopausal patients with a history of gynecologic cancer (group B). The 20 patients in group B also were breast cancer survivors. Patients received two laser treatments with a nonablative erbium laser (Fotona) with 3-week intervals between treatments. They were followed up to 3 months posttreatment. All patients reported improvement in all measured endpoints including dryness, dyspareunia, improvement in sexual life, and overall satisfaction (B)(2b) [29].

Gaviria et al. conducted a pilot study on 21 patients receiving treatment with nonablative erbium laser (Intimalase, Fotona) for vaginal tightening between June 2011 and January 2012. All patients received two treatments with 15–30-day intervals between treatments and were followed up to 3 months. Vaginal relaxation syndrome (VRS) is quite common and associated with vaginal child delivery and natural aging. Multiple pregnancies and deliveries contribute to a worsening of the VRS condition, as well as the onset of menopause, which causes a decline in hormone levels and vaginal atrophy. Ninety-five percent of patients reported significant (moderate and strong) improvement of their vaginal tightness, and also all of their partners confirmed an improvement of vaginal tightness during sexual intercourse. Ninety-five percent of patients reported better sex after the treatment. Five patients had prolapse (stage 1–3 in severity) before receiving the treatment; all experienced improvement in prolapse after the laser treatment. Three patients with SUI reported significant improvement in two and complete resolution in one. Limitations of this study were small size, lack of a control group, and short follow-up time (B)(1b) [1].

Gaviria et al. conducted a prospective study examining VRS treated with laser with 3-year follow-up. A total of 103 patients suffering from vaginal relaxation syndrome (VRS) were treated with a nonablative erbium laser (Intimalase, Fotona) between June 2011 and May 2014. Sixty patients received follow-up at 3 years after the last laser procedure. The patients reported that the average duration of effect was 16 months, with significant improvement of SUI and prolapse. The majority of the results lasted 18–24 months, and the effect of the therapy started to fade 2 years after the treatment. Results showed that 83.33% of participants would be willing to repeat the therapy. The majority (67%) of the patients with persisting results received two treatments (B)(1b) [30].

Ablative Fractional Erbium for VRS

In a prospective study, Lee et al. treated 30 postpartum women with VRS or vaginal atrophy.

They received four laser treatments at 1–2 weekly intervals using an ablative erbium laser (Petit Lady, Lutronic). They were followed up to 2 months. Patients' partners were asked for input and 76.6% reported increased perception of vaginal tightening. Seventy percent of patients reported improved sexual satisfaction. This study was limited by small sample size and very short follow-up (C) [31].

Ablative Fractional CO_2 for Vaginal Atrophy

In this pilot study, Salvatore et al. treated 50 postmenopausal women with three applications of fractional CO_2 laser (Monalisa, Deka) over 12 weeks. Results showed improvement in vaginal dryness and dyspareunia at 12-week follow-up. Satisfaction with the laser procedure was reported by 84% of the women treated. One patient could not be treated because her vagina was too narrow and the laser probe could not be inserted. Pain reported during the study was related to insertion and movements of the laser probe during treatment. The limitations of this study are small sample size, short duration of the study, lack of long-term follow-up, and absence of a comparator (placebo or other active treatment) (C)(2b) [32].

Zerbinati worked with Salvatore in this pilot study [32] and recruited 5 out of the 50 postmenopausal women, nonestrogenized, for the histological study. The microscopic and ultrastructural findings obtained from the vaginal mucosa biopsies of these five women showed restoration of the normal structure and functionality in the epithelial and connective tissue, restoring the vaginal mucosa structure to a premenopausal condition without any hormonal therapy. These histologic findings corresponded to the clinical relief from symptoms reported by the patients after fractional CO_2 laser treatment (B)(2b) [28].

Salvatore treated 15 women with 3 applications of fractional CO_2 laser (Monalisa, Deka) over 12 weeks. Results showed improvement in vaginal dryness and dyspareunia. There was also significant improvement in sexual function and quality of life. The major limitation of this study was its small sample size, short duration of the study, and lack of long-term follow-up (C)(2b) [33].

Perino et al. treated 48 postmenopausal women with symptoms related to vulvo-vaginal atrophy with a fractional CO_2 laser (Monalisa, Deka). They received three sessions with 1 month between treatments. They were followed up to 30 days posttreatment. Results showed improvement in vaginal dryness and dyspareunia. As many as 91.7% of patients reported satisfaction with the treatment. The limitations of this study were absence of a control group (i.e., traditional local estrogen therapy), small sample size, extremely short follow-up, and lack of long-term follow-up (at least 1 year) (C)(2b) [34].

Nonablative Erbium for SUI

Fistonic et al. conducted the first study using nonsurgical laser treatment for SUI. This first-time open-labeled prospective single-center pilot study had a total of 39 women suffering from mild to moderate SUI who underwent one treatment with nonablative erbium laser (Fotona) and were followed up to 6 months. The patients all showed improvement in measurements used to assess reduction in SUI symptoms and also reported improved sexual gratification. These preliminary results showed that the nonablative erbium laser offers efficacious treatment for SUI and is associated with a high level of safety, and patients find it comfortable and noninvasive with no recovery period (B)(2b) [19].

Khalafalla et al. conducted a prospective study on 50 women with SUI who were treated with a nonablative erbium laser (Incontilase, Fotona) following the Incontilase protocol. They were followed up to 6 months posttreatment. SUI was diagnosed by patients' symptoms, urine analysis, and urodynamic studies. All measurements of SUI were improved after treatment (B)(2b) [35].

In another prospective study, Tien et al. treated 35 women with SUI with a nonablative erbium laser (Incontilase, Fotona) and found that the

effect of the laser for mild SUI was moderate at 6-month follow-up but was not effective for pad weight >10 g. The overall success rate of the 1-h pad test at 6 months posttreatment was 78.6% [36]. It improved lower urinary tract symptoms, qualify of life, and sexual function of both partners. They concluded that further studies should be performed to assess long-term sustained efficacy. They also noted that subjective and objective improvements in SUI symptoms were not as extensive as those that follow midurethral sling surgeries (MUS) especially in moderate and severe cases [37]. MUS surgery which has a long-term subjective cure rate of 77–85% remains one of the first-line surgeries for SUI [38, 39]. They stated that the laser procedure should not replace MUS surgery as standard therapy for SUI patients who fail to improve following first-line therapy. In addition, the injection of bulking agents has been reported to have a cure rate of 53–73.2% [40, 41] which is better than the cure rate of the laser procedure. The authors further state that the laser procedure should not replace the injection of bulking agents as the sole minimally invasive procedure for SUI [36]. The authors concluded that based on its minimally invasive nature and the lack of significant side effects, the nonablative erbium laser (Incontilase, Fotona) may be used as an alternative therapy for mild SUI cases and that further studies should be performed to assess long-term sustained efficacy (B)(2b) [36].

Pardo et al. conducted a prospective study on 42 women with mild to severe SUI who were treated with a nonablative erbium laser (Incontilase, Fotona). Improvement was evident almost immediately after treatment and lasted at least 6 months. As many as 78.6% reported improvement (including patients with severe SUI), 38.1% a complete healing of SUI at follow-up, 66.7% reported high satisfaction, and 81.8% of sexually active women reported improvement of sexual gratification. Only mild pain during the treatment was reported as an adverse effect in some patients. No other adverse effects were reported in any patient. The authors concluded that nonablative erbium laser seems to provide a quick and highly successful ambulatory procedure for treatment of SUI, producing significant reduction of SUI symptoms, lasting at least 6 months. The procedure is minimally invasive, with no cutting, no ablation, and no bleeding, virtually painless, and requires no anesthesia or special pre- or postoperative preparation. The authors also discussed that the use of fractional CO_2 and ablative erbium laser for vaginal rejuvenation treatment, addressing also SUI symptoms, has been described but is based on ablation of mucosal tissue, and although described as minimally invasive, a long recovery time was still needed, accompanied by bleeding, pain, and burning sensation after the treatment [26]. In contrast, the nonablative erbium laser provides a safer option, creating a controlled temperature increase within the mucosal tissue without any ablation, having no recovery time and no significant adverse effects (B)(2b) [14].

Fistonic et al. treated 73 women in a prospective cohort, single-center study with a nonablative erbium laser (Incontilase, Fotona) followed up to 6 months. Results showed there was a clinically relevant, short-term improvement of SUI with minimal adverse events. The reduction was significantly higher in women with normal body mass index and in younger women (B)(2b) [42].

In a pilot study, Fistonic et al. treated 31 women with SUI with a nonablative erbium laser (Inctonilase, Fotona). This is a pilot study with lack of a control group, high loss to follow-up, and relatively short follow-up time. All patients with SUI showed improvement in the measured efficacy endpoints. The authors concluded that the nonablative erbium laser induces deep thermal effect on the vaginal wall, which seems to result in a clinically meaningful improvement of female SUI, but that randomized control trials are needed for further evaluation (C)(3a) [43].

In another prospective study, Ogrinc et al. treated 175 women with stress urinary incontinence (SUI) (66%) and mixed urinary incontinence (MUI) (34%) with symptoms ranging from mild to very severe with a nonablative erbium laser (Incontilase, Fotona). SUI is the most prevalent type of UI and is defined as involuntary loss of urine due to sphincter failure during physical activity, coughing, or sneezing, which all cause

an increase in abdominal pressure. MUI is a combination of SUI and urge urinary incontinence (UUI). UUI, sometimes also termed overactive bladder syndrome, encompasses the symptoms of urgency, frequency, and nocturia and is associated with urgency contraction due to detrusor overactivity. MUI has a prevalence of 7.5–25% [44, 45]. Patients received two laser treatments a month apart and were followed up to 12 months posttreatment. At 1-year follow-up, 62.3% of the patients were dry. Seventy-seven percent of SUI patients improved. Thirty-four percent of MUI patients improved. The outcome was significantly dependent on the type of incontinence diagnoses before the induction of therapy. While the procedure cured the majority of women with SUI, it was of benefit only in one third of women with MUI. The percent of women cured after 1 year in the study was similar to the results obtained after surgical procedures; yet, compared to surgical outcome, the reported side effects were negligible [44, 46]. The authors concluded that the nonablative erbium laser efficiently improved SUI in the majority of patients, but on the other hand, it seems that the therapy is not suited for the treatment of MUI (B)(1b) [46].

Multicenter Studies of Nonablative Erbium on VRS and SUI

The results of multicenter clinical studies of the nonablative erbium laser (Intimalase and Incontilase, Fotona) are presented in this chapter [13]. All five centers involved in the studies of the Intimalase treatment reported positive results in a large majority of patients (i.e., improvement in vaginal tightness). Similarly, all four studies of the Incontilase treatment showed improvement in SUI in a large majority of patients (A)(1a) [13]. Rivera reported on two studies of laser vaginal tightening using the nonablative erbium laser (Intimalase, Fotona). The first group of 135 patients was treated in the period from June 2009 to September 2010. On 1-month follow-up after the first session of Intimalase treatment, 90.4% of patients expressed their satisfaction with the tightening improvement, while 9.6% declared improvement but asked for a second session. On the next follow-up interviews at 3 months and 6 months, all patients expressed their satisfaction with tightening improvement. The second group of 27 patients was treated during March 2011 with a single session of Intimalase therapy. Patients reported improvement in sexual gratification. Vaginal tightening was achieved in all patients, ranging from 3% to 28%, resulting in an average shrinkage of 17% (or 12 mm) [47].

Fistonic et al. evaluated the efficacy and safety of the nonablative erbium laser (Intimalase, Fotona) procedure in this pilot study conducted on 17 women for vaginal tightening in a period between September 2010 and January 2011. Patients were followed up to 3 months. Six patients also had SUI on which Fistonic performed also the Incontilase (Fotona) treatment. All patients with SUI showed improvement at the 1- and 3-month follow-ups (B)(2b) [48].

Guimaraes et al. reported on a laser vaginal tightening study using the nonablative erbium laser Intimalase (Fotona) treatment protocol. Twenty-three patients were treated during a period from August to December 2011. All patients received one treatment and were followed up to 4 months. In this study, the patients' male partners were also interviewed regarding any improvement of tightness sensation. At 1-month follow-up, 87% of patients reported mild-to-excellent improvement, while 13% responded that there was no improvement. At 4 months after the treatment, 69% of partners assessed their improvement as excellent, 27% as good, 4% as mild. None of the patients' partners claimed "no improvement" either at the 2- or 4-month follow-ups (B)(2b) [49].

Gaviria et al. reported on a study which was performed during June 2011 and January 2012 on 21 patients, with two sessions of the nonablative erbium laser Intimalase (Fotona) treatment with 15–30 days between sessions and followed up to 3 months. Ninety-five percent assessed the change of their vaginal tightness as strongly or moderately improved, 5% as mildly improved. Twenty out of 21 patients reported better sex after treatment. Five patients had prolapse of stages

1–3, but all of them improved after the first session of Intimalase (B)(2b) [50].

Garcia et al. presented their results of laser vaginal tightening using the nonablative erbium laser Intimalase (Fotona) treatment performed on 29 patients in a period between October 2011 and January 2012. Improvement in vaginal tightness was reported in 96.6% of the cases. Results of the feminine sexual function index also improved after treatment (B)(2b) [51].

Rivera et al. treated 115 patients suffering from SUI using the nonablative erbium Incontilase (Fotona) protocol during the period from March to August 2009. At follow-up at 1 month after the second treatment, the success rate was 97.4% for mild SUI and 89.5% for moderate SUI (B)(2b) [47].

Guimaraes et al. treated 28 patients with SUI using the nonablative erbium laser Intimalase (Fotona) protocol during the period from August to December 2011. At the first follow-up at 1 month, there were 87% of patients with improvement and 17% of patients without changes. Over time, the SUI further improved so that at 4 months, only 6% of patients were still reporting no change, while 94% of patients reported improvement and 68% of all patients claimed to be free of SUI symptoms (B)(2b) [49].

Saracoglu et al. reported on his experiences with treating SUI and laser vaginal tightening using a single session of the Incontilase or Intimalase protocols (Fotona), depending on the patients' indication. Thirteen patients were recruited in this pilot study, nine of them having reported SUI, while the remaining four had vaginal relaxation syndrome. All 13 patients had various stages of prolapse, 9 had prolapse of stage 1, while 3 had stage 2, and one patient had stage 3. At follow-up at 6 weeks, 50% improved their prolapse stages, five patients by one stage, while one patient (having stage 3) improved by two stages. Measurements of SUI were all improved [52].

The initial clinical results from these nine clinical studies from six centers using the Intimalase and Incontilase (Fotona) treatment protocols showed safety and efficacy in patients suffering from VRS and SUI [13]. These studies were limited by short follow-up but later studies used larger number of patients and with longer follow-up times, some of which have already exceeded 12 months (B)(2b) [1, 19].

Multicenter Study of Nonablative Erbium on GSM and SUI

The protocol and rationale and design for a large multicenter study on the evaluation of the efficacy and safety of vaginal erbium laser for the treatment of GSM and SUI were presented in a paper published by the Vaginal Erbium Laser Academy Study (VELAS). This study will evaluate the effects of three laser applications using the nonablative erbium laser (Fotona) in 1500 postmenopausal women. They will be followed up to 1 year [53]. They carefully considered all the available evidence on nonablative erbium and fractional CO_2 laser before concluding that the nonablative erbium would be the ideal candidate for the thermal treatment of vaginal walls. Studies using nonablative erbium laser [11, 12, 22, 31, 54–56] showed advantages compared to fractional CO_2 laser because it provides a nonablative option for correction of GSM. In addition, nonablative erbium but not CO_2 laser treatment has been reported to induce a significant decrease of clinical symptoms in postmenopausal women suffering from SUI [11, 12, 22, 31, 54–56].

Studies using fractional CO_2 laser [27, 28, 34, 57, 58] showed that it may improve vaginal health in postmenopausal women. The effects measured were vaginal dryness and dyspareunia. However, it is important to note that fractional CO_2 was rarely used in studies to examine SUI and not been used in studies to examine pelvic organ prolapse. Only the nonablative erbium laser (Fotona) has been used in studies examining SUI or prolapse and shown to be effective and safe for treatment of SUI and pelvic organ prolapse [21, 53]. The VELAS selected the nonablative erbium laser because it has been safely used to treat GSM in women suffering from SUI, but not CO_2 laser [53].

The VELAS study obtained all the available data with the fractional CO_2 laser and nonabla-

tive erbium laser. Although both lasers were reported to be effective in reducing clinical symptoms of postmenopausal vaginal atrophy, only the nonablative erbium laser treatment was associated with a reduction in SUI symptoms. The nonablative erbium laser is performed using a particular vaginal speculum introduced as a guide for the handpiece laser beam delivery system. Thus, the patients do not feel the several longitudinal passes performed using a step-by-step retraction of the handpiece, and the nonablative erbium laser effects on vaginal mucosa induce ideal treatment compliance [12, 53]. In comparing data available on fractional CO_2 with nonablative erbium laser, the VELAS groups discussed that the innovative techniques used in the nonablative erbium laser procedures can guarantee not only efficacy but also an intrinsic safety, since the nonablative erbium beam cannot damage the tissues in depth. This eliminates the risk of tissue necrosis, in a nonablative form, without cut, abrasion, or bleeding. These characteristics make the nonablative erbium laser an ideal candidate for the thermal treatment of the vaginal walls. The characteristics of the CO_2 laser are different and may induce different compliance and patient satisfaction [53]. Table 29.3 shows Adrian Gaspar's study comparing the effects of these two systems [53].

Table 29.3 Difference between CO_2 and Er:YAG lasers in the treatment of genitourinary syndrome of menopause (GSM) [53]

	CO_2	Er:YAG
Absorption in water	15 × less than Er:YAG	15 × more than CO_2
Optical penetration	50 μm	3–5 μm
Mechanism of action	Ablation	Thermal diffusion
Aggressiveness of treatment	Always partial necrosis and associated adverse effects	Surface of mucosa is not ablated (damaged)
Depth of penetration	3 mm or more	200–500 um
Operative time (min)	20	15
Pain level during treatment on scale of 0–10	5	0
Pain level posttreatment on scale of 0–10	3–5	0
Treatment zone	Vaginal canal	Vaginal canal and introitus
Tissue-healing phase	20 days	2 days
Return to normal sexual activity	10 days	3 days
Laser release	Operator-dependent	Uniform and controlled

The VELAS is the largest multicenter prospective study underway to evaluate effects of laser on GSM. The protocol does not include a placebo-treated arm since a double-blind treatment with a sham procedure is not feasible, the effect of laser on vaginal tissue being physically evident during the treatment [53]. The VELAS groups concluded that the nonablative erbium laser has unique properties that make it ideally suited for treatment of the vaginal mucosa and gynecologic conditions due to its ability to deliver uniform controlled tissue heating, in a safe and harmless ambulatory procedure without ablation and carbonization of the tissue, and ability to avoid the risk of perforation with accidental lesions of the urethra, bladder, or rectum (a feature unique and specific only to the Fotona laser modality) [53]. Findings from the VELAS have the potential to affect clinical care practice and health decisions for millions of women worldwide for a nonhormonal treatment for GSM and a noninvasive treatment for SUI.

Gaspar et al. conducted a prospective study comparing treatment group with control group. Forty-three patients were in the laser treatment group and received 3 treatment sessions of a nonablative erbium laser (Incontilase, Fotona) with intervals of 1 month in between the sessions. Twenty-nine patients were placed in the control group and received 2 weekly sessions of pelvic floor muscles exercises with perineometry, which lasted 3 months (24 sessions in total). Only patients with SUI were recruited into the study. Follow-ups were performed at 3, 6, and 12 months. Standardized 1-h pad test was used to evaluate the efficacy of the treatment. The decrease in pad weight was more pronounced in

the laser group. More importantly, the effect in the laser group remained constant up to the 12-month follow-up, while the results in the control group showed a diminishing trend. The author concluded that the results can last for at least a year after treatment. He also concluded that since the treatment is noninvasive, it could also be repeated once the results start diminishing (B)(1b) [59].

Gaspar et al. treated eight patients with SUI with three sessions of a nonablative erbium laser (Incontilase, Fotona) with 1-month interval between the sessions. They were followed up to 12 months. The largest average reduction of leaking frequency and quantity was measured at 2-month follow-up. There continued to be significant reduction of frequency and quantity up to 12 months. The author concluded that 3-day voiding diary was a useful objective tool to measure effects on SUI and that the results of this small pilot study show that the laser therapy could produce significant reduction of SUI symptoms which is lasting at least 12 months (B)(3b) [60].

Gaspar et al. treated 43 patients with SUI in the laser group with 3 sessions of a nonablative erbium laser (Incontilase, Fotona) with 1-month interval between the sessions. The control group of 29 patients received perineometry sessions (Kegel exercises plus perineometry) (2 per week during 3 months). In the first phase of the study, both groups were followed up to 18 months after the initial session. The control group then exited the study, while the laser group received three additional maintenance sessions of laser treatment—at 18, 24, and 30 months—and was followed up to 36 months after the study start. Results of the pad test and SUI questionnaire showed that the laser group insignificantly improved after 6, 12, and 18 months. After three maintenance sessions at 18, 24, and 30 months, the scores again dramatically improved at 24-, 30-, and 36-month follow-ups. There was no significant improvement in the control group. The authors concluded that the nonablative erbium laser is a highly efficient, minimally invasive nonsurgical therapy for SUI with long-term results (B)(1b) [61].

Lukanovic et al. separated 120 patients with SUI and sexual dysfunction into a laser treatment group [62] and a control "sham" laser group [62]. Each group was treated with one session of a nonablative erbium laser (Incontilase, Fotona) and followed up to 3 months after the treatment. One patient dropped out of each group. In all measured values, the laser group achieved better results than control group. In the two most important assessment tools for SUI and sexual dysfunction, the improvements of the laser group were significantly better than the control group (B)(2b) [63].

Ablative Erbium for SUI

Leshunov et al. treated 37 women with mild and moderate SUI with an ablative erbium laser (Juliet, Asclepion). They were followed up to 6 months posttreatment. The measurements of SUI showed improvement. There were significant side effects. Fifty-five percent of the patients had presence of bloody discharge, 16% had low-grade fever, and 6% had cystalgia (C) [64].

Fractional CO_2 Laser for SUI

Bader treated one patient with SUI using a fractional CO_2 laser (FemiLift, Alma). The patient received three laser sessions performed at 4-week intervals. The author states that the patient had complete remission of symptoms but did not have a follow-up visit for this patient. The author did state at the end of the paper that results "… reach their peak six months after the end of the third session" but did not provide any evidence to back this up (D) [23, 62].

A retrospective multicenter evaluation of 133 patients with SUI symptoms who underwent fractional CO_2 laser treatments (FemiLift, Alma) appeared in an Alma white paper. Patients were interviewed 3–12 months following completion of treatment to evaluate their symptoms and satisfaction. As many as 66.7% of patients reported satisfactory global improvement. They stated that no adverse events were

reported by any patients or recorded in patient charts (D) [65].

Perino et al. treated 30 postmenopausal women with a fractional CO_2 laser (Monalisa, Deka), receiving three treatments over a period of 30 days. Nine of the 30 patients who suffered from incontinence episodes had improvement after the laser treatment. Results also showed improvement in vaginal dryness and dyspareunia. The major limitations of this study are the small sample size, lack of long-term follow-up, and absence of randomization or a control group of patients. The authors recommend that based on these preliminary results, it would be advisable to perform a new study that includes a control arm (i.e., intravaginal estriol administration) to compare CO_2 laser with other proposed therapeutic options evaluating the long-term outcomes (C)(2b) [66].

Nonablative Erbium for Treatment of Prolapse

In this pilot study, Ogrinc et al. treated 28 patients with grades 2–4 cystocele using a nonablative erbium laser (Intimalase and Incontilase, Fotona). They received between one and three treatment sessions with intervals of 2 months in between the sessions. They were followed up to 6 months. All but 1 patient reduced their prolapse grades by at least one grade (96.4%), 12 of them by two grades (42.9%), and 2 by three grades (7.1%). In conclusion, the author stated they are planning longer follow-ups at 12 and 24 months (C)(1b) [27, 67].

Ogrinc et al. treated 65 patients with grades 2–4 cystocele using a nonablative erbium laser (Fotona). Patients received between one and five treatment sessions with intervals of 2 months in between the sessions. Patients were followed up to 12 months. Improvement was achieved in all stages of pelvic organ prolapse. A reduction of 1.6 stages on average was achieved. Ninety-eight percent of patients achieve an improvement of at least one stage. All of the stage 4 patients achieved an improvement of two grades or more. Patients reported high satisfaction with the procedure and better quality of life. There were no adverse events. The author concluded that the treatment should be included as a first line of defense in early pelvic organ prolapse in order to avoid or postpone surgery (B)(1b) [68].

Summary of Laser-Based Devices for Vaginal Rejuvenation

The vast majority of articles published on vaginal laser treatment has been for the Fotona nonablative erbium laser. It is the only laser on the market which utilizes a nonablative laser that causes no injury to the vaginal mucosa. All other laser devices utilize either fractional CO_2 or ablative erbium laser which cause ablation and injury to the vaginal mucosa. Radiofrequency devices are also noninvasive, but the published studies are few compared to the large number of articles published on the nonablative erbium laser and has been for GSM and VRS and not for SUI and pelvic organ prolapse. There is rightful concern in the medical communities that so many laser companies are trying to claim efficacy and safety using the fractional CO_2 or ablative erbium which have higher risk of adverse effects without providing long-term studies especially when the convincing evidence to treat these conditions has been produced with the nonablative laser which is a better and safer option—both from the standpoint that it has the scientific studies to back it up and there is minimal risk with the procedure. When faced with a more invasive option with higher adverse effects with less scientific data compared to a safer noninvasive option with no adverse effects with high volume of scientific data, it would appear prudent for a physician considering performing procedures in this area to consider the noninvasive option especially if they were already skeptical about whether these procedures have any effect.

Lasers also have important applications in treatment of conditions involving the external genitalia. Ablative erbium laser has many useful applications for treatment of gynecologic disorders such as ablating various lesions on the cer-

vix and vaginal wall, for the removal of genital warts, resurfacing, whitening and tightening of the vulvar region, as well as labioplasty, lichen sclerosus et atrophicus, and many other procedures [16].

Radiofrequency Devices for Vaginal Rejuvenation

Although multiple radiofrequency (RF) devices are being used for vaginal rejuvenation, few studies have been published showing efficacy and safety for this application. The RF devices are not FDA approved for use in the vaginal or genital region—all their use in these areas has been off-label.

Steven conducted a single-center study with 14 healthy female patients investigating the safety and efficacy of a bipolar RF device (ReVive, Viora) for labial skin laxity and texture. This bipolar RF device utilizes three distinct RF frequency channels (0.8 MHz, 1.7 MHz, and 2.45 MHz) and an additional fourth multichannel mode, combining all three RF frequencies using the unit's V-ST handpiece. Patients received an average of 5.6 treatments with no anesthesia, and duration of session was 30 min and intervals of 2–3 weeks between sessions. Results showed moderate improvement in labial skin laxity and texture with 67% of the patients reporting satisfaction with the treatment results (C) [69].

BTL (Boston, MA) has a new intravaginal monopolar RF device called the Ultra Femme which is the first of its kind on the market. They incorporate a "ring solution" which is a circumferential 360° band of RF delivery at the end of a phallus-shaped intravaginal probe that is inserted into the vaginal canal. This ring solution provides homogeneous heating throughout the entire vaginal canal and introitus. There is also a separate external tip that is used to treat the external genitalia. The intravaginal procedure takes 10 min and the external genitalia requires 20 min.

Fistonic et al. treated 17 female patients with labial laxity with a focused monopolar RF device. They received four treatments at 7-day intervals and were followed up to 1 month after the last treatment. Improvement was measured on a 1–4 scale determined by three blinded evaluators. An average of 2.9 (maximum of 4) points improvement rate in vulvar appearance was observed. They also reported improvement in sexual gratification with statistical significance. The author concluded that this study demonstrates the positive effect of a focused monopolar RF device for noninvasive labial tissue tightening. This study was limited by a small sample size, lack of a control group, and short follow-up (C)(2b) [70].

ThermiVa from ThermiAesthetics (Southlake, TX), another RF device, uses an S-shaped, long, thin treatment probe with a thermistor tip that can treat the internal and external vaginal tissue by direct contact requiring the operator to use a rubbing back and forth or thrusting motion. Compared to the BTL Ultra Femme, the ThermiVa has complicated movements, does not heat homogeneously (there are cold spots), and is reliant on the operator's manual thrusting motions to deliver heat in an inconsistent manner, requiring a longer treatment time (30 min to treat only the intravaginal canal) without the assurance that the tissue is heated uniformly. The BTL Ultra Femme heats homogeneously in all directions and eliminates operator error, and tissue is heated to the target temperature in a shorter time.

In a prospective study, Alinsod treated 23 female patients with mild to moderate vulvovaginal laxity, sexual dysfunction, and mild to moderate SUI using a transcutaneous temperature-controlled radiofrequency (TTCRF) device (ThermiVa, ThermiAesthetics) for approximately 5 min per zone (left and right labia majora; ventral, dorsal, left, and right surfaces of the vaginal wall). Clinical endpoint was achievement of the target temperature in the range of 40–45 ° C for approximately 3–5 min per zone. Total treatment time was <30 min. A complete treatment course consisted of three treatments with intervals of 4–6 weeks between treatments and followed up to 30 days after the last laser treatment. Six patients were lost to follow-up. Results showed statistically significant improvement in laxity with visible aesthetic improvement and significant reduction of orgasmic dysfunction. The patients with SUI and atrophic

vaginitis also reported resolution of these symptoms. The limitations of this study are small sample size, lack of a control group, and extremely short follow-up time (C)(2b) [71].

A proprietary procedure called the Geneveve treatment is performed using the only cryogen-cooled monopolar RF (CMRF) (Viveve, Sunnyvale, CA). The reverse thermal gradient cools and protects the surface mucosa, while delivering significant volumetric deep heating. Capacitive coupling ensures energy is distributed evenly across the treatment tip for uniform heating, while parameters and algorithms are preset for reproducible delivery of controlled heating and cooling. It is a 30-min treatment that works by targeting the vaginal introitus to rejuvenate collagen production, resulting in tightening and increase in sensation.

A pilot study by Millheiser in 2010 investigated transurethral monopolar radiofrequency (RF) for vaginal laxity after vaginal childbirth. Twenty-four premenopausal women who had at least one full-term vaginal delivery were included in this study. A seven-point vaginal laxity scale was used to assess subjective patient perception of laxity. Cryogen cooling was used concurrently with the RF probe inside the vagina to manage potential unwanted thermal damage due to overtreatment. At 1 month posttreatment, 67% of patients reported improvements of 2–4 points on the scale and all patients reported at least 1 point of improvement. By follow-up at 6 months, 87% of subjects reported improvement of 2–4 points. Of the 12 patients who had reported diminished sexual function following delivery, all reported notable improvement in sexual function as well. The procedure was well tolerated and no adverse events were reported. The author concluded that these findings warrant further study (C)(2b) [72].

Sekiguchi et al. more recently reported on a prospective study of low-energy radiofrequency (Viveve) for vaginal introital laxity of 30 premenopausal women, each receiving a 30-min treatment with follow-up at 6 and 12 months. Results showed statistically significant improvements in sexual function, vaginal laxity, and reductions in distress during sexual activity were noted at 6 months and maintained through the 12-month endpoint (C)(1b) [75].

The Viveve I trial is a prospective, randomized, single-blinded, and sham-controlled study. Nine study centers in Canada, Italy, Spain, and Japan participated. Premenopausal women presenting with vaginal laxity and having at least one full-term vaginal delivery were included in this study. Patients were randomized (2:1) to receive RF therapy Active (90 J/cm2) vs. Sham (1 J/cm2). Patients were followed up to 6 months posttreatment. A single treatment of RF therapy was found to be safe and associated with both improved vaginal laxity and improved sexual function. Treatment adverse events were reported by 11.1% in the Active group and 12.3% in the Sham group. This was the first randomized, controlled, blinded, clinical study of RF for the treatment of vaginal laxity (A)(1a) [76].

Observations and Recommendations

Nonablative erbium laser is an effective and safe treatment for a wide variety of gynecological disorders including but not limited to vaginal laxity and VRS, vaginal atrophy, GSM, and other symptoms associated with menopause, SUI, and uterine and pelvic organ prolapse (A). There is only one device (Intimalase and Incontilase, Fotona) that utilizes a nonablative erbium laser in an intravaginal device that delivers thermal energy to the entire vaginal wall without causing injury or ablation to the vaginal mucosa. The vast majority of studies in the medical literature on this subject are using the nonablative erbium laser (Intimalase and Incontilase, Fotona) which is the only device (with rare exception) that has been used on a large number of patients with long-term follow-up for SUI and pelvic organ prolapse (B).

Many different types of lasers including nonablative erbium, ablative and fractional erbium, fractional CO_2 lasers, and radiofrequency (RF) devices have been shown to be effective and safe for treatment of vaginal laxity, vaginal atrophy, and enhancement of sexual gratification (A).

Some preliminary observations and small studies have been made looking at the possibility of using ablative and fractional erbium, fractional CO_2, and RF devices for the treatment of SUI (none for pelvic organ prolapse), but there are limitations in performing adequate studies due to the invasive nature of the various lasers that may prevent the operator from being able to deliver enough heat to significantly tighten the pelvic floor and surrounding wall structures and delicate tissue around the urethral meatus without causing injury to the tissue, and also limitations in the delivery device to reach all areas within the vaginal canal and treat surrounding structures safely (C).

Randomized controlled trials with long-term follow-up, including comparative effectiveness trials to established procedures/treatments, are necessary to further evaluate the efficacy of these technologies. In the USA, the current view by the medical establishment thus far is that vaginal rejuvenation and vaginal tightening for any indication regardless of the procedure/device utilized are considered *investigational*.

In 2007 (reaffirmed 2014), the American College of Obstetrics and Gynecology (ACOG) issued a Committee Opinion number 378: Vaginal "Rejuvenation" and Cosmetic Vaginal Procedures that states: So-called 'vaginal rejuvenation,' 'revirgination,' and 'G-spot amplification' are vaginal surgical procedures being offered by some practitioners. These procedures are not medically indicated, and the safety and effectiveness of these procedures have not been documented. Clinicians who receive requests from patients for such procedures should discuss with the patient the reason for her request and perform an evaluation for any physical signs or symptoms that may indicate the need for surgical intervention. Women should be informed about the lack of data supporting the efficacy of these procedures and the potential complications, including infection, altered sensation, dyspareunia, adhesions, and scarring.

The ACOG position statement was issued in 2014 and there have been many studies published since then. The new research has been very promising, so the medical establishment may need to reexamine their opinion based on the newer evidence and especially as more studies are published. Despite the promising research, the skepticism and caution expressed by the medical establishment are warranted due to confusion and lack of understanding of the many different lasers being marketed for vaginal rejuvenation without adequate studies being performed by the vast majority of the companies. Most of the companies are copying the design of the nonablative erbium laser but using a different ablative laser wavelength and then marketing the device to physicians saying the laser can be used for the same applications and indications but without any studies to prove that the ablative laser would have the same efficacy and safety profile.

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Self-Assessment Questions

1. What types of lasers are used for vaginal rejuvenation?
   (a) Nonablative erbium
   (b) Ablative erbium
   (c) Fractional CO_2
   (d) Combination fractional ablative erbium and nonablative diode
   (e) All of the above
2. What types of radiofrequency devices are used for vaginal rejuvenation?
   (a) Cryogen-cooled monopolar RF
   (b) Transcutaneous temperature-controlled RF
   (c) Bipolar RF
   (d) Monopolar RF with ring applicator
   (e) All of the above
3. What are the factors contributing to vaginal relaxation syndrome (VRS)?
   (a) Aging
   (b) Multiple pregnancies
   (c) Obesity
   (d) Cesarean deliveries
   (e) a and b
   (f) All of the above

4. What is the gold standard for treatment of stress urinary incontinence?
   (a) Diet reduction
   (b) Kegel exercise
   (c) Tension-free vaginal tape
   (d) Pessary
   (e) Electrical stimulation
5. What are risk factors for stress urinary incontinence?
   (a) Childbirth
   (b) Hyperestrogenism
   (c) Pregnancy
   (d) a, b, and c
   (e) a and c

Correct Answers

1. e
2. e
3. e: Obesity contributes to stress urinary incontinence and pelvic organ prolapse. VRS is associated with vaginal child delivery, natural aging, multiple pregnancies [vaginal deliveries, not C-section], and menopause.
4. c: Initial therapy consists of diet reduction, smoking cessation, bladder training, and pelvic floor muscle training such as Kegel's, but if these do not work, then the gold standard therapy has been tension-free vaginal tape.
5. e: Risks factors for SUI include congenital factors, pregnancy, childbirth, hypoestrogenism (not hyperestrogenism), cognitive impairment, obesity, and advanced age.)

Cosmeceuticals

30

Zoe Diana Draelos

Abstract

The terms cosmeceutical and evidence-based may not belong in the same phrase. Cosmeceuticals are considered by many scientists to represent fluff without stuff, and indeed the reader may come to a similar conclusion at the end of this chapter. Nevertheless, it is worthwhile to examine the state of the science for cosmeceuticals as they represent an ever-expanding field in dermatology with perhaps much yet unrealized promise. Cosmeceuticals extend beyond cosmetics to enhance skin functioning, usually aiming to return the skin to a more youthful state. For example, wrinkle-reducing moisturizers, antioxidant serums, and skin-lightening salves all fall into this category. Cosmeceuticals are somewhat confusing, however, as both prescription and over-the-counter (OTC) products have been labeled by this term. Drug cosmeceuticals include topical retinoids for improving dermal collagen production, topical minoxidil for enhanced scalp hair growth, and eflornithine for facial hair growth reduction. These products will not be discussed, as they are not available to the consumer except by prescription. The second category of cosmeceuticals includes OTC drugs, such as sunscreens and antiperspirants. These also are outside the realm of this chapter. The discussion will focus on cosmeceuticals that are topically applied for the purpose of improving skin appearance.

Keywords

Cosmeceuticals · Growth factors · Antioxidants Carotenoids · Flavonoids · Polyphenols

Introduction

The terms cosmeceutical and evidence-based may not belong in the same phrase. Cosmeceuticals are considered by many scientists to represent fluff without stuff, and indeed the reader may come to a similar conclusion at the end of this chapter. Nevertheless, it is worthwhile to examine the state of the science for cosmeceuticals as they represent an ever-expanding field in dermatology with perhaps much yet unrealized promise. Cosmeceuticals extend beyond cosmetics to enhance skin functioning, usually aiming to return the skin to a more youthful state. For example, wrinkle-reducing moisturizers, antioxidant serums, and skin-lightening salves all fall into this category. Cosmeceuticals are somewhat confusing, however, as both prescription and over-the-counter (OTC) products have been

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labeled by this term. Drug cosmeceuticals include topical retinoids for improving dermal collagen production, topical minoxidil for enhanced scalp hair growth, and eflornithine for facial hair growth reduction. These products will not be discussed, as they are not available to the consumer except by prescription. The second category of cosmeceuticals includes OTC drugs, such as sunscreens and antiperspirants. These also are outside the realm of this chapter. The discussion will focus on cosmeceuticals that are topically applied for the purpose of improving skin appearance.

Cosmeceutical Development

The marketing of new ingredients and formulations with captivating advertising claims drives the cosmeceutical realm. The unending introduction of new products on a monthly basis makes generalization difficult, yet there are some basic concepts that apply to cosmeceutical development. These will be reviewed to help the reader better interpret the evidence to support cosmeceutical efficacy. First, cosmeceuticals are basically cosmetics and as such must be safe. This means that the best source of new materials for formulation would be substances derived from either plants or food components. Second, cosmeceutical additives must be available as a powder or liquid, since the majority of cosmeceuticals must be elegantly applied to the external body. Third, cosmeceuticals must have some easily identifiable benefit upon which to base a functional claim. For all of these reasons, the majority of cosmeceutical ingredients have their origin in the botanical realm or in foods.

New cosmeceutical ingredients in the botanical realm are identified based on the algorithm presented in Table 30.1. Once the botanical active is identified and synthesized, it is typically applied to a fibroblast gene chip to determine if it affects any key cellular event. After demonstration of a presumed physiologic effect, the active is tested in vitro to determine an effect on cultured fibroblasts. If positive data are obtained, the active is studied in a mouse model for confirmation. The active is then placed in a vehicle suitable for human application and clinical studies are undertaken. Successful human clinical studies pave the way for successful introduction into the marketplace via ingredient licensing arrangements.

The search for botanicals suitable for formulation into cosmeceuticals has led to the gathering of flowers, seeds, roots, leaves, twigs, and berries from plants all over the world. It is important to remember, however, that the constituents of a plant component are influenced by the season in which the plant material was picked, the growing conditions, and the processing of the agent. These variables are summarized in Table 30.2.

Table 30.1 Steps in cosmeceutical ingredient development

1. New botanical material received in the laboratory
2. Various fractions of the botanical extracted
3. Fractions analyzed for relationship to known chemical compounds
4. Purified fraction exposed to gene array chip
5. Analysis completed for upregulation or downregulation of key events in cellular oxidation, inflammation, or irritation
6. New isolate studied in an in vitro model of cell culture for confirmation of gene array results
7. Positive in vitro findings lead to isolate analysis in mouse model, focusing on markers of possible cutaneous benefit
8. Positive mouse findings lead to formulation in a vehicle suitable for human use
9. Human model testing conducted to determine if active has any cutaneous value
10. Formulation fine-tuned and patented
11. New ingredient licensed to cosmetic manufacturer
12. New technology enters the marketplace

Table 30.2 Sources of cosmeceutical actives

Plant source Leaves, roots, fruits, berries, stems, twigs, barks, flowers
Growing conditions Soil composition, amount of available water, climate variations, plant stress
Harvesting conditions Time from harvest to transport, care of plant materials during shipping, storage conditions prior to manufacture
Preparation method Crushing, grinding, boiling, distilling, pressing, drying
Final extract status Liquid, powder, paste, syrup, crystal
Concentration Sufficient amount of active to produce biologic effect

Cosmeceutical Efficacy

Cosmeceuticals have been introduced for many different purposes including improving skin texture, radiance, smoothness, tone, and pigmentation. The main benefit of most cosmeceutical formulations is a reduction in transepidermal water loss from the application of occlusive and humectant ingredients to the skin surface. Occlusive substances include petrolatum, mineral oil, vegetable oils, lanolin, and silicone oils. Humectant substances include glycerin, sodium pyrrolidone carboxylic acid (PCA), hyaluronic acid, propylene glycol, and proteins. There is no doubt that skin hydration is an important cosmeceutical benefit known as moisturization. Most cosmeceutical ingredients are placed in a moisturizing vehicle, making placebo-controlled studies inadequate. Cosmeceutical efficacy must be determined based on a double-blind comparison between the vehicle and the cosmeceutical active as compared to the vehicle alone. This study design would provide the most compelling evidence that the cosmeceutical ingredient produced a documented benefit. As the reader will discover, few cosmeceutical ingredients are studied with this methodology.

The claims pertaining to skin texture, radiance, and smoothness are moisturizer claims. These are primarily derived from vehicle effects. The more novel antiaging claims that this chapter will investigate are improvements in skin tone and pigmentation. Skin tone is a somewhat ambiguous term by design to allude to improvement in the characteristics of the skin associated with aging. Most of the ingredients that deliver on this benefit are antioxidants. The claim of pigmentation improvement is related to the ability of the cosmeceutical to lighten melasma and lentigines while overall improving skin color. The rest of this chapter will be devoted to the evidence surrounding the efficacy of antioxidants and pigment-lightening ingredients in cosmeceutical formulations.

Antioxidants

Antioxidants form one of the most popular categories of cosmeceutical ingredients. This is due to the fact that the major cause of cutaneous aging is oxidation of skin structures from highly reactive oxygen molecules present in our oxygen-rich environment. It is amazing to think that the life-giving oxygen required to survive is also the same oxygen responsible for aging the human body. The primary source of cosmeceutical antioxidant ingredients is botanical extracts, since all plants must protect themselves from oxidation following UV exposure.

Antioxidant botanicals function by quenching singlet oxygen and reactive oxygen species, such as superoxide anions, hydroxyl radicals, fatty peroxy radicals, and hydroperoxides. There are many botanical antioxidants available from raw material suppliers to the cosmeceutical industry, which can be classified into one of three categories as carotenoids, flavonoids, and polyphenols. Carotenoids are chemically related to retinoids, while flavonoids possess a polyphenolic structure that accounts for their antioxidant, UV-protectant, and metal chelation abilities. Lastly, polyphenols represent a chemical subset of flavonoids. These classes of antioxidants are discussed utilizing popular ingredients to take an evidence-based approach.

Carotenoids

Carotenoids are derivatives of vitamin A and have found widespread use in cosmeceuticals due to the established topical antiaging benefits associated with the prescription retinoid tretinoin. The carotenoids are a large family of orange-, red-, and yellow-appearing substances that perform vital antioxidant roles when ingested and are less well established as topical antioxidants.

Astaxanthin

Astaxanthin is a pink carotenoid found in high concentration in salmon, accounting for the characteristic pink color of the fish. This is the rationale for antiaging diets recommending the ingestion of a serving of salmon five times weekly [1] (IV,B). For topical application purposes, astaxanthin is obtained from the marine microalgae *Haematococcus pluvialis.*

The efficacy of astaxanthin is attributed to its cell membrane, composed of two external lipid layers, which has been touted to possess stronger antioxidant abilities than vitamin E [2] (IV,B). It is both water and oil soluble, only being produced by algae when exposed to intense UV radiation.

Few topical studies exist to confirm the topical effect of astaxanthin [3] (VI,C), but it has been studied extensively as an oral supplement [4] (IV,B). It is used as a homeopathic treatment for macular degeneration because unlike canthaxanthin, another carotenoid, it does not crystallize in the eye. It crosses the blood–brain barrier and has been studied in brain dysfunction to include spinal cord injuries and Parkinson's disease [5] (VI,C). Even though other carotenoids, such as beta-carotene, have been proven ineffective in reducing the oxidative stress associated with cardiovascular disease, astaxanthin is currently undergoing further investigation [6] (IV,B).

Astaxanthin in concentrations of 0.03–0.07% produces a pink-colored cream. This limits the concentration that can be used, but no topical adverse reactions have been associated with this carotenoid. The topical antioxidant benefits of astaxanthin have not been established.

Lutein

Another carotenoid found in topical cosmeceuticals is lutein. It is naturally found in green leafy vegetables, such as spinach and kale. Lutein is an antioxidant in the plant kingdom, also being used for blue light absorption. In the animal kingdom, lutein is found in egg yolks, animal fats, and the corpus luteum. It is a lipophilic molecule, not soluble in water, characterized by a long polyene side chain composed of conjugated double bonds. These double bonds are degraded by light and heat, a universal characteristic of carotenoids to a greater or lesser degree [7] (IV,B).

Lutein is used as a natural colorant due to its orange-red color resulting from the absorption of blue light. Its largest use is as a food supplement for chickens, which results in more vivid yellow yolks. In humans, lutein is concentrated in the macula and has been linked to the prevention of macular degeneration [8] (IV,B). It has been available as a nutritional supplement since 1996 and can be administered as a sublingual spray for elderly patients with macular degeneration. Most well-conducted studies evaluating the benefit of lutein for macular degeneration have been inconclusive [9] (IV,B). No recommended daily allowance has been established for lutein, but 6 mg/day has been published [10] (VI,C). Most of the lutein used for food additives is derived from marigolds.

The question remains as to whether lutein topically is of value. Again, data are lacking, but excess lutein intake can result in carotenodermia, and excess topical application results in bronzing of the skin. It may be of interest that lutein fed to chickens results in the characteristic yellow appearance of chicken skin, which is felt to be more attractive than the natural white skin. I am not sure that this would be the case in humans.

Lycopene

Another potent carotenoid is lycopene, found in most fruits and vegetables with a red color including tomatoes, watermelon, pink grapefruit, papaya, gac, red bell pepper, and pink guava. The highest lycopene-containing food is ketchup, but lycopene is not an essential human nutrient. The Mayo Clinic website rates the evidence for the use of lycopene as an antioxidant as a C, since it is not clear if lycopene has these effects on the human body [11] (IV,B). Lycopene oral supplements have been purported to reduce the risk of prostate cancer, but the FDA concludes there is little scientific evidence to support this claim [12] (VI,C).

Lycopene is a highly unsaturated hydrocarbon containing 11 conjugated and 2 unconjugated double bonds, which makes it a longer molecule than any other carotenoid. This makes its absorption into the skin doubtful. It undergoes *cis*-isomerization possibly when exposed to sunlight. Even though lycopene was the new oral supplement added to many commercial multivitamins this year, its topical value has never been documented. It is safe for skin application, but may stain the skin in high concentration.

Table 30.3 Cutaneous effects of topical retinoids

Gross dermatologic effects
Improvement in fine and coarse facial wrinkling
Decreased tactile roughness
Reduction of actinic keratoses
Lightening of solar lentigines
Histologic dermatologic effects
Reduction in stratum corneum cohesion
Decreased epidermal hyperplasia
Increased production of collagen, elastin, and fibronectin
Reduction in tonofilaments, desmosomes, melanosomes
More numerous Langerhans cells
Angiogenesis
Decreased glycosaminoglycans
Reduced activity of collagenase and gelatinase
Normalization of keratinization of the pilosebaceous unit

Retinol

Of all the topical carotenoids, retinol is the best understood, since it is necessary for vision and possesses a well-characterized skin receptor [13] (II,A). Prescription retinoids, such as tazarotene and tretinoin, are well studied for their ability to induce the skin changes noted in Table 30.3; however, OTC retinoids may demonstrate some of the same effects, to a lesser degree [14, 15] (II,A).

It is theoretically possible to interconvert the retinoids from one form to another. For example, retinyl palmitate and retinyl propionate, chemically known as retinyl esters, can become biologically active following cutaneous enzymatic cleavage of the ester bond and subsequent conversion to retinol. Retinol is the naturally occurring vitamin A form found in red, yellow, and orange fruits and vegetables. It is the pigment responsible for vision, but is highly unstable. Retinol can be oxidized to retinaldehyde and then oxidized to retinoic acid, also known as prescription tretinoin. It is this cutaneous conversion of retinol to retinoic acid that is responsible for the biologic activity of some of the new stabilized over-the-counter vitamin A preparations designed to improve the appearance of benign photodamaged skin [16] (II,A). Unfortunately, only small amounts of retinyl palmitate and retinol can be converted by the skin, accounting for the increased efficacy seen with prescription preparations containing retinoic acid.

The main problem with prescription retinoids is their irritancy. Unfortunately, as the biological efficacy of the retinoid increases, so does the irritancy. This is also the case with the OTC retinoids. Retinol is more irritating than the retinyl esters and also more unstable. It is for this reason that cosmeceutical formulations not manufactured under strict oxygen-free conditions prefer to add retinyl palmitate to moisturizing creams. However, the retinyl palmitate may present to act as an antioxidant for the lipids present in the moisturizer.

The topical benefit of retinol has been documented by well-controlled studies [17] (II,A). It is commonly felt among dermatologists that retinol is of benefit [18] (IV,B), but it is difficult in moisturizer studies that do not include vehicle control to separate the retinol benefit from the moisturizer benefit. Nevertheless, of all the carotenoids available for formulation, retinol has the most evidence to support topical application efficacy.

Flavonoids

Flavonoids are aromatic compounds, frequently with a yellow color, that occur in higher plants. Five-thousand flavonoids have been identified with a similar chemical structure possessing 15 carbon atoms and possessing a variety of biologic activities (Table 30.4) [19] (VI,C). Flavonoids can be divided into flavones, flavonols, isoflavones, and flavanones, each with a slightly different chemical structure. Currently, the most

Table 30.4 Biologic activity of flavonoids

Photoprotection against UVB
Quenching of reactive oxygen species
Metal chelation
Inhibition of targeted enzymes
Hormonal modulation
Anti-inflammatory activity
Microorganism growth inhibition
Antioxidant effect of multiple organ systems

common isoflavones incorporated into cosmeceuticals are daidzein and genistein derived from soybeans. Other sources of flavonoids include curcumin, silymarin, pycnogenol, and gingko. These will be discussed next.

Soy

The soybean-derived isoflavones genistein and daidzein function as phytoestrogens when orally consumed and have been credited with the decrease in cardiovascular disease and breast cancer seen in Asian women [20] (III,B). These isoflavones are present when the soy is fermented [21] (II,B). Other purported systemic benefits include improvement in immunity [22] (IV,C), reduction of prostate cancer [23] (IV,C), and improvement in cognition [24] (IV,C). Some of the cutaneous effects of soy have been linked to its estrogenic effect in postmenopausal women. Topical estrogens have been shown to increase skin thickness and promote collagen synthesis [25] (II,A). It is interesting to note that genistein increases collagen gene expression in cell culture; however, there are no published reports of this collagen-stimulating effect in topical human trials. Genistein has also been reported to function as a potent antioxidant scavenging peroxyl radicals and protecting against lipid peroxidation in vivo [26] (III,B). The only studies that document the ability of soy to protect against UVB-induced skin damage are in mice where a topical application of nondenatured soy extracts reduced UVB-induced cyclooxygenase-2 expression and prostaglandin-E2 secretion and inhibited p38 mitogen-activated protein (MAP) kinase activation [27] (II,B).

Curcumin

Curcumin is a popular natural yellow food coloring used in everything from prepackaged snack foods to meats. It is sometimes used in skin care products as a natural yellow coloring in products that claim to be free of artificial ingredients. Curcumin comes from the rhizome of the turmeric plant and is consumed orally as an Asian spice, frequently found in rice dishes to color the otherwise white rice yellow. However, this yellow color is undesirable in cosmetic preparations, since yellowing of products is typically associated with oxidative spoilage. Tetrahydrocurcumin, a hydrogenated form of curcumin, is off-white in color and can be added to skin care products not only to function as a skin antioxidant but also to prevent the lipids in the moisturizer from becoming rancid. The antioxidant effect of tetrahydrocurcumin is said to be greater than vitamin E by cosmetic chemists. It is said to provide antioxidant skin benefits by quenching oxygen radicals and inhibiting nuclear factor-κB [28, 29] (V,C).

The effects of curcumin as a topical antioxidant in the skin have not been as well studied as its oral ingestion in rodents for the correction of cystic fibrosis defects and inhibition of tumor proliferation [30, 31] (V,C).

Silymarin

Silymarin is an extract of the milk thistle plant (*Silybum marianum*), which belongs to the aster family of plants including daisies, thistles, and artichokes. The plant is named milk thistle because the oldest recorded use of the extract was to enhance human lactation and the plant produces a white milky sap. The extract consists of three flavonoids derived from the fruit, seeds, and leaves of the plant. These flavonoids are silybin, silydianin, and silychristine. Homeopathically, silymarin is used to treat liver disease, but it is a strong antioxidant preventing lipid peroxidation by scavenging free radical species. Its antioxidant effects have been demonstrated topically in hairline mice by the 92% reduction of skin tumors following UVB exposure [32, 33] (VI,C). The mechanism for this decrease in tumor production is unknown, but topical silymarin has been shown to decrease the formation of pyrimidine dimers in a mouse model [34] (VI,C). It has also been found to improve the healing of burns in albino rats [35] (VI,C).

Silymarin is found in a number of high-end moisturizers for benign photoaging to prevent cutaneous oxidative damage and to reduce facial redness. A double-blind placebo-controlled study

in 46 subjects with stage I–III rosacea found improvement in skin redness, papules, itching, hydration, and skin color [36] (III,B). This was felt to be due to its direct activity on modulating cytokines and angiokines. Other well-controlled human trials are lacking.

Pycnogenol

Pycnogenol is an extract of French marine pine bark (*Pinus pinaster*), which grows only on the southwest coast of France in Les Landes de Gascogne. The extract is a water-soluble liquid containing several phenolic constituents, including taxifolin, catechin, and procyanidins. It also contains several phenolic acids, including p-hydroxybenzoic, protocatechuic, gallic, vanillic, p-couric, caffeic, and ferulic [37] (VI,C). It is a trademarked ingredient that is sold for oral consumption as a preventative for cardiovascular disease [38], a treatment for diabetic microangiopathy [39], and a pain reliever for muscle cramps [40] (IV,B). It is a potent-free radical scavenger that can reduce the vitamin C radical, returning the vitamin C to its active form [41] (VI,C). The active vitamin C in turn regenerates vitamin E to its active form, maintaining the natural oxygen-scavenging mechanisms of the skin intact.

Pycnogenol is the ideal antiaging additive since it demonstrates no chronic toxicity, no mutagenicity, no teratogenicity, and no allergenicity [42] (VI,C). It is consumed orally to enhance the production of nitric oxide, which inhibits platelet aggregation in coronary artery disease, thus it is also deemed safe for topical use. Its use for skin indications is less well documented, however. In B16 melanoma cells, it was shown to inhibit tyrosinase activity and melanin biosynthesis [43] (IV,B). Many discussions of antioxidant flavonoids include a mention of pycnogenol, but little quality data are presented [44] (VI,C).

Ginkgo

Ginkgo biloba, also named the maidenhair tree, is the last member of the Ginkgoaceae family, which grew on earth some 200–250 million years ago. For this reason, ginkgo contains flavonoids not found in other botanicals. It possesses bilobalide (a sesquiterpene), ginkgolides (diterpenes with 20 carbon atoms), and other aromatic substances such as ginkgol, bilobdol, and ginkgolic acid. It is a plant with numerous purported benefits which has been a common part of homeopathic medicine in the Orient for 4000 years. The plant leaves are said to contain unique polyphenols such as terpenoids (ginkgolides, bilobalides), flavonoids, and flavonol glycosides that have anti-inflammatory effects. These anti-inflammatory effects have been linked to antiradical and antilipoperoxidant effects in experimental fibroblast models [45] (IV,C). Ginkgo flavonoid fractions containing quercetin, kaempferol, sciadopitysin, ginkgetin, and isoginkgetin have been demonstrated to induce human skin fibroblast proliferation in vitro. Increased collagen and extracellular fibronectin were also demonstrated by radioisotope assay [46] (IV,C). Thus, ginkgo extracts are added to many cosmeceuticals to function as antioxidants and promoters of collagen synthesis based on nonhuman models of oxidative damage.

Polyphenols

Polyphenols are a subset of flavonoids used in many cosmeceuticals. Two main sources of polyphenols are teas and fruits. This section presents green tea and pomegranate as examples of the evidence available to support polyphenol biologic activity.

Green Tea

Tea, also known as *Camellia sinensis*, has been botanically popular in the Orient for 5000 years, used both topically and orally. Teas are a rich part of the Oriental culture used to stay alert during extended meditation. An Indian legend tells of a Prince Siddhartha Gautama, the founder of Buddhism, who tore off his eyelids in frustration over his inability to stay awake

during meditation. A tea plant is said to have sprouted from where his eyelids fell, providing the ability to stay awake, meditate, and reach enlightenment. Tea reached Western cultures during the sixth century from Turkish traders.

There are several different types of teas: green, black, oolong, and white. The different teas come from the same plant, but different processing imparts different properties. Green tea is made from unfermented tea leaves and contains the highest concentration of polyphenol antioxidants [47] (VI,B). Black tea leaves are fermented days before heating. Oolong tea originates in the Fukien province of China, and the leaves are treated much like black tea, except that the withering and fermentation times are minimized. White tea comes from young tea leaves that are harvested for a few days each spring when the plant emerges from the ground. These leaves are said to be very high in antioxidants. The highest-quality white tea is obtained from buds that are just ready to open, known as needles or tips.

The evidence to support the anticancer benefits of topical and oral green tea use was felt to be inadequate by the FDA. On June 30, 2005, the FDA concluded, "that there is no credible evidence to support qualified health claims for green tea consumption and a reduced risk of gastric, lung, colon/rectal, esophageal, pancreatic, ovarian, and combined cancers. Thus, the FDA is denying these claims. However, FDA concludes that there is very limited credible evidence for qualified health claims specifically for green tea and breast cancer and for green tea and prostate cancer, provided the claims are appropriately worded so as not to mislead consumers" [48] (VI,C). In addition, the evidence to support cardiovascular benefits was inadequate. On May 9, 2006, in response to "Green Tea and Reduced Risk of Cardiovascular Disease," the FDA concluded "there is no evidence to support qualified health claims for green tea or green tea extract and a reduction in a number of risk factors associated with cardiovascular disease" [49] (VI,C). Some FDA advisers have voiced concern that teas may contain high levels of pesticides and heavy metals.

Green tea is manufactured from both the leaf and bud of the plant. Orally, green tea is said to contain beneficial polyphenols, such as epicatechin, epicatechin-3-gallate, epigallocatechin, and eigallocatechin-3-gallate (EGCG), which function as potent antioxidants [50] (IV,B). EGCG is the most potent of the polyphenols, sold as a white caffeine-free powder [51] (VI,C). Oral studies with EGCG have demonstrated increased fat oxidation and improvements in heart rate and serum glucose levels with 300 mg [52, 53] (V,B). Other alkaloids present in green tea include caffeine, theobromine, and theophylline.

Green tea can be easily added to topical creams and lotions designed to combat the signs of photoaging, but it must be stabilized itself with an antioxidant, such as butylated hydroxytoluene. The Mayo Clinic Drugs and Supplements rates the evidence to support green tea as a photoprotectant as a C [54] (VI,C).

A study by Katiyar et al. demonstrated the anti-inflammatory effects of topical green tea application on C3H mice. A topically applied green tea extract containing GTP ((−)-epigallocatechin-3-gallate) was found to reduce UVB-induced inflammation, as measured by double skin-fold swelling [55] (IV,B). They also found protection against UV-induced edema, erythema, and antioxidant depletion in the epidermis. This work was further investigated by applying GTP to the back of humans 30 min prior to UV irradiation, which resulted in decreased myeloperoxidase activity and decreased infiltration of leukocytes as compared to untreated skin [56] (III,B).

The application of topical green tea polyphenols prior to UV exposure has also been shown to decrease the formation of cyclobutane pyrimidine dimers [57] (IV,B). These dimers are critical in initiating UV-induced mutagenesis and carcinogenesis, which represent the end stage of the aging process. Thus, green tea polyphenols can function topically as antioxidants, anti-inflammatories, and anti-carcinogens, making them a popular cosmeceutical additive [58, 59] (III,B).

Pomegranate

Similar to lycopene, another oral supplement appearing in health drinks and vitamin is pomegranate extract. Pomegranate, botanically known as *Punica granatum*, is a deciduous tree bearing a red fruit native to Afghanistan, Pakistan, Iran, and Northern India [60]. It was brought to California by the Spanish settlers in 1769 and is commercially cultivated for its juice. The pomegranate became famous in Greek mythology when Persephone was kidnapped by Hades and taken to the Underworld to be his wife. Persephone had consumed four pomegranate seeds while in the Underworld and thus had to spend 4 months every year in Hades, during which time nothing would grow. This gave rise to the season of winter.

Pomegranate juice, commonly consumed in the Middle East, provides about 16% of the adult requirement of vitamin C per 100 mg serving. It also contains pantothenic acid, also known as vitamin B5, potassium, and antioxidant polyphenols. These substances have been demonstrated to protect against UVA- and UVB-induced cell damage in SKU-1064 human skin fibroblasts [61] (IV,B). Pomegranate juice has also been purported to reduce oxidative stress, affect low-density lipoprotein (LDL), and platelet aggregation in humans and apolipoprotein e-deficient mice [62, 63] (IV,B). It has also been studied for improving hyperlipidemia in diabetic patients [64] (IV,B).

Other Antioxidants

Aloe Vera

Probably the most widely used cutaneous botanical anti-inflammatory is aloe vera. The mucilage is released from the plant leaves as a colorless gel and contains 99.5% water and a complex mixture of mucopolysaccharides, amino acids, hydroxy quinone glycosides, and minerals. Compounds isolated from aloe vera juice include aloin, aloe emodin, aletinic acid, choline, and choline salicylate [65] (VI,C). Reported cutaneous effects of aloe vera include increased blood flow, reduced inflammation, decreased skin bacterial colonization, and enhanced wound healing [66] (VI,C). The anti-inflammatory effects of aloe vera may result from its ability to inhibit cyclooxygenase as part of the arachidonic acid pathway.

The MedlinePLus Herbs and Supplements rates the evidence to support the use of aloe vera in the treatment of dry skin and burns as a C. Other studies have evaluated the effect of aloe vera on burn wounds and acne [67, 68] (V,C). Aloe vera cream was found to show no tanning or sunburn protection and no efficacy in sunburn treatment as compared to placebo [69] (III,B). Reuter et al. studied a 97.5% concentration of aloe vera for its anti-inflammatory effects and demonstrated positive results in a sunburn cell assay as compared to 1% hydrocortisone [70] (III,B). These data provide evidence for the anti-inflammatory effect of pure aloe vera gel; however, most products sold over-the-counter for under $10 do not contain a high enough percentage of aloe vera to induce clinically relevant inflammation reduction.

Coenzyme Q10

An endogenous antioxidant that has been incorporated into antiaging moisturizers is Coenzyme Q10, also known as ubiquinone or CoQ10. For a topical antioxidant to be clinically effective, it must penetrate into the skin. Hoppe and colleagues from Beiersdorf demonstrated the topical penetration of Coenzyme Q10 into the viable epidermis and a reduction in oxidation as measured by weak photon emission. They were also able to show a significant decrease in the expression of collagenase in human dermal fibroblasts following UVA radiation and improvement in orbital wrinkling [71, 72] (III,B). However, oral supplementation had no effect on the main antioxidant defenses or prooxidant generation in tissues in mice. It also did not affect the life span in mice according to Sohal et al. [73] (III,B). A human study by Passi et al. administered 50 mg

vitamin E, 50 mg Coenzyme Q10, and 50 mg selenium. An increase in stratum corneum Coenzyme Q10 was noted after 15 and 30 days of ingestion, but the significance of this finding was not evaluated [74] (II,B).

Other evidence suggests that topical Coenzyme Q10 may provide additive antioxidant benefits when combined with colorless carotenoids phytoene and phytofluene. This effect was demonstrated in fibroblast cultures [75] (IV,C).

Pigment-Lightening Agents

Facial hyperpigmentation is one of the most common signs of photoaging. Many different patterns can be seen. Focal hyperpigmentation in the form of small lentigines across the lateral cheeks usually begins at about age 25–30, depending on cumulative sun exposure, with continued accumulation of lesions throughout life. Pigmentation can also present in the form of melasma with reticulated pigment over the sides of the forehead, lateral jawline, and upper lip. Lastly, hyperpigmentation can present as overall darkening of the skin from a combination of melanin pigment, fragmented elastin fibers, and residual hemosiderin. Cosmeceutical treatments for hyperpigmentation are problematic. A successful treatment must remove existing pigment from the skin, shut down the manufacture of melanin, and prevent the transfer of existing melanin to the melanosomes.

Many cosmetic products are available to lighten skin and improve even skin tone. These products typically do not contain hydroquinone, but rather other botanically derived products that interrupt melanin synthesis. These botanicals include ascorbic acid, licorice extract, alpha-lipoic acid, kojic acid, aleosin, and arbutin. Hydroquinone has been eliminated from most cosmetics, since the European Union and Asia have removed hydroquinone from the over-the-counter market. Most cosmetic companies are international in their distribution and formulate for the global market and not the US market specifically, where over-the-counter hydroquinone is still allowed. This section evaluates the data to support the efficacy of the most popular botanicals in skin lightening.

Ascorbic Acid

Ascorbic acid, also known as vitamin C, is used in cosmeceuticals for hyperpigmentation because it interrupts melanogenesis by interacting with copper ions to reduce dopaquinone and blocks dihydrochinindol-2-carboxyl acid oxidation [76] (II,A). Ascorbic acid, an antioxidant, is rapidly oxidized when exposed to air with limited stability. For this reason, many cosmeceuticals are using the more stable magnesium ascorbyl phosphate, which is metabolized to ascorbic acid in the skin. High concentrations of ascorbic acid must be used with caution, however, as the low pH can be irritating to the skin. Pigment-lightening cosmeceuticals may contain ascorbic acid as a pH adjustor or to function as an antioxidant preservative. It is important to recognize that ascorbic acid is a multifunctional ingredient with very minimal pigment-lightening capabilities.

Licorice Extract

Licorice extracts are found in cosmeceuticals to decrease facial redness and reduce pigmentation. The extract contains liquiritin and isoliquiritin, which are glycosides containing flavonoids [77] (III,B), which induce skin lightening by dispersing melanin. To see clinical results, the liquiritin must be applied in the dose of 1 g/day for 4 weeks. Irritation is not a side effect as is so frequently observed with hydroquinone and ascorbic acid, but efficacy is minimal.

Alpha-Lipoic Acid

Alpha-lipoic acid is found in a variety of antiaging cosmeceuticals to function as an antioxidant [78] (II,B), but it may also have very limited pigment-lightening properties. It is a disulfide derivative of octanoic acid that is able to inhibit tyrosinase. However, it is a large molecule, and

cutaneous penetration to the level of the melanocyte is challenging, significantly reducing its efficacy.

Kojic Acid

Kojic acid, chemically known as 5-hydroxymeth yl-4H-pyrane-4-one, is one of the most popular cosmeceutical skin-lightening agents found in cosmetic over-the-counter skin-lightening creams distributed worldwide. It is a hydrophilic fungal derivative obtained from *Aspergillus* and *Penicillium* species. It is the most popular agent employed in the Orient for the treatment of melasma; however, it is highly unstable [79] (IV,B). Newer formulations have incorporated kojic dipalmitate, but the efficacy of this derivative has not been well studied. Some research indicates that kojic acid is equivalent to hydroquinone in pigment-lightening ability [80] (IV,B). The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper.

Aleosin

Aleosin is a low-molecular-weight glycoprotein obtained from the aloe vera plant. It is a natural hydroxymethylchromone functioning to inhibit tyrosinase by competitive inhibition at the DOPA oxidation site [81, 82] (IV,B). In contrast to hydroquinone, it shows no cell cytotoxicity; however, it has a limited ability to penetrate the skin due to its hydrophilic nature. The effects of aleosin have been largely demonstrated in pigmented skin equivalents, not human use studies [83] (IV,B). It is sometimes mixed with arbutin, our next topic of discussion, to enhance its skin-lightening abilities.

Arbutin

Arbutin, chemically known as 4-hydroxyphenyl-beta-glucopyranoside, is obtained from the leaves of the *Vaccinium vitis-idaea* and other related plants. It is a naturally occurring glucopyranoside that causes decreased tyrosinase activity without affecting messenger RNA expression [84] (IV,C). It also inhibits melanosome maturation. Arbutin is not toxic to melanocytes and is used in a variety of pigment-lightening preparations in Japan at concentrations of 3%. Higher concentrations are more efficacious than lower concentrations, but a paradoxical pigment darkening may occur. Arbutin-beta-glycosides have been produced that are less cytotoxic than arbutin [85] (VI,C).

Growth Factors

Growth factors are the newest cosmeceutical ingredients to enter the marketplace. Since growth factors are instrumental in modulating cellular behavior, their ability to improve the functioning of aging skin cells represents intriguing technology. Of the many human growth factors, epidermal growth factor (EGF) is most important due to its direct influence on keratinocyte growth and differentiation [86] (5,A). The concept of growth factor incorporation into moisturizers began with the utilization of spent fibroblast media derived from the culture of fetal foreskins [87] (5,A). This spent media was previously discarded as the fibroblasts were cultured for a variety of medical uses. The spent media contained some remaining unused nutrients and numerous substances secreted by the fibroblasts during their growth [88] (5,B). The spent media product utilized a unique two-chamber design whereby the fibroblast media was dispensed from one orifice while the moisturizer was expressed from a second separate orifice. The two chambers were encased in a single tube dispenser.

This early growth factor introduction and the increased ability to engineer problems led to synthesis of recombinant growth factors and their incorporation into cosmeceutical moisturizers. The recombinant manufacturing technique removed the materials obtained from the host, insuring increased purity and quality, without possible contamination. Further, the technique allowed a standardized dose to be obtained, which provided for better clarification of how a

specific amount of growth factor affected skin appearance. However, growth factors are large protein molecules with limited penetration through the stratum corneum, thus the recombinant growth factor can be formulated as a lyophilized powder subsequently placed into a nano-liposome solution for enhanced delivery [89] (5,C). This novel approach to delivery overcomes some of the prior challenges in formulating growth factor-containing cosmeceuticals.

Another technology involves deriving growth factors from neonatal fibroblasts cultured in a bioreactor on dextran microcarrier beads under low oxygen conditions (1–5%) mimicking embryonic conditions. The cells are cultured for 8 weeks without the need for fetal bovine serum constituents in the final product. This method creates two products. The first is a naturally secreted extracellular matrix (ECM) used in wound healing, and the second is the hypoxic conditioned culture media (HCCM) for antiaging appearance improvement purposes. The HCCM is then concentrated using a 10 kDa filter and tested for sterility, as well as the following constituents: endotoxin, vascular endothelial growth factor (VEGF), and keratinocyte growth factor (KGF) [90] (5,A). An analysis of the HCCM material as compared to standard cell conditioned media cultured under normoxic conditions revealed that the hypoxic culture environment resulted in a 11.51-fold increase in KGF and a 4.33-fold increase in VEGF-B [91] (5,B). This multipotent growth factor has been investigated in healing diabetic foot ulcers [92] (5,C), improving appearance in facial aging [93] (5,C), and treating adverse events associated with photodynamic therapy [94] (5,C).

Cosmeceutical Barrier Cream Devices

A new use of cosmeceuticals is approval through the 510 K route of devices designed to improve the skin barrier. These creams utilize ingredients found in OTC products, but obtain approval to become medical devices and are designed to be used in conjunction with prescription products in the treatment of dermatoses demonstrating barrier defects, such as eczema and atopic dermatitis. While these products are regulated as devices, they are utilized as cosmeceuticals because they contain moisturizing ingredients combined with other OTC technologies to improve skin appearance and functioning.

Typically, these cosmeceuticals contain a moisturizing vehicle to which ingredients to build the intercellular lipids, minimize itch, and reduce inflammation are added. Most vehicles contain dimethicone and petrolatum as occlusive moisturizers to create a temporary skin barrier, combined with glycerin as a humectant to attract and hold water in the stratum corneum and epidermis. In order to speed barrier repair, some products contain pseudoceramides, which are synthetic ceramides designed to augment the natural ceramides present in the intercellular lipids deficient in many eczematous dermatoses. One example of such a ceramide is ceramide PC-104, with the corresponding chemical name *N*-(3-hexadecyloxy-2-hydroxypropyl)-*N*-2-hydroxyethylhexadecanamide. It is a synthetic pseudoceramide free of contaminants, as many natural ceramides are derived from bovine sources [95] (5,A) [96] (5,A). Topical pseudoceramides have been shown to improve stratum corneum water holding properties and facilitate barrier repair important in sensitive skin conditions [97] (5,B), [98] (5,B), [99] (5,B).

The second need of a sensitive skin moisturizer is itch reduction. Palmitoylethanolamine (PEA), also known as palmitamide MEA, belongs to the family of *N*-acylethanolamines (NAE). Cells naturally produce these substances in order to downregulate the inflammatory response via cannabinomimetic action on cannabinoid (CB) receptors [100] (5,A). This observation has led to the postulation that this family of molecules might possess analgesic, antioxidant, and anti-inflammatory skin benefits. CB 1 receptors are found in the brain and peripheral tissues, while CB 2 receptors are distributed throughout the immune system and in cutaneous nerve fibers [101] (5,A). Cannabinoid receptor agonists, such as PEA, reduce histamine-induced itch and

vasodilation when applied topically prior to histamine [102] (5,A), [103] (5,A).

The third need of sensitive skin is inflammation reduction. Many of the antioxidants previously discussed in this chapter also function as anti-inflammatory ingredients and are used in barrier repair cosmeceuticals for this purpose. Commonly used anti-inflammatory botanicals include grape seed extract, which contains the antioxidants proanthocyanidin and polyphenol, and a licorice extract, containing glycyrrhetinic acid. Proanthocyanidin possesses antioxidant free radical neutralizing effects 20 times more potent than vitamin C and 50 times more potent than vitamin E [104] (5,C).

Summary

Cosmeceuticals form an important part of the over-the-counter skin treatment market, but evidence for efficacy is clearly lacking. This chapter has scanned the reputable literature looking for research to substantiate the use of topical antioxidants and pigment-lightening agents to improve skin functioning and appearance. It may be surprising that so little good research has been conducted on products that are ubiquitous in the current marketplace. While there is never a good rationale for product sales without documentation, many cosmetic manufacturers are slow to engage in this type of research. Data that demonstrate convincing efficacy in large double-blind, vehicle-controlled trials would possibly raise the specter that a previously classified over-the-counter formulation could be reclassified as a drug.

An excellent example of reclassification is a lash growing cosmetic that was removed from the market by the FDA. A liquid for stimulating lash growth was recently marketed by a physician and spa dispensed cosmeceutical company. The product performed amazingly well, resulting in documentable lash lengthening after 3 months of use. The product enjoyed high sales until it was discovered that the product contained a chemical similar to a prescription glaucoma drug. The product was removed from the market because the FDA felt that the drug had been misbranded as a cosmetic. Products that perform too well are subject to inspection.

Development of a cosmeceutical category, similar to the quasi-drug category in Japan, would pave the way for better evidence in the cosmeceutical realm. This would provide an open opportunity for manufacturers to fully understand the efficacy or lack thereof for specific ingredients and final formulations. Until this legislation in enacted, cosmeceuticals will lack the evidence-based knowledge required for legitimacy.

Evidence-Based Summary

1. Cosmeceuticals are unregulated cosmetics that do not always adhere to evidence-based scientific methods of study.
2. The most active ingredients in cosmeceuticals are the moisturizing ingredients that compose the vehicle, which is challenging when conducting vehicle-controlled studies as part of an evidence-based approach.
3. Antioxidants are a major category of cosmeceuticals, which include carotenoids, flavonoids, and polyphenols.
4. Developing evidence-based therapeutic antioxidants is challenging because antioxidants provide protection against future oxidative skin insults and cannot repair past damage, requiring large sample size multiyear longitudinal studies.

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Self-Assessment Questions

1. How do antioxidants function to prevent oxidative damage?
   (a) Antioxidants quench singlet oxygen through electron translocation.
   (b) Antioxidants donate an electron to reactive oxygen species.
   (c) Antioxidants consume oxygen to stabilize reactive oxygen species.
   (d) a and b
   (e) b and c
   (f) a and b and c
2. The carotenoids include
   (a) Astaxanthin
   (b) Soy
   (c) Lutein
   (d) Lycopene
   (e) a and b and c
   (f) a and c and d
3. Cosmeceutical pigment-lightening agents function by
   (a) Inhibiting tyrosinase
   (b) Stabilizing melanin
   (c) Providing photoprotection
   (d) a and b
   (e) a and c
   (f) a and b and c
4. Cosmeceuticals are classified in the United States as
   (a) Over-the-counter drugs
   (b) Quasi-drugs
   (c) Prescription drugs
   (d) No classification currently exists
   (e) a and b
   (f) a and d
5. Cosmeceutical ingredients are derived from
   (a) Leaves
   (b) Twigs
   (c) Animals
   (d) Algae
   (e) a and b
   (f) All of the above

Correct Answers

1. b: Antioxidants donate an electron to reactive oxygen species. Reactive oxygen species are highly energetic and damaging to the skin due to loss of an electron. Antioxidants possess an extra electron that can be donated. Once the antioxidant donates an electron, it becomes oxidized itself.
2. f: a and c and d. Astaxanthin, lutein, and lycopene are all carotenoids. Lycopene is rich in tomatoes, while lutein is found in egg yolks and is necessary for oxidative protection of the retina. Astaxanthin is present in salmon.
3. e: a and c. Unfortunately, there are no substances yet discovered that stabilize melanin. Substances that induce skin lightening do so by decreasing melanin production. This can be accomplished by decreasing tyrosinase, the rate-limiting step in melanin synthesis, or preventing pigment darkening through photoprotection.
4. d: No classification currently exists. Cosmeceuticals are considered cosmetics by the US FDA, and thus no classification currently exists.
5. f: All of the above. All parts of the plant are used as botanical ingredients in cosmeceuticals. Each part possesses different ingredients, which are largely antioxidants, conferring different purported skin benefits.

Repairs of the Ear

31

Sean R. Christensen and Christopher R. Stamey

Abstract

The external ear, or auricle, is a complex three-dimensional structure with an intricate topography that presents unique reconstructive challenges. Consideration of the anatomic, functional, and cosmetic requirements of the auricle facilitates effective surgical reconstruction. Repairs of the ear can be divided into four major categories that address these requirements in different ways: linear and wedge repairs, skin grafts, single-staged flaps, and multi-staged flaps. There is strong evidence to support the efficacy and safety of auricular reconstruction, and specific categories of repair are optimally suited to particular types of defects. However, with few exceptions, there is a paucity of high-level evidence that directly compares the outcomes of one repair type to another. This chapter provides an evidence-based review of each of the major categories of auricular reconstruction. As an alternative to reconstruction, healing by second intention can be a viable option for surgical defects of the ear, and long-term functional and cosmetic outcomes may be comparable to primary repair for appropriately selected defects.

Keywords

Surgical reconstruction · Linear repair · Wedge repair · Local cutaneous flap · Chondrocutaneous flap · Interpolation flap · Skin graft · Second intention healing

Introduction

The external ear, or auricle, is a complex three-dimensional structure with an intricate topography. An understanding of this structure and its individual anatomic subunits is essential for optimal surgical reconstruction. Different reconstructive techniques may be best suited for specific auricular defects based on size, depth, and anatomic subunits affected. In the most simplistic categorization, the ear can be considered to have two surfaces: the anterior (lateral) and posterior (medial) surfaces. The posterior surface of the auricle is composed of epidermis, dermis, and a thin layer of subcutaneous adipose that is loosely affixed to the relatively smooth contour of the underlying cartilaginous structure. The skin of the posterior surface has moderate laxity, is adjacent to a large reservoir of redundant skin in the

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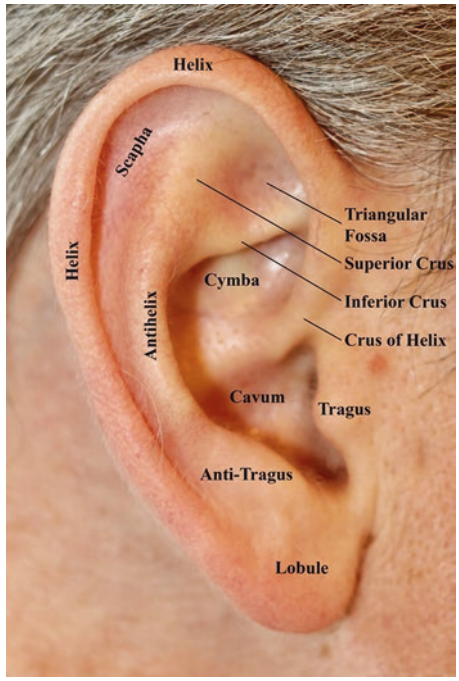

Fig. 31.1 Surface anatomy of the anterior (lateral) auricle. As discussed in the text, the main cartilaginous ridges are the helix with its crus and the antihelix with its superior and inferior crura. The cymba and the cavum together comprise the conchal bowl, which is contiguous with the external auditory canal. The lobule is largely devoid of cartilaginous support

postauricular crease, and is generally amenable to various methods of surgical manipulation. The skin of the anterior surface, in contrast, is composed of epidermis and a thinner dermis that is adherent to the undulating ridges and furrows of the more complicated cartilaginous structure. These ridges define the key anatomic subunits of the auricle as depicted in Fig. 31.1. Recognizable cartilaginous ridges are the helix and its crus, the antihelix and its crura, and the tragus and antitragus. The concavities between these ridges include the scapha, triangular fossa, and the cymba and cavum, which together comprise the conchal bowl that is contiguous with the external auditory canal. The lobule is the inferior portion of the ear that is largely devoid of cartilaginous support.

Consideration of the anatomic, functional, and cosmetic requirements of the auricle facilitates effective surgical reconstruction while minimizing the risk of significant complications. This chapter aims to provide an evidence-based framework with which to guide auricular reconstruction. While there is substantial evidence to support the efficacy and safety of auricular reconstruction in general, there is limited high-quality evidence comparing different operative techniques. Experience and judgment are required to select the optimal method of reconstruction for individual defects in unique patients and clinical scenarios.

Indications for Auricular Reconstruction

For dermatologic surgeons, the majority of reconstructive needs arise after surgical excision of malignant neoplasms including basal cell carcinoma, squamous cell carcinoma, and melanoma. While the resulting surgical defects may be extensive, the remaining adjacent skin and cartilage of the ear usually provide an adequate framework for immediate reconstruction. It is critical, however, to ensure that all surgical margins are free of carcinoma prior to surgical reconstruction, particularly in cases that require significant tissue rearrangement. In cases when immediate pathologic margin verification is not possible, delayed reconstruction should be considered. The surgeon can be confident that a delay of 1–3 weeks will not affect the final outcome, particularly in light of the fact that most excisional wounds of the auricle are able to heal completely by second intention (see Alternative Procedures below).

Aside from excision of malignant tumors, other conditions of the ear may benefit from surgical reconstruction. Benign tumors such as epidermal cysts can often be simply excised, and the resulting defects repaired with simple or more advanced reconstructive techniques as indicated (4) [1]. Keloids and hypertrophic scars can be repaired with a variety of reconstructive techniques but with the important addition of adjuvant therapy such as intralesional corticosteroids to prevent recurrence (4) [2–5]. Traumatic injury of the ear, most commonly affecting the helical rim or lobule, is also amenable to reconstruction

with many of the surgical approaches described in this chapter. Complete ear reconstruction for congenital malformations or massive thermal or physical injury is outside the scope of practice of most dermatologic surgeons and will not be discussed here. The reader is referred to the otolaryngology and plastic surgery literature for detailed discussion of these techniques [6, 7].

Effectiveness of Auricular Reconstruction

The goal of auricular reconstruction is to achieve complete wound closure while preserving the cosmetic appearance and functional requirements (patent external auditory meatus for sound conduction and physical support structure for eyeglasses or hearing aids) of the external ear. This should be accomplished with a minimum of discomfort or risk to the patient. Based upon published studies in the literature, auricular reconstruction in general is remarkably effective in appropriately selected patients. As outlined in Tables 31.1, 31.2, 31.3, and 31.4, over 2500 cases have been reported with successful outcomes and a low rate of complications (<5% overall). In most reported studies, cosmesis and adequate closure of the surgical defect were primary outcomes. Cosmesis was primarily measured in terms of ear contour, symmetry, and normal projection angle from the head (lack of protrusion or pinning of the affected ear). Many studies also described patient perceptions of cosmetic outcome in the form of visual analog scales, which may provide a more reliable measure of patient satisfaction. Most published studies on auricular reconstruction, as discussed in detail below, are retrospective series without defined inclusion and exclusion criteria and without systematic outcomes assessment. This somewhat limits the applicability of these results to all patients, and the surgeon must therefore exercise care in appropriate patient selection when considering reconstructive techniques. Additional research is likely to improve our understanding of which techniques are best suited to specific defects or clinical scenarios and which techniques may optimize efficiency in terms of healing time and financial burden.

Preoperative Evaluation

During the preoperative evaluation, past medical and surgical history, social history (including substance use), medication use, and overall functional status are essential factors to consider. It is important to note that older patients or patients in poor general health may be unable to tolerate lengthy or complex procedures. In these patients, simpler methods of reconstruction, even those that result in less than optimal cosmetic results, may be more appropriate, although there is a lack of specific evidence to support this. Tobacco use is often noted as a critical factor affecting reconstructive outcomes. In a prospective trial of antibiotic use for skin grafts on the nose, Kuijpers et al. found that smoking was associated with an increased rate of graft failure: at 1 week, mean graft survival was 81% in non-smokers and only 38% in smokers (2b) [8]. This finding is supported by larger studies in patients undergoing plastic surgery revealing higher rates of wound healing complications and dehiscence in smokers. Goltsman et al. found that smokers had a higher likelihood of surgical complications (OR, 1.37; $p < 0.0001$), medical complications (OR, 1.24; $p = 0.0323$), wound complications (OR, 1.49; $p < 0.0001$), and wound dehiscence (OR, 1.84; $p < 0.0001$) (2b) [9]. Additional studies also provide evidence to support grade A/B recommendations in favor of discontinuing smoking prior to reconstructive surgery procedures [10].

Indications for prophylactic antibiotic use to prevent infection at the site of ear reconstruction, as in dermatologic surgery in general, remain poorly defined. The majority of studies on ear reconstruction do not specifically comment on the use of prophylactic antibiotics. In three studies utilizing second intention healing and full-thickness skin grafting, prophylactic antibiotics were prescribed although the criteria for use were not specified [11–13]. However, the overall rate of soft tissue skin infections in all reconstructive methods, with or without antibiotics, was

Table 31.1 Wedge and linear

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Reddy (2004)	[31]	Retrospective case series	Linear repair (among others for various defects)	9 linear repairs	No complications reported	Satisfactory form and function (not specifically defined)	4
Ibrahim (2014)	[30]	Retrospective case series	Linear repair (among others for various defects)	4 linear repairs	No complications reported	Satisfactory form and function (not specifically defined)	4
Kitchens (1989)	[33]	Retrospective case series	Wedge repair of auricular defects	30 patients	No complications reported	Subjectively reported as good cosmesis in all patients	4
Taylor (2014)	[34]	Retrospective case series	Wedge repair of helix defects	12 patients	Mild ear projection in all patients	Satisfactory cosmesis, mean score 9.08 (of 10) on visual analog scale	4

Table 31.2 Grafts

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Full-thickness skin grafts (FTSG)							
Dessy (2010)	[19]	Randomized prospective trial	Pedicled flap vs FTSG for conchal defects	40 patients (20 flaps and 20 FTSG)	30% of FTSG had partial necrosis and delayed healing	Significantly higher visual analog scores with flap reconstruction	2b
Hochwalt (2015)	[11]	Retrospective cohort study	FTSG vs second intention healing of helix defects	18 FTSG vs 29 defects with second intention healing (SIH)	No difference in minor complications (12% SIH vs 14.3% FTSG)	No statistical difference in VAS scores	2b
Trufant (2016)	[35]	Retrospective case series	FTSG	1519 grafts	1.2% graft failure, 0.3% hematoma, 0.1% infection rate	Subjectively reported as good to excellent cosmesis	4
Leibovitch (2006)	[12]	Prospective case series	FTSG	216 grafts	<3% partial failure, <1% contracture, trapdoor, complete failure, infection, acute bleeding	Satisfactory form and function (not specifically defined)	4
Petersen (2015)	[36]	Retrospective case series	FTSG	43 grafts	Partial necrosis/crusting in 2 patients, 1 infection	Subjectively reported as good cosmesis	4
Split-thickness skin grafts (STSG)							
Wines (2001)	[40]	Retrospective case series	Skin graft (and other) repairs of conchal bowl	152 STSG, 32 FTSG	Graft failure: 9.4% in FTSG and 3.9% in STSG; other complications <5%	Satisfactory form and function (not specifically defined)	4
McCary (1995)	[39]	Retrospective case series	STSG to external auditory canal	16 patients	12 patients (75%) with partial or complete canal stenosis, majority had conductive hearing loss	Satisfactory form and function (not specifically defined)	4
Lear (2010)	[38]	Retrospective case series	Combined FTSG and STSG to helix	4 patients	1 patient had partial necrosis of FTSG	Subjectively excellent cosmesis in 3 of 4 cases	4
Composite grafts							
Sage (2012)	[41]	Retrospective case series	Composite grafts to auricle (and other sites)	16 of 307 grafts used for auricle	Of all sites: 12.5% had nodularity; other complications <5%	Satisfactory form and function (not specifically defined)	4
Kontis (2003)	[42]	Retrospective case series	Composite graft to scapha and helical rim	2 patients	None reported	Subjectively assessed acceptable to excellent cosmesis	4

Table 31.3 Single-stage skin flaps

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Local cutaneous flaps							
Goldberg (1996)	[44]	Retrospective case series	Postauricular advancement flap for helical defects	12 patients	1 patient flap with mild necrosis	Subjectively assessed excellent cosmesis in all cases	4
Kimyai-Asadi (2008)	[48]	Retrospective case series	Helical rim advancement flap for superior helix	7 patients	No complications reported	Subjectively assessed excellent cosmesis in all cases	4
Alam (2003)	[49]	Retrospective case series	Bilobe flap for helical rim defects	2 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Suh (2014)	[47]	Retrospective case series	Double triangular flap to lobule	10 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Singh (2003)	[46]	Retrospective case series	Limberg flap to lobule	6 cases	Tip necrosis of 3 cases (50%)	Subjectively assessed good cosmesis	4
Kang (2013)	[45]	Retrospective case series	Double triangular flap to lobule	5 patients	No complications reported	Subjectively assessed satisfactory cosmesis	4
Eser (2015)	[43]	Retrospective case series	Rotation-advancement flap to lobule	5 patients	No complications reported	Subjectively good satisfaction with cosmesis in all patients	4
Chondrocutaneous flaps							
Noel (2014)	[53]	Retrospective case series	Chondrocutaneous flap for helical rim defects	15 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Zilinsky (2015)	[56]	Retrospective case series	Chondrocutaneous flap for helical rim defects	13 patients	No complications reported	Subjectively assessed fair to excellent cosmesis	4
Medeiros (2009)	[52]	Retrospective case series	Chondrocutaneous flap for helical rim and antitragus defects	12 patients	No complications reported	Satisfactory function, noted constricted or protruding ear in 2 patients	4
Ramirez (1989)	[54]	Retrospective case series	Chondrocutaneous flap for helix, antihelix, or scapha defects	7 patients	No complications reported	Subjectively assessed good to excellent cosmesis	4
Valesky (2015)	[55]	Retrospective case series	Chondrocutaneous flap for helix defects	5 patients	No complications reported	Subjectively assessed excellent cosmesis	4
Antia (1967)	[50]	Retrospective case series	Chondrocutaneous flap for helical rim defects	3 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Single-stage pedicled flaps							
Dessy (2010)	[19]	Randomized prospective trial	Pedicled flap vs FTSG for conchal defects	40 patients (20 flap and 20 FTSG)	30% of FTSG had partial necrosis and delayed healing	Significantly higher visual analog scores with flap reconstruction	2b

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Cordova (2008)	[58]	Retrospective case series	Postauricular pedicled (island) flap	216 patients	Transient venous congestion in 2 cases	Subjectively assessed excellent cosmesis	4
Papadopoulos (2008)	[24]	Retrospective case series	Postauricular pedicled (island) flap to antihelix and concha	62 patients	6 patients with suspected infection treated with antibiotics and resolved	Subjective cosmesis was excellent in 46 patients, average in 15 and poor in 1	4
Cordova (2008)	[18]	Retrospective case series	Postauricular pedicled (island) flap for superior auricle	51 patients	Transient venous congestion in 2 cases	Subjectively assessed as excellent cosmesis	4
Schonauer (2010)	[26]	Retrospective case series	Postauricular pedicled flap for auricle including helical rim	57 patients	3 patients (5%) with partial necrosis	Subjective assessment: Satisfactory in 53 patients, unsatisfactory in 4	4
McInerney (2013)	[59]	Retrospective case series	Postauricular pedicled (trapdoor) flap to concha and scapha	45 patients	1 hematoma	Subjectively assessed excellent cosmesis	4
Larcher (2011)	[17]	Retrospective case series	Postauricular pedicled (pull-through) flap to scapha	20 cases	No complications reported	Satisfactory form and function (not specifically defined)	4
Krespi (1994)	[23]	Retrospective case series	Postauricular pedicled (myocutaneous) flap	14 patients	No complications reported	Subjectively assessed as good cosmesis	4
Fader (1999)	[21]	Retrospective case series	Postauricular pedicled (flip-flop) flap to conchal bowl and antihelix	13 patients	No complications reported	Subjectively assessed excellent cosmesis	4
Talmi (1996)	[27]	Retrospective case series	Postauricular pedicled (flip-flop) flap to conchal bowl	11 patients	1 dehiscence, 1 local wound infection	Subjectively assessed as excellent cosmesis	4
Turan (2006)	[28]	Retrospective case series	Postauricular pedicled (island) flap to conchal bowl and antihelix	6 patients	1 dehiscence	Subjectively assessed excellent cosmesis	4

Table 31.4 Multi-stage skin flaps

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Postauricular scalp interpolation flap							
Johnson (1997)	[62]	Retrospective case series	Staged postauricular interpolation flap to helix	26 patients	No complications reported	Subjectively assessed good to excellent cosmesis	4
Farber (2012)	[61]	Retrospective case series	Staged interpolation flaps to facial and auricular sites	20 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Ottat (2010)	[63]	Retrospective case series	Staged postauricular interpolation flap to auricle	19 patients	No complications reported	Subjectively assessed good to excellent cosmesis	4
Deng (2014)	[60]	Retrospective case series	Staged postauricular interpolation flap with cartilage graft	14 patients	3 hematomas, 7 hypertrophic scars (4 treated with corticosteroids)	Subjectively assessed good cosmesis	4
Tubed flap							
Iljin (2016)	[68]	Retrospective case series	Multi-stage tubed flap from postauricular skin to helical rim	12 patients	Transient venous congestion in 2 cases, delayed healing in 2 cases	Subjective patient assessment: 10 completely satisfied, 2 moderately satisfied	4
Di Mascio (2004)	[66]	Retrospective case series	Multi-stage tubed flap from postauricular skin to helical rim	7 patients	No complications reported	Subjectively assessed satisfactory cosmesis	4
Ellabban (2003)	[67]	Retrospective case series	Two-stage tubed flap from postauricular skin to helical rim	3 patients	No complications reported	Satisfactory form and function (not specifically defined)	4
Temporoparietal fascial flap							
Demirdover (2011)	[73]	Retrospective case series	Temporoparietal fascial flap reconstruction to the auricle, orbit, and face	57 patients, 7 with auricle reconstruction	No complications reported in auricle reconstruction	Satisfactory form and function; donor site scalp alopecia was noted in 2 of 7 cases	4
Cheney (1993)	[72]	Retrospective case series	Temporoparietal fascial flap to auricle and orbit	21 cases, 14 with auricle reconstruction	1 partial flap necrosis, 1 delayed complete flap necrosis requiring second reconstruction	Satisfactory form and function (not specifically defined)	4
Olson (2002)	[74]	Retrospective case series	Temporoparietal fascial flap for various sites including auricle	15 patients, 5 with auricle reconstruction	1 case mild conductive hearing loss after reconstruction of external auditory canal	Satisfactory form and function (not specifically defined)	4
Rose (1990)	[75]	Retrospective case series	Temporoparietal fascial flap for various sites including the auricle	12 patients, 4 with auricle reconstruction	No complications reported in auricle reconstruction	Satisfactory form and function (not specifically defined)	4

Table 31.5 Second intention healing (SIH)

Author, year	Reference	Study type	Intervention	Size of study	Complications/adverse events	Outcome	Level of evidence
Hochwalt (2015)	[11]	Retrospective cohort study	FTSG vs second intention healing of helix defects	29 defects SIH vs 18 FTSG	No difference in minor complications (12% SIH vs 14.3% FTSG)	No statistical difference in VAS scores	2b
Levin (1996)	[13]	Retrospective case series	Second intention healing of various auricular defects	133 defects SIH	3 local wound infections (2.3%)	Satisfactory function in all; 71% with acceptable cosmesis; unacceptable in 58% of helical rim or lobule	4
Reddy (2004)	[31]	Retrospective case series	Review of various auricular defects	12 defects SIH	No complications reported	Satisfactory form and function (not specifically defined)	4

exceedingly low at less than 1% of all patients (Tables 31.1, 31.2, 31.3, and 31.4).

Antibiotic prophylaxis may also be used to decrease the risk of hematogenous infection in selected high-risk patients. The American Heart Association and American College of Cardiology have provided guidelines, recently updated in 2014, for prophylactic antibiotic use in cardiac patients. From a dermatologic surgery perspective, prophylaxis is recommended for prevention of infective endocarditis only in cases with breach of mucosa or infected skin in select high-risk patients [14, 15]. This includes patients with prosthetic valves, a history of infective endocarditis, transplant patients with structural valve abnormalities, patients with unrepaired congenital cyanotic heart disease, or repaired cyanotic heart disease with a prosthetic valve or residual structural defects. The use of prophylactic antibiotics to prevent septic arthritis in patients with artificial joint replacements, however, remains poorly defined [16]. Without clear evidence, preoperative antibiotics may be considered for minor surgical procedures in the first 6–12 months following artificial joint replacement.

Modification of anticoagulant therapy may be considered prior to reconstruction of the ear, but is often not required, and was not performed in the majority of studies described here. The only identified study to discontinue anticoagulants was that of single-stage pedicled flaps by Larcher et al. [17]. All patients on anticoagulants had their medications held 7 days prior to the procedure. It is not clear whether this decreased bleeding complications as other studies utilizing a similar reconstructive technique did not hold anticoagulation therapy and complications related to postoperative bleeding were rare [17–28]. Kirkorian et al. found that, in their respondents to a national survey, the majority of surgeons discontinue prophylactic aspirin, nonsteroidal anti-inflammatory medications, and Vitamin E, while only a minority of surgeons discontinue perioperative therapeutic aspirin and warfarin [29]. Antiplatelet medications and newer anticoagulants were not included in the data.

Best Techniques and Performance

There is a wide array of approaches to auricular reconstruction that offer the surgeon a large armamentarium from which to choose for a given defect. Given the complex anatomy and contour of the ear, certain techniques are more suitable for certain sites. The body of knowledge regarding appropriate strategies to reconstruct surgical deficits of the ear is primarily based on case series and experiential findings as few large retrospective or prospective studies exist. Despite the general lack of high-level evidence, the literature nevertheless provides a foundation of how to apply these techniques in an evidence-based fashion. Herein we present an overview of these reconstructive approaches. They are best divided into increasing order of complexity. In general, linear repairs are the most simplistic while staged interpolation flaps based on an established vascular supply are the most complex. For simplicity, we have organized them into four major groups: (1) linear and wedge repairs, (2) skin grafts, (3) single-stage flaps, and (4) multi-stage flaps. A summary of published studies, including the level of evidence provided by each, is provided in Tables 31.1, 31.2, 31.3, 31.4, and 31.5.

Linear and Wedge Repairs

Many defects of the ear are amenable to direct closure in a linear fashion. There are limited reports of direct linear closure in ear reconstruction, perhaps because of publication bias favoring more novel reconstructive techniques. Nevertheless, two series have examined closure methods among Mohs surgeons and have determined that linear closure is one of the most commonly performed reconstructive procedure for defects of the auricle (4) [30, 31]. Reddy et al. found that for defects up to 0.7 centimeters in diameter with little to no cartilaginous defect, linear closure was the most utilized reconstructive technique. In their study of nine patients repaired with linear closure, this was applicable to posterior (medial) auricular defects, lobule defects, and defects over the helical rim, and all were

described as successful (4) [31]. Ibrahim et al. found that linear closure was performed for defects with sizes ranging from 9 mm to 30 mm, also with universal success (4) [30].

Wedge excision, although inherently more complex than linear closure, can provide a relatively simple single-staged method for reconstruction of defects involving the helical rim. The technique surrounding wedge repairs rests on the proper design of its shape. It consists of an isosceles triangle with a base located along the helical rim and the apex tapering medially toward the conchal bowl [32]. This wedge of tissue is excised in a full-thickness manner, including cartilage and both anterior and posterior cutaneous surfaces. The remaining free edges of the cartilage and skin are directly approximated in a linear fashion. Wedge excision has been employed for helical rim defects ranging in size from 0.4 to 3.0 cm with subjectively reported good cosmetic and functional results (4) [31, 33, 34]. However, an important limitation to wedge repair is that larger defects are more prone to anterior/lateral protrusion and cupping of the ear. To counteract this, Taylor et al. have reported a modified wedge with a shorter triangular shape that does not extend into the conchal bowl [34]. In a small series of 12 patients with average helical rim defects of 2.19 centimeters, this modification provided good cosmetic results with no reports of significant complications (4) [34].

Skin Grafts

Skin grafting proves a viable technique for repairing defects of varying sizes at many different sites of the auricle. Full-thickness skin grafts (FTSG), comprised of epidermis and dermis, are usually preferred by dermatologic surgeons because of their superior cosmetic match to the surrounding skin compared to split-thickness skin grafts (STSG). In addition, donor sites for auricular reconstruction are often less than a few centimeters in diameter and are amenable to direct linear repair. In general, skin grafts for auricular reconstruction are harvested from the ipsilateral postauricular mastoid or preauricular region. Some authors suggest utilizing supraclavicular skin for larger donor site excisions to prevent pinning of the ear caused by repair of a large donor site from the postauricular skin [35]. After templating the defect and excising the graft from the donor site, FTSG are thinned by removing fat from the undersurface of the dermis. The graft is then trimmed to size and secured in the defect with peripheral and, if needed, central basting sutures. Fenestrations may be placed in the graft itself to facilitate wound bed drainage [36]. Tie-over bolster dressings may be used to enhance graft approximation to the wound bed, but are not universally required (4) [37].

The available literature suggests that full-thickness grafting can be utilized at many auricular sites (Table 31.2). Historically it has been used for upper-third helical defects with variable cartilaginous deficits [11, 35]. Trufant et al. complied a large, retrospective review of 1519 grafts to the auricle and showed that the upper helix was the most common site to utilize this reconstructive method [35] However, they also showed that FTSG can be utilized at all sites on the auricle with good functional results and minimal complications (4). The mean postoperative defect reconstructed in this series was 2.09 centimeters with a range of 0.7–5.5 centimeters. Complications were exceptionally rare, with local infection, hematoma, or graft failure identified in only 0.1%, 0.3%, and 1.2% of patients, respectively. In two smaller series, 259 total FTSG were reported with functional success and a consistently low rate of complications, including rare instances of necrosis, infection, and bleeding [12, 36].

In addition to the above case series, Hochwalt et al. performed a retrospective cohort study comparing FTSG to second intention healing (SIH) of the helix. Defects in the study ranged in size from 1.3 to 3.0 centimeters. The investigators used a standardized visual analog scale to compare cosmetic outcomes between the two repair methods. There was not a statistically significant difference in cosmetic outcomes between SIH and FTSG (2b) [11]. Additionally, Dessy et al. performed a randomized prospective trial comparing FTSG to a single-stage pedicled flap

(see below) for Mohs defects of the conchal bowl, using a visual analog scale to compare the two groups [19]. The pedicled flap had statistically significantly better outcomes with regard to the visual analog score compared to FTSG (2b). The authors attribute this to the higher rates of graft failure, color mismatch and external auditory canal stenosis seen with FTSG. Thus, it is likely that FTSG is less efficacious than single-stage pedicled flaps for selected defects of the conchal bowl. However, the evidence described above also suggests that FTSG can have exceptional cosmetic and functional outcomes in the appropriate clinical circumstances.

Split-thickness skin grafts (STSG) are utilized less frequently than FTSG but may be appropriate for defects in the conchal bowl, where tissue bulk is not required. After the defect has been templated onto the donor site and adequate local anesthesia is obtained, the STSG is harvested (either manually or with a dermatome) within the dermal plane. This creates a thinner graft than a FTSG and leaves a variable portion of the dermis in the donor site intact to facilitate healing by second intention. The graft is then trimmed to fit and secured in the defect in an analogous fashion to FTSG. Split-thickness grafting has been included in several studies of repairs of the conchal bowl, antihelix, and external auditory canal (4) [38–40]. Wines et al. reported reduced rates of graft failure with STSG compared to FTSG, as expected from the relatively decreased nutritional requirements of STSG [40]. STSG may be particularly well suited for repair of the external auditory canal, where thin grafts are advantageous. Even with STSG, however, canal stenosis has been reported [39]. Overall, the studies presented in Table 31.2 provide limited evidence that STSG can provide functional healing and adequate cosmesis for selected defects of the auricle.

Composite grafts, composed of cartilage plus epidermis, dermis, and a variable amount of subcutis, may also be used in auricular reconstruction. Composite grafts may be harvested as a contiguous graft of cartilage and skin or may be harvested separately as an isolated cartilage graft resurfaced with a FTSG. There is very limited data describing outcomes of composite grafts for ear reconstruction. Sage et al. described the use of cartilage grafts from the antihelix and conchal donor sites for repair of Mohs surgical defects in general (4) [41]. Of 307 cartilage grafts in the study, 16 were used to reconstruct the auricle (typically the helical rim). While auricular composite grafts were not described in detail, most cartilage grafts were effectively resurfaced with a separate FTSG, and the reported complication rate was low (less than 5%). There is one additional study that includes only two patients and is listed in the table for completeness [42]. The authors used composite grafts to effectively repair scapha and helical defects from acquired and congenital causes (4).

Single-Stage Flaps

Single-stage flaps may be technically more complex than primary closures or grafts but may have great utility in reconstruction of the ear. They are best conceptualized by dividing into three categories that include local cutaneous flaps, chondrocutaneous flaps, and single-stage pedicled flaps. Within each of these categories, there are still numerous variations on each type of flap that can be utilized. Here we present an overview of the three categories and an evidence-based approach to their use in ear reconstruction.

Local Cutaneous Flaps

Local cutaneous flaps are tissue rearrangements of adjacent skin and soft tissue without manipulation of the cartilaginous framework of the auricle. The vascular supply of these flaps derives from adjacent dermis and subcutis. While there are comparatively few studies reported with local cutaneous flaps specifically for auricular reconstruction, several groups have described the use of typical advancement, rotation, rhombic, and bilobe flaps on the ear (Table 31.3) [43–48]. Goldberg et al. and Kimyai-Asadi et al. described small case series of effective helical rim reconstruction via local advancement flaps (4) [44, 48]. In addition, Alam and Goldberg reported their anecdotal experience of helical rim reconstruction with a modified bilobe flap with excellent results (4) [49].

Local cutaneous flaps are also widely utilized for repair of lobule defects, in which the lack of an underlying cartilaginous framework facilitates local tissue rearrangement. Several studies have utilized modifications of rhombic flaps, Z-plasty, and W-plasty for lobule repair, particularly after traumatic injury resulting in a cleft lobule [43, 45–47]. These reconstructions have been shown to produce satisfactory functional and cosmetic outcomes as assessed subjectively by the authors (4). The only complications mentioned were by Singh and Singh and included tip necrosis that did not affect the final cosmetic result [46].

Chondrocutaneous Flaps

The prototypical chondrocutaneous flap is the Antia-Buch advancement flap for reconstruction of helical rim defects, first described in 1967 [50]. Flap execution involves incision and advancement of the skin of the anterior ear along with the underlying cartilage of the helical rim (or antihelix, depending on the specific defect). This skin and cartilage incision often extends the entire length of the helical rim to the tissue reservoir of the lobule. Skin of the posterior surface of the ear may or may not be incised to facilitate advancement. Because these flaps require incision and mobilization of the cartilaginous framework of the ear, they are best suited for defects with either missing or compromised cartilage (e.g., from ischemia or desiccation).

The majority of the evidence supporting the use of chondrocutaneous flaps is in the form of case series (4) [50–56]. In over 50 reported cases, these flaps have been used for reconstruction of the helical rim and also modified to repair defects of the antihelix, scapha, and triangular fossa. The smallest defect reported in these series was approximately 1.2 centimeters while the largest was 4.2 centimeters [50, 54]. All repairs achieved restoration of form and function without reported complications. Given the robust vascular supply of the helical rim, ischemic complications of these flaps, when properly executed, are rare. Chondrocutaneous advancement flaps are generally perceived as superior to wedge excision for helical rim defects greater than 1 centimeter, since these advancement flaps are less prone to cupping, protrusion, or distortion of the auricle. It should be noted, however, that no direct comparative studies have been performed. In addition, chondrocutaneous flaps do not replace lost cartilage, they merely advance the remaining helical rim into the defect. Thus, there is an inherent loss of tissue volume in the reconstructed ear, which may be noticeably smaller than the contralateral ear.

Single-Stage Pedicled Flaps

Single-stage pedicled flaps are an extremely versatile technique that can be tailored to reconstruct many different anatomic locations of the anterior auricle. Here, we use the term pedicled flap to describe several variations of single-stage skin flaps based on a subcutaneous or muscular pedicle from the postauricular or mastoid surface that is transposed or advanced to the anterior surface of the auricle. In the literature, these flaps have been variably described as retroauricular island flaps, pull-through flaps, tunneled flaps, revolving door flaps, and flip-flop flaps. Execution of the repair is generally performed by first using a template of the anterior surface defect to mark the flap and a sufficient subcutaneous pedicle on the posterior auricular surface, postauricular crease, or mastoid area. Descriptive anatomic studies have indicated that the vascular supply of this area, loosely based on the posterior auricular artery and the superior auricular artery (both branches of the superficial temporal artery), is sufficiently robust to support a random pattern subcutaneous or muscular pedicle [18, 57]. The flap is incised and completely separated from its dermal attachments, preserving a subcutaneous vascular pedicle that is dissected in a supra-perichondrial or periosteal plane. The flap is then pulled through the ear to the anterior surface defect and sutured in place, with excision of intervening cartilage as needed. Depending upon the location of the defect and the flap donor site, a subcutaneous tunnel may be created in the postauricular area to allow passage of the flap's vascular pedicle. The flap donor site is typically repaired in a linear fashion.

Compared to other methods of auricular reconstruction, there is strong evidence to support the use of single-stage pedicled flaps for defects of the conchal bowl and antihelix (Table 31.3). As

noted above, Dessy et al. performed a randomized prospective trial comparing single-stage pedicled flap reconstruction to full-thickness skin grafting for defects of the conchal bowl with a maximum diameter between 2 and 4 centimeters [19]. The investigators noted that there were no complications in 20 patients with single-stage pedicled flap repair, while partial necrosis and delayed healing were observed in 6 of 20 patients (30%) repaired with FTSG. In addition, visual analog scores (VAS) by blinded physician observers were significantly greater (indicating superior cosmetic outcomes) for pedicled flap repair versus FTSG. While this is only a single study and outcomes will certainly depend on surgical technique, this study provides level 2b evidence to support the use of single-stage pedicled flaps for reconstruction of the conchal bowl, an area where skin grafts may be sub-optimal.

Several retrospective case series have also described effective reconstruction of the ear with single-stage pedicled flaps (Table 31.3). Similar to the randomized trial described above, these flaps are most often used on conchal bowl defects of varying sizes but have also been applied to other defects on the scapha and antihelix as well (4) [17, 18, 21, 23, 24, 26–28, 58, 59]. The cosmesis achieved with these flaps is generally satisfactory to excellent; however 16 of 62 patients in one study had adequate to poor outcomes in subjective patient assessments [24]. Notable cosmetic sequelae that may result include pinning of the ear from repair of the flap donor site and excess bulk of the skin flap leading to the trapdoor phenomenon. The overall rate of flap necrosis, failure or infection, however, remains very low. Overall, there is a substantial body of evidence to support the use of single-stage pedicled flaps for various defects on the anterior surface of the auricle (level 2b–level 4, depending on anatomic site).

Multi-stage Flaps

Multi-stage flaps comprise some of the most complex methods for reconstruction of the auricle and may be effective when other methods are not appropriate for more extensive surgical defects. Multi-stage flaps often rely on a named vascular supply and afford the ability to move a large volume and surface area of tissue into place. They require a greater investment of time from both the patient and the surgeon since at least two operative sessions, usually separated by an interval of several weeks, are required. While all of the flaps can be performed under local anesthesia, more complex or extensive cases have historically been performed under general anesthesia. Three major categories of multi-staged flaps used in dermatologic surgery are postauricular scalp interpolation flaps, tubed flaps, and temporoparietal fascial flaps.

Postauricular Scalp Interpolation Flaps

Postauricular scalp interpolation flaps are most often utilized to reconstruct large defects of the helical rim. Execution of the flap begins with an assessment of the overall defect size and creation of a template from the defect on the postauricular scalp, sometimes extending to the postauricular sulcus and posterior ear. The flap is incised and elevated, and the anterior aspect is sutured to the defect on the anterior ear, leaving the vascular pedicle intact in the mastoid area of the scalp. After 3–4 weeks of vascularization and collateral blood supply development, the flap is incised posteriorly, thinned as needed, draped over the posterior aspect of the defect, and sutured into place [60–62].

As mentioned above, these flaps have been utilized predominately for defects comprising a substantial portion of the helix that cannot be restored by local flaps without unacceptable loss of helical volume. While the evidence base for these flaps comprises only small case series, all of the cosmetic outcomes reported have been satisfactory to excellent at restoring normal form of the helix, and complications are uncommon (Table 31.4). Perhaps as expected from the more complex nature of the flap, postoperative complications may be more likely than with simpler repairs. Hematoma is a known possible complication and was reported in 3 of 14 patients (21%) by Deng et al. [60]. Hypertrophic scars may also be more common and were reported in 7 of 14 patients (50%) in the same study, yet all

patients reported good cosmesis at 12 months (4). The remaining case series in the literature have not reported similar complications, and additional research is needed to define the optimal use and execution of these flaps (Table 31.4) [60–63].

Tubed Flaps

Tubed flaps have been in use for decades and were described by Harold Gillies as early as 1917 [64, 65]. Since that time they have been adapted to various surgical defects of the helix. The tissue reservoir for the flap is derived from either pre- or postauricular skin and is typically created and transferred to the helix in three separate surgical stages. First, the flap is created by incising a vertical band (1–2 centimeters wide) in the donor site and suturing it to itself to create a cutaneous tube that remains attached by a pedicle at both the superior and inferior edges. In the second stage, the tube is freed at one of these edges and partially sutured to the helical defect. After appropriate vascular maturation, the remaining pedicle is freed and the flap is thinned and completely inset into the defect.

There are only a small number of case series regarding the use of tubed flaps in helical reconstruction and they were performed in patients with traumatic injuries (Table 31.4) [66–68]. While there are no case series utilizing this technique for reconstruction of Mohs surgical defects, it has been applied in single case reports [69, 70]. As stated previously, the flap is best utilized for large helical defects, and Di Mascio and Castagenetti used 2.5 centimeters as a minimum-size threshold to perform this procedure (4) [66]. There were no complications reported in any of the series and cosmesis was subjectively reported by the authors as satisfactory. Data is significantly lacking on the use of this flap in dermatologic surgery and additional research would be helpful to define its optimal use.

Temporoparietal Fascial Flaps

The temporoparietal fascial flap (TPFF) is an axial pattern flap utilizing the richly vascularized temporalis muscle and fascia, which is supplied by the superficial temporal artery. The flap is typically used in multi-stage reconstruction to provide volume and vascular support that is then resurfaced with a skin graft. It has been adapted to various sites on the face and auricle. The flap can be executed with local anesthesia but has historically more commonly been performed under general anesthesia.

There are several small- to medium-size studies (Table 31.4) utilizing this technique to repair auricular defects of varying etiologies, notably including those from skin cancer excision (4) [71–76]. All of the included series were performed under general anesthesia, but there are case reports of repair after Mohs surgery that were performed under local anesthesia (4) [77]. The majority of defects in which the flap was best suited were subtotal or complete loss of the auricle requiring a combination of a cartilage framework, vascular supply from the TPFF, and skin graft resurfacing. There were few complications listed across all of the studies; however Cheney et al. reported distal flap necrosis and partial distal flap loss in 2 of 14 cases (14%) [72]. Based on the available evidence, the TPFF may be a useful reconstructive technique for particularly large or challenging defects of the ear. In these cases, reconstruction using the TPFF with cartilage and skin grafts as needed can restore a functional structure with a cosmetic resemblance to a natural auricle. Additional research to define the use of this technique in dermatologic surgery will be informative.

Safety

The safety profile is excellent for nearly all reported methods of ear reconstruction. In all of the studies examined there were no reports of any serious adverse events or death. Minor complications in these studies were rare. Rates of infection or bleeding were exceedingly low when reported. In the wedge and linear repair studies, there were no reported complications of postoperative bleeding, infection, or wound dehiscence (Table 31.1). It was noted that the

most common complication in wedge excision was ear projection, tissue redundancy at the site, and slight reduction in the size of the auricle. In full-thickness skin grafting there were reports of contracture, graft failure, local infection, and acute bleeding that all were generally less than 3% (Table 31.2). The complication rate in split-thickness skin grafts was relatively low as well, but McCarey et al. did note that 12 out of 16 patients (75%) who underwent STSG of the external auditory canal had stenosis in the weeks to months after the procedure [39]. Wines et al. noted partial graft necrosis in 9.4% of FTSG and 3.9% of STSG in the conchal bowl; this increased rate of necrosis compared to other studies may be due to the specific location with relatively immobile tissue and diminished vascular supply [40]. The safety profile was excellent in all single-stage flaps with few complications other than rare tip necrosis of the flaps or hematoma (Table 31.3). Multi-stage flaps also had low complication rates, although hematoma formation may be more common in these more complex procedures (Table 31.4). Given the general lack of direct comparative studies, however, there is insufficient data to compare rates of adverse events of any of the reconstructive approaches to one another.

Postoperative Care and Follow-Up

Following reconstruction of the auricle, routine postoperative wound care and follow-up is recommended and does not differ from that of other reconstructive procedures. Most patients will require at least one postoperative visit in the first few weeks for a wound check or suture removal. Additional visits may be required for staged procedures or if the patient develops symptoms or signs of complications. None of the studies examined compared wound care regimens or dressing types. In the majority of studies, follow-up for long-term cosmesis was generally conducted between 1 and 6 months or longer. As with all reconstruction, it is important to note that beneficial scar maturation can continue for 12–18 months.

Alternatives Procedures and Modifications

Second intention healing (SIH) has been long recognized as a viable alternative to primary repair of surgical defects on many body sites. However, studies on SIH are relatively sparse with regard to auricular repairs (Table 31.5). Levin et al. performed a retrospective study of 133 patients examining SIH of auricular wounds ranging in size from 63 mm^2 to 3500 mm^2 on all aspects of the ear (4) [13]. The majority of the cases on the helix achieved acceptable results with SIH when perichondrium was intact. If there was a loss of perichondrium, wound healing was delayed but still successful. If a true cartilaginous deficit was present, many of the cases resulted in notching of the helix. Favorable healing was reported as well with the concha, but webbed scar formation was noted if the defect traversed a large area. The study also achieved acceptable to excellent results with wounds on the tragus, pretragus, and posterior aspect of the auricle, while SIH of the lobule generally produced unfavorable results. This poor healing on the lobule was attributed to the lack of a cartilaginous framework for proper healing and led most often to distortion. The authors noted that the deeper the cartilaginous defect at any site, the less favorable the site was for SIH.

While almost any site on the auricle is amenable to SIH, there are few studies comparing it to other reconstructive techniques. There is, however, a single retrospective cohort study of FTSG vs SIH of the helix that showed no statistically significant differences in adverse events or in visual analog scores for cosmetic outcome (2b) [11]. This suggests that FTSG and SIH can produce comparable cosmetic outcomes with minimal complication risk for appropriately selected defects. This study was limited to defects ranging in size from 1 to 3 centimeters without significant cartilage defects. It is likely that SIH can provide a viable alternative to primary reconstruction of auricular defects in specific clinical scenarios, although additional studies are needed to confirm this.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Surgical reconstruction of the ear is a safe and effective mechanism to restore function and cosmesis of the auricle	B
For defects of the conchal bowl, reconstruction with a single-stage pedicled flap may provide faster healing and superior cosmesis compared to reconstruction with full-thickness skin grafts	C
Various skin flaps and full-thickness grafts can be effective for auricular defects of different anatomic subunits, and selection of the type of repair should depend upon the size, depth, and location of the defect	C
Second intention healing can provide long-term function and cosmesis that is comparable to full-thickness skin grafts for auricular wounds of 1–3 centimeters without significant cartilage loss	C

Level of Evidence

Evaluating level of evidence for individual studies: Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence

Level	Therapy/prevention, etiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR validated in different populations	SR (with homogeneity) of level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with >80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical center	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none	All or none case series	Absolute SpPins and SnNouts	All or none case series	Absolute better-value or worse-value analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level > 2 diagnostic studies	SR (with homogeneity) of 2b and better studies	SR (with homogeneity) of level > 2 economic studies
2b	Individual cohort study (including low-quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation or validated only on split-sample or databases	Retrospective cohort study or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence or single studies; and including multi-way sensitivity analyses

(continued)

Level	Therapy/prevention, etiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
2c	"Outcomes" research; ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual case-control study		Non-consecutive study or without consistently applied reference standards	Non-consecutive cohort study or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case series (and poor quality cohort and case-control studies)	Case series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009
SR systematic review; *RCT* randomized clinical trial; *CDR* clinical decision rule, i.e. an algorithm or scoring system that leads to a prognostic estimation or a diagnostic category; *SpPin* a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis; *SnNout* a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis

Assigning quality of evidence for each recommendation: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect Several high-quality studies with consistent results In special cases: one large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate One high-quality study Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate One or more studies with severe limitations
D	Very low	Any estimate of effect is very uncertain Expert opinion No direct research evidence One or more studies with very severe limitations

Source: GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team). Reprinted with permission from Essential Evidence Plus

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Self-Assessment Questions

1. Based on the available evidence, allowing a Mohs defect to heal by second intention would be least favorable for which of the following sites:
   (a) Helical rim defect of 7 mm with intact perichondrium
   (b) Conchal bowl defect of 5 mm
   (c) Helical rim defect of 7 mm with loss of perichondrium
   (d) Defect of 7 mm of the lobule
   (e) A defect on the antihelix of 5 mm without loss of perichondrium
2. Which of the following statements is true:
   (a) Second intention healing has shown significantly higher scores in visual analog scales compared to full-thickness skin grafts for helical defects.
   (b) Single-stage pedicled flaps have shown significantly higher visual analog scale scores when compared to full-thickness skin grafts for repair of conchal defects.
   (c) Full-thickness skin grafts have shown significantly higher visual analog scores when compared to split-thickness skin grafts for defects of the helix.
   (d) Single-stage pedicled flaps have shown significantly lower visual analog scale scores when compared to full-thickness skin grafts for repair of conchal defects.
   (e) Second intention healing has shown significantly lower scores in visual analog scales as compared to full-thickness skin grafts for helical defects.
3. Based on the available literature, chondrocutaneous advancement flaps are best utilized in which of the following situations:
   (a) A defect of 2 centimeters on the helical rim with cartilage loss
   (b) A defect of 1 centimeter on the helical rim with cartilage loss
   (c) A defect of 1 centimeter on the helical rim without cartilage loss
   (d) A defect of 1 centimeter in the conchal bowl with cartilage loss
   (e) None of the above
4. Which of the following is true regarding expected complications in appropriately selected wounds of the auricle repaired with full-thickness skin grafts:
   (a) Local infection occurs in approximately 5% of cases.
   (b) Acute bleeding occurs in approximately 3% of cases.
   (c) Hematoma formation occurs in approximately 1–3% of cases.
   (d) Graft failure/necrosis occurs in approximately 5% of cases.
   (e) Graft failure/necrosis occurs in 1–3% of cases.
5. For small (<1 centimeter) surgical defects of the auricle following Mohs micrographic surgery, which of the following is the most commonly employed reconstructive technique:
   (a) Linear repair
   (b) Wedge repair
   (c) Full-thickness skin graft
   (d) Chondrocutaneous advancement flap
   (e) Single-stage pedicled flap

Correct Answers

1. d: According to Levin et al. in their review of 133 cases, lobular defects with second intention healing produced contracture and deformity of the lobule in the majority of cases. While loss of perichondrium on the helix was shown to delay healing and produce some degree of notching, this was generally not significant.
2. b: Dessy et al. found in their prospective, randomized trial that single-stage pedicled flaps provided significantly higher VAS scores compared to full-thickness skin grafts for defects of the concha.
3. a: The literature available on helical reconstruction suggests the use of chondrocutaneous advancement flaps can be appropriately applied to larger defects of the helix that involve cartilaginous loss. Defects of 1 centimeter or less, or without loss of supporting cartilage can be repaired by simpler methods or allowed to heal by second intention.
4. e: In two of the largest studies of full-thickness skin grafts for auricular reconstruction (Trufant et al. and Leibovitch et al.), the most common complication was partial or complete graft failure in 1–3% of cases. All other complications occurred in less than 1% of patients.
5. a: While many different reconstructive methods can be utilized effectively and it is difficult to account for patient and surgeon variables, two studies (Reddy et al. and Ibrahim et al.) have documented that small defects of the auricle are most commonly repaired with linear closure.

Repairs of the Nose

32

Mark E. Burnett and John A. Zitelli

Abstract

Few anatomic sites challenge the skill of a reconstructive surgeon as the nose. With preservation of airway function as a sine qua non, the surgeon must also adhere to complex aesthetic demands. Topographic complexity, limited laxity, high adnexal density, and regional variation in skin thickness combine to present a formidable challenge to restoring form and function. The conspicuity of the nose also provides little latitude for error in execution, making the slightest degree of asymmetry perceptible. Reliable operative results require a systematic reconstructive approach based on wound size, depth, anatomic location, and characteristics of adjacent skin.

Keywords

Nasal · Reconstruction · Nose · Flaps · Grafts
Secondary intention

Introduction

Few anatomic sites challenge the skill of a reconstructive surgeon as the nose. With preservation of airway function as a sine qua non, the surgeon must also adhere to complex aesthetic demands. Topographic complexity, limited laxity, high adnexal density, and regional variation in skin thickness combine to present a formidable challenge to restoring form and function. The conspicuity of the nose also provides little latitude for error in execution, making the slightest degree of asymmetry perceptible. Reliable operative results require a systematic reconstructive approach based on wound size, depth, anatomic location, and characteristics of adjacent skin.

Objective scientific evidence supporting procedure selection, however, is limited. With few exceptions, the reconstruction literature is composed primarily of observational studies, evidence which is largely subjective in nature and thus considered to be relatively low in the hierarchy of study designs. Nonetheless, there are a select number of well-designed observational studies which provide high clinical value to the reconstructive surgeon. Unfortunately, the crucial components of more desirable study designs, such as blinded participants or placebos, are incompatible with the ethical practice of reconstructive surgery.

It should be noted that a thorough appraisal of each of the many flaps described in the nasal

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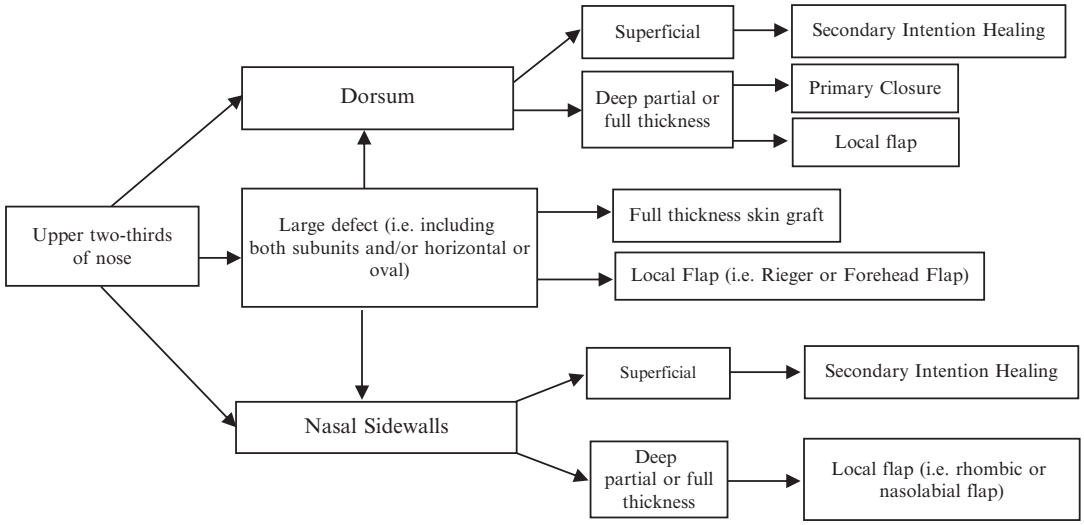

Fig. 32.1 Algorithmic approach to nasal defects of the upper two-thirds of nose

reconstruction literature would be both onerous to the reader and subject to bias. Furthermore, most of the data supporting various repair options is similar in quality, limiting the ability to discern a meaningful difference. Lastly, it is important to recognize that even slight variations in the surgical techniques used to carry out a particular repair may result in strikingly different outcomes. To that end, we provide a conceptual framework of nasal construction in which surgical defects are bifurcated into those that fall on the upper two-thirds of the nose and those that occur within the lower third of the nose (Fig. 32.1). A limited number of reliable repair options for each of the nasal cosmetic subunits are discussed within these two larger categories. Secondary intention healing, primary closure, graft, and flap options are discussed sequentially within each subsection.

Secondary Intention Healing: *Primum non nocere*

Few surgeons in recent history ever had as much experience with secondary intention healing for facial defects as Frederic E. Mohs, whose use of zinc chloride for in situ tissue fixation often necessitated subsequent granulation. In 1946, he first reported on the excellent outcomes achieved through healing by second intent on the nose (4) [1]. More than three decades ago, Zitelli described the first set of guidelines on the use of secondary intention healing of facial defects (3b) [2, 3]. These guidelines demonstrated that anatomic location was the most important predictor of cosmetic outcome and have since been substantiated by numerous separate studies (3b, 4) [4–14]. Broadly speaking, concave surfaces predictably heal with excellent cosmesis, while flat surfaces heal with satisfactory results and convex surfaces heal with relatively unpredictable results (Fig. 32.1). In practice, however, the decision to allow secondary intention healing is a much more nuanced process and will be described below. When applied appropriately, the cosmetic outcomes attainable from secondary intention healing are often superior to those obtained through the application of a flap or graft (Fig. 32.2).

The decision to pursue second intention healing should be informed by an understanding of wound healing biology and wound contraction. Wounds that are very superficial in nature undergo a negligible degree of contraction and are primarily healed through the process of re-epithelization. In contrast, wound contraction plays a more prominent role in the healing process of partial- and full-thickness defects. Wound

contraction in these defects is mediated by myofibroblasts through a complex process resulting in collagen production and remodeling. Once a wound has fully contracted, the remaining granulation tissue is replaced by comparatively acellular scar tissue [15, 16]. This implies an inverse relationship between the extent of wound contraction and the amount of scar tissue formed. Clinically, this relationship is influenced by variables which are unique to each anatomic location, including local tissue architecture, free-margin proximity, surrounding laxity, and motion or adherence from underlying musculature and/or tissue. The sum of these factors must be considered when attempting to predict outcomes of healing by second intention.

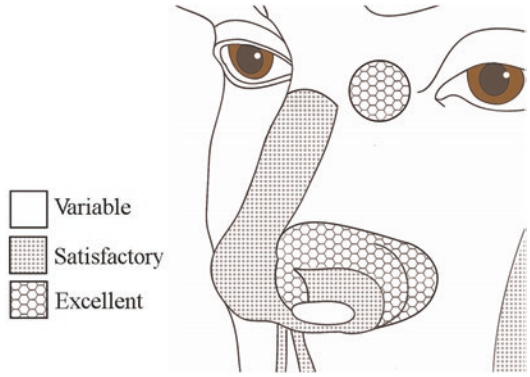

Fig. 32.2 Anticipated cosmetic results of second intention healing for wounds on the nose by anatomic location

Upper Two-Thirds of Nose

The upper two-thirds of the nose includes the sidewalls and dorsum above the nasal tip. In contrast to the lower third of the nose, the skin of the upper two-thirds is typically more mobile and less sebaceous and lacks the complex juxtaposition of concave and convex surfaces.

Nasal Dorsum

Partial- and/or full-thickness defects on the nasal dorsum can be expected to heal secondarily with satisfactory cosmetic results (Fig. 32.3) (4) [2, 3]. In an observational study of 24 patients who underwent secondary intention healing for full-thickness defects on the nasal dorsum, "acceptable" cosmesis was achieved in 67% (16/24) of patients (4) [8]. The authors noted a correlation between the area of the full-thickness defect and cosmetic outcomes, suggesting that only small full-thickness defects (average defect area = 288 mm^2) may be suitable for granulation. As such, primary fusiform closure should be considered the first repair option for midline defects of the appropriate size and shape on the nasal dorsum (4) [14, 17].

If primary closure is utilized, careful attention to closure design should be taken to avoid

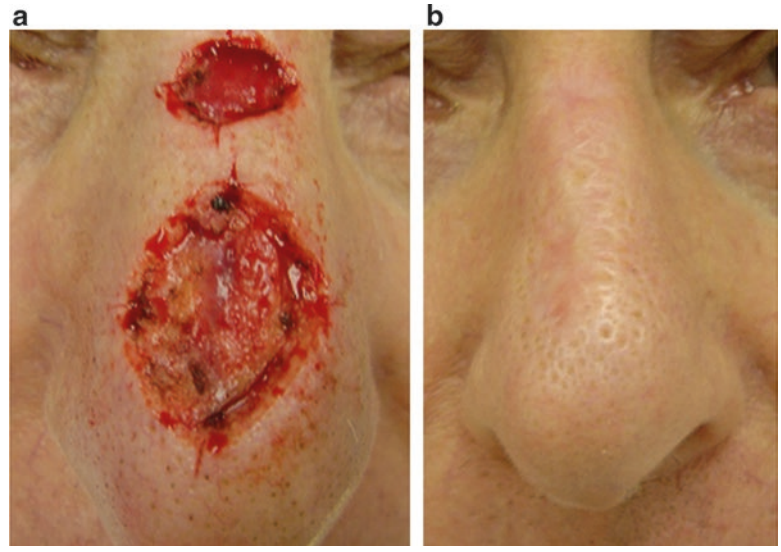

Fig. 32.3 (**a**) Two superficial defects of the nasal dorsum in a 76-year-old man. (**b**) Result at 1-year follow-up after healing by secondary intention

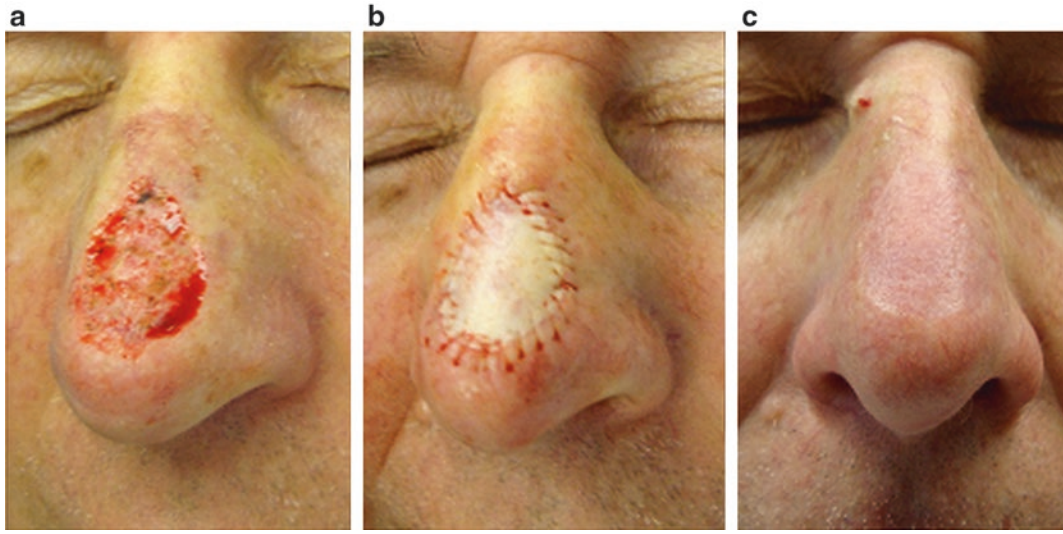

Fig. 32.4 (**a**) Defect of the nasal dorsum in a 67-year-old man. (**b**) Reconstruction of nasal dorsum defect with a full-thickness skin graft. (**c**) Result at 5-month follow-up

distortion of the nasal profile by standing cone deformities. Extension of the length:width ratio of the fusiform repair to 5:1 (or greater) has been shown to overcome this problem. This is frequently accomplished by extending the distal pole of the ellipse onto the inferior nasal tip and the proximal pole superior to the junction of the nasal bone and cartilaginous septum (4) [17].

Large defects or insufficient tissue laxity may seem initially to preclude linear closure on the nasal dorsum. However, extensive undermining may facilitate recruitment of adjacent tissue reservoirs, such as the skin of the remaining dorsum or sidewall in order to allow the appropriate closure. This approach offers the advantages of excellent color and texture match. For very large defects on the nasal dorsum, which cannot be adequately closed using adjacent skin, a full-thickness skin graft (Fig. 32.4) or forehead flap (Fig. 32.5) may be the only suitable repair option.

Nasal Sidewall

The cosmetic outcome of secondary intention healing for nasal sidewall defects is variable. In the observational study referenced above, 34 patients had defects confined to the nasal sidewall for which secondary intention healing was utilized. The authors described these defects as "mostly superficial" (to subcutaneous tissue) and reported that 85% (29/34) achieved an "acceptable" cosmetic result with second intention healing. While the average defect area was 308 mm^2, the authors noted that there was no obvious relationship between wound size and cosmetic or functional outcome (4) [8]. Conversely, a much smaller retrospective chart review of secondary intention healing outcomes for sidewall defects of any thickness reported poor outcomes in 58% (10/17) of patients (4) [11]. Contrasting outcomes such as these underline the unpredictability of healing by second intention for defects on the nasal sidewall.

For small defects on the nasal sidewall amenable to linear closure, the design of ellipse should be oriented obliquely, running parallel to a line extending from the inner canthus to the nasal tip [14]. When large defects on the nasal sidewall are closed in a fusiform fashion, however, upward alar retraction may result on the ipsilateral side. Instead, large surgical defects on the nasal sidewall are ideally repaired with a local transposition flap, with the donor site closed in a vertical line. Regional differences between the inferior and superior nasal sidewall direct the optimal repair approach.

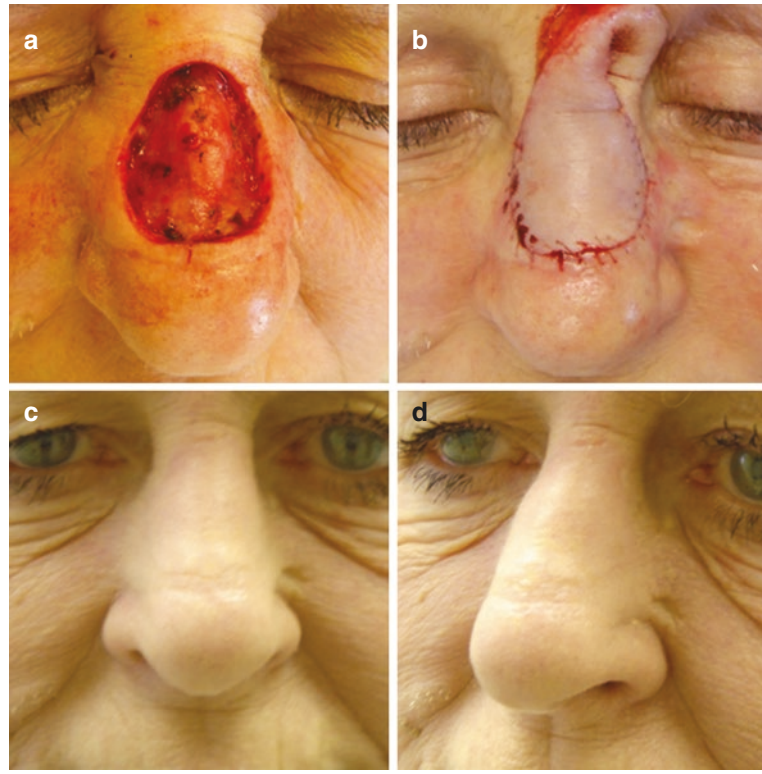

Fig. 32.5 (**a**) Defect of the nasal dorsum in a 65-year-old woman. (**b**) Reconstruction of nasal dorsum cosmetic subunit with forehead flap. (**c, d**) Results at 6-month follow-up

The rhombic transposition flap is one of the most reliable, efficient, and cosmetically elegant local flaps for defects on the superior or lateral nasal sidewall. In most cases, the laxity of the superior sidewall favors an inferiorly based flap as a donor site. Defects located on the inferior or medial aspect of the nasal sidewall may be more optimally repaired using a bilobed flap, as the skin of the upper sidewall and nasal root can be easily mobilized (4) [18]. The defect size suitable for these repair types is a function of the amount of laxity available but is typically ≤1.5 cm in diameter.

Surgical defects measuring greater than 1.5 cm on the lateral or inferior portion of the lateral sidewall are readily repaired with a nasolabial transposition flap (Fig. 32.6). In 1990, Zitelli reported a case series of 32 patients describing the use of this repair technique. Of the 32 patients, 7 patients had defects confined strictly to the nasal sidewall. All defects were repaired in a single stage and none required a revision over an average follow-up period of 3.5 years (4) [19].

Lower Third of the Nose

The lower third of the nose includes the subunits of the tip, soft triangles, alae, and columella (Fig. 32.7). The limited mobility of the skin in this area makes it difficult to manipulate freely, magnifying even the slightest amount of tissue movement.

Nasal Tip

For small, superficial defects on the nasal tip, the process of healing by secondary intention often yields cosmetic results superior to surgical incisions. This is especially useful for patients with thick, sebaceous skin where suturing may be difficult and result in a less predictable outcome. However, partial- or full-thickness defects of the nasal tip do not typically heal favorably by second intention. In a study reporting the results of secondary intention healing by cosmetic subunit on the nose, only 32% (24/74) of defects of the nasal tip healed with an acceptable cosmetic result, suggesting that this approach should be used sparingly [8]. Special

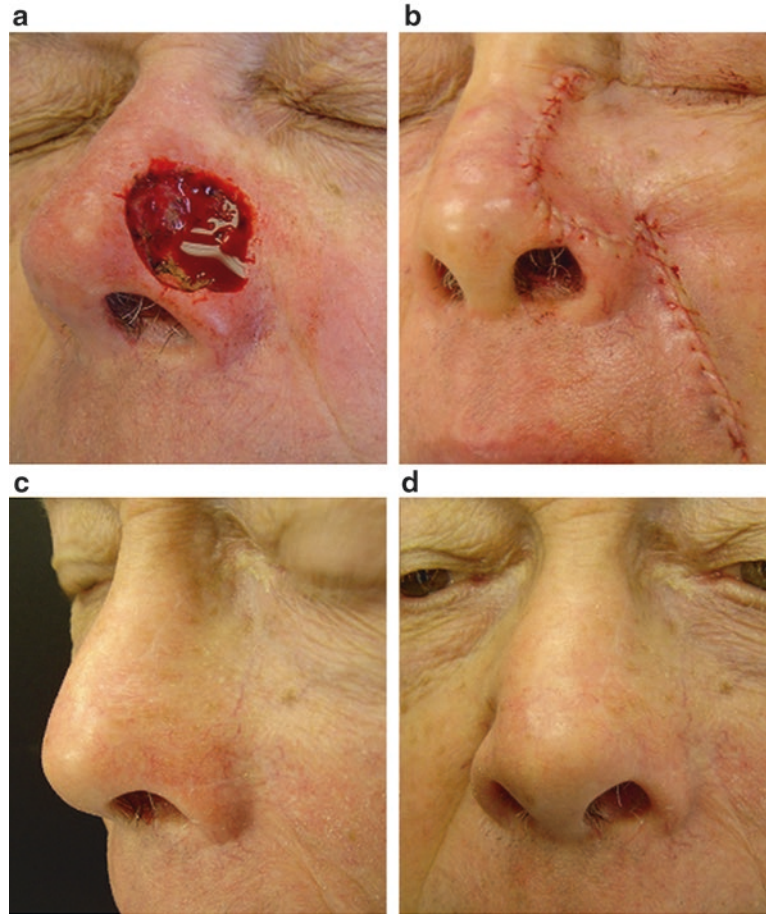

Fig. 32.6 (**a**) Defect of the nasal sidewall and ala in an 80-year-old man. (**b**) Reconstruction with a single-stage nasolabial transposition flap. (**c**, **d**) Results at 9-month follow-up

attention should be paid to avoiding secondary intention healing on the cosmetic subunits of the soft tissue triangles. Defects isolated to these concave subunits rarely heal favorably by secondary intent.

One approach reported to optimize the final outcome of nasal tip defects allowed to heal secondarily may be the use of immediate dermabrasion, which aims to soften the transition between the defect and surrounding skin. The particular method by which this "shave and sand" technique is accomplished has been outlined elsewhere [20]. In a series of 1334 nasal reconstruction cases, primary dermabrasion was reported to optimize cosmetic outcomes when used at the wound margins, irrespective of the defect location or type of repair (4) [21].

A caveat to second intention healing on the nasal tip is the unpredictability of the cosmetic outcome in patients with thin, non-sebaceous skin. In these patients, excellent functional and cosmetic results can be obtained with surgical repair of full-thickness defects of the nasal tip [17]. This is because surgical incisions are often less perceptible in patients whose skin lacks a significant sebaceous component.

Grafts

Skin from the pre- or post-auricular area is often utilized as a donor site for full-thickness skin grafts. However, the skin of the conchal bowl may provide the best cosmetic outcome on the nasal tip. This is because color and texture similarity between the nose and conchal bowl is underpinned by histologically comparable sebaceous gland density (4) [22]. Furthermore, the donor site may be allowed to heal secondarily for even large grafts given the rigid support of the underlying cartilage.

Primary Closure

Results from primary closure on the midline of the nasal tip are largely dependent on the skin type in which the defect occurs. Thin, non-sebaceous skin is easier to manipulate and repair primarily than thick, sebaceous skin. When complete closure with a fusiform repair is unattainable, excellent cosmesis can be obtained by shaping a Burow's graft to fit the remaining defect (4) [23–26].

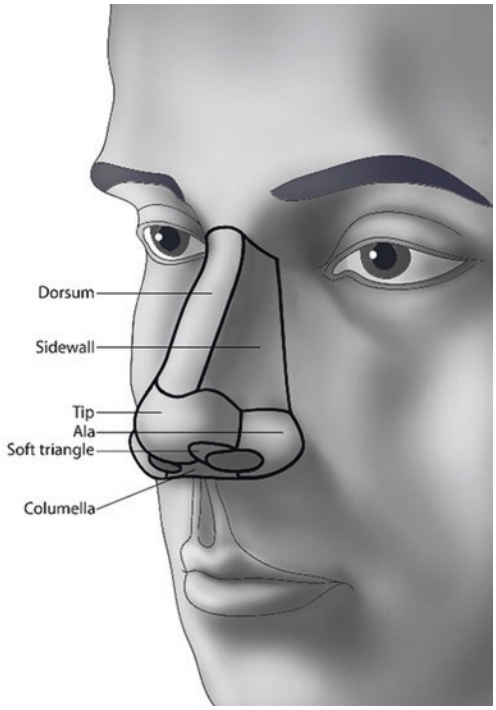

Fig. 32.7 The nine cosmetic subunits of the nose include the dorsum, paired sidewalls, alae, and soft triangles as well as the nasal tip and columella

Local Flaps

Off-midline defects on the nasal tip warrant consideration of an advancement, rotation, or transposition flap. Small off-midline nasal tip defects can often be readily repaired with a Burow's advancement flap. This repair utilizes offset tissue triangles above and below the defect to provide reliably excellent results (Fig. 32.8).

In many cases, the skin of the nasal tip may be especially limited in its laxity. Such a situation frequently requires recruitment from donor skin from the upper two-thirds of the nose where greater tissue mobility can be found. Among the several options available for nasal tip defects measuring ≤1.5 cm, the bilobed flap provides optimal tissue dynamics. The double transposition movement of the bilobed flap is analogous to the motion of a double Z-plasty. When designed and executed correctly, the resulting redistribution of tension vectors prevents distortion to either the primary defect or surrounding free margin. The modification described by Zitelli [18] in a case series of 20 patients with nasal tip defects has been successfully implemented and reported by numerous reconstructive surgeons (4) [27–34]. Critical to avoiding alar rim distortion is vertical

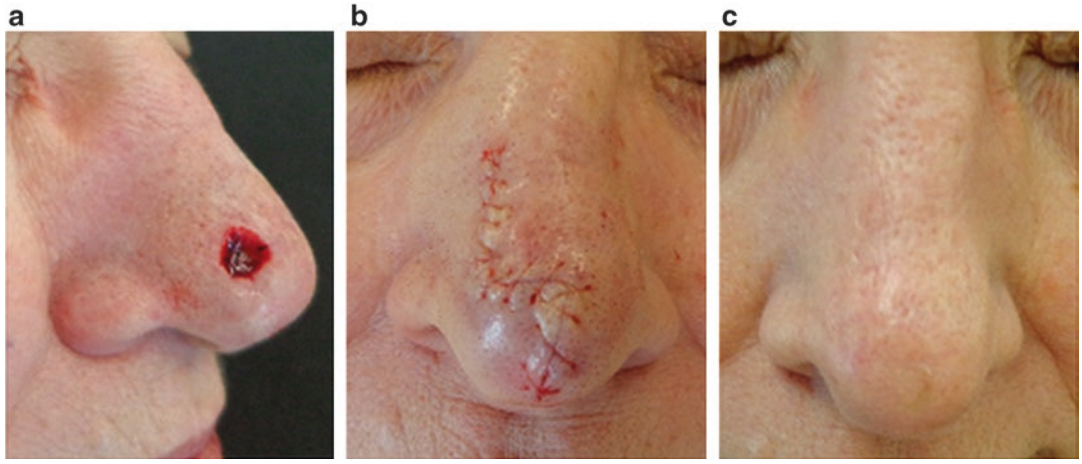

Fig. 32.8 (**a**) Defect on the lateral nasal tip in a 71-year-old woman. (**b**) Burow's advancement flap on the nasal tip. (**c**) Results at 3-month follow-up

orientation of the secondary defect and wide undermining over both sidewalls (4) [35, 36].

For very large defects of the nasal tip, maintenance of the cosmetic subunit approach to reconstruction is best achieved through the use of a forehead flap. However, patients for whom a forehead flap is being considered, but who may also have difficulty with the necessary follow-up, a single-stage local rotation flap may be a more suitable option. The dorsal nasal (aka dorsonasal or Rieger flap) flap was popularized by Rieger in 1967 for the repair of nasal tip defects ≤2 cm in diameter [37]. Numerous authors have reported excellent results for the repair of defects on the lower third of the nose using this approach (3b, 4) [38–44]. A retrospective analysis of 48 cases in which the dorsal nasal flap was used to repair nasal tip defects outlined optimization of its use when three criteria are met: a defect diameter of ≤2 cm, no defect extension onto the soft triangles or columella (so-called tip-defining points), and a defect location ≥1 cm from the alar rim (4) [45]. Other authors have reported its use for defects located ≥5 mm from the alar rim (5) [46]. Numerous modifications have been made to overcome some of the drawbacks to this particular flap, which include the development of bulkiness secondary to the presence of glabellar skin on the nasal dorsum and the conspicuous angled scars required to elevate the flap.

Forehead Flaps

Originally described by Burget and Menick, the subunit principle as it applies to nasal reconstruction dictates the replacement of an entire subunit if the defect involves over 50% of the subunit [47]. This approach is most relevant for defects of the nasal tip for which a forehead flap would provide the best aesthetic outcome. Improved aesthetic outcomes are achieved when the remainder of the cosmetic subunit of the nasal tip is resected prior to reconstruction. This is because removal of the remainder of the nasal tip along the borders of neighboring cosmetic subunits effaces the contour asymmetry that might otherwise result from a repair through the center of this conspicuous subunit (Fig. 32.9).

Cadaveric and human studies have reported on the central function of the supratrochlear artery

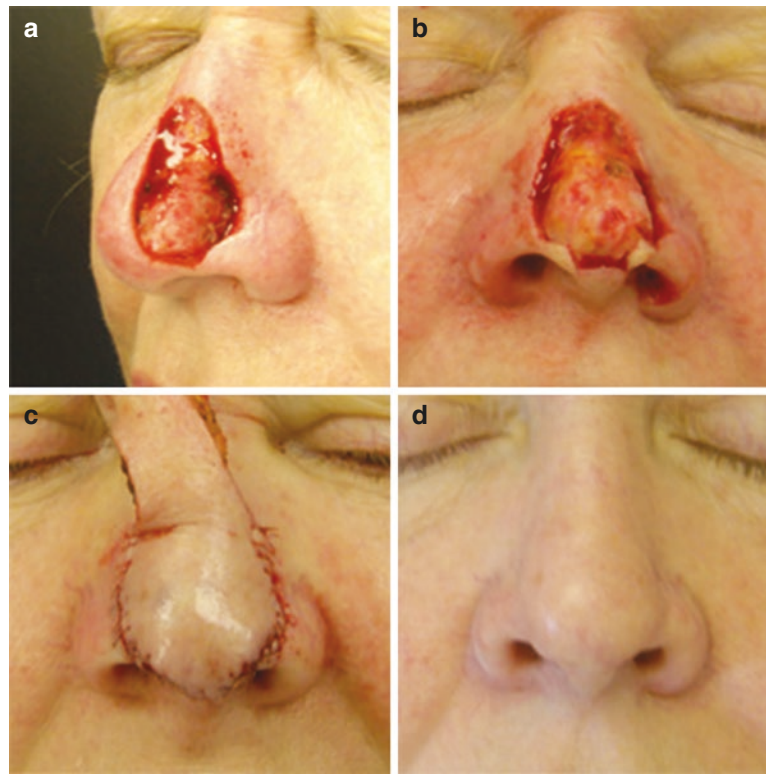

Fig. 32.9 (**a**) Defect of the lateral nasal tip and lower dorsum in a 60-year-old woman. (**b**) Remainder of nasal tip cosmetic subunit excised. (**c**) Reconstruction of entire nasal tip subunit with forehead flap. (**d**) Results at 6-month follow-up

as the primary blood supply for the traditional design of the paramedian forehead flap [48, 49]. However, a recent microanatomic study of flap vascularity in 50 forehead flaps demonstrated equivalent clinical outcomes and complication rates between flaps whose pedicles were based by simply measuring 1.2 cm from the glabellar midline ("paramidline") and those which intentionally included the supratrochlear artery ("paramedian") design [50]. Notably, the paramidline designs had more arteries within their pedicles than Doppler-based paramedian designs, suggesting that the blood supply for this flap may be based on a plexus of arterioles rather than a single artery. Thus, the flap may be safely and consistently designed as a random pattern flap using surface landmarks.

Ala

Repair of alar defects is complicated by the presence of highly sebaceous skin, limited tissue mobility, and the proximity of a free margin. As such, both superficial and deep wounds which are small and limited to the area of the concave alar crease may be allowed to heal by second intent (4) [3]. Recently, a small case series suggests an expanded range of nasal alar defects for which secondary intention healing may be appropriately applied. The authors reported excellent functionality and cosmesis, even for large or deep defects. This included patients whose defects extended from the alar sulcus onto the convex surface of the ala. They emphasized the importance of adequate structural support of the alar rim as an important consideration in patient selection (4) [51]. Proximity of the defect to the alar rim was also emphasized in the study by Becker et al. [8] as a sensitive predictor of alar retraction deformity. Wound healing in this area is via a contraction process that may result in subtle elevation of the entirety of alar rim. In contrast, wounds on the ala which are close to the rim may heal with a more noticeable notched appearance. The use of cartilage grafts to support the rim may prevent elevation and notching.

Grafts

Repair of alar defects with full-thickness skin grafts are typically limited by a resultant skin color discrepancy. However, for alar defects for which full-thickness skin grafts are appropriate, the conchal bowl should be the preferred donor site. The skin thickness and sebaceous quality from this area provide the best possible match, compared to pre- or post-auricular skin.

Flaps

Small partial- or full-thickness alar defects measuring ≤1.5 cm may be reliably repaired using a medially based bilobed flap (Fig. 32.10).

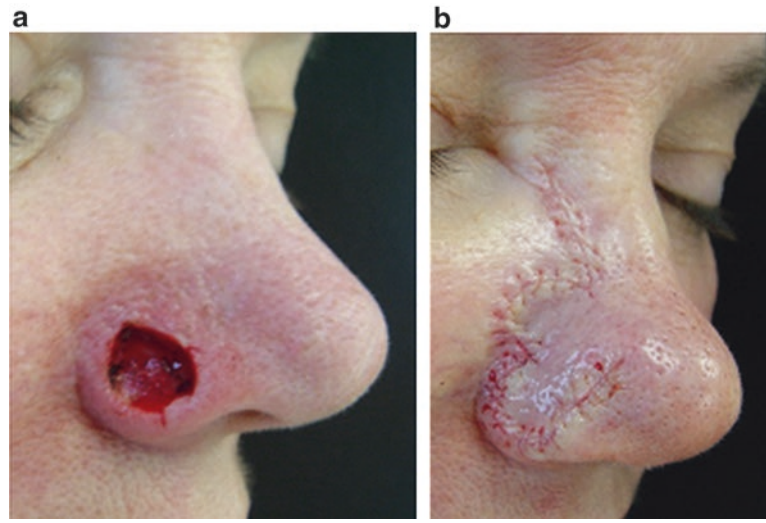

Fig. 32.10 (**a**) Full-thickness defect of the ala in a 54-year-old woman. (**b**) Reconstruction with a medially based bilobed flap

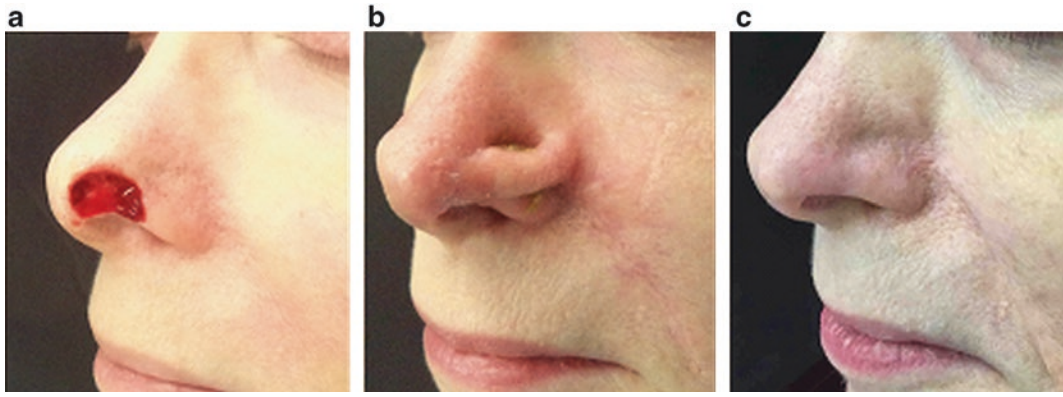

Fig. 32.11 (**a**) Partial-thickness defect on the nasal ala and lateral tip of a 66-year-old woman. (**b**) Reconstruction with an interpolated melolabial flap. (**c**) Result at 6-month follow-up

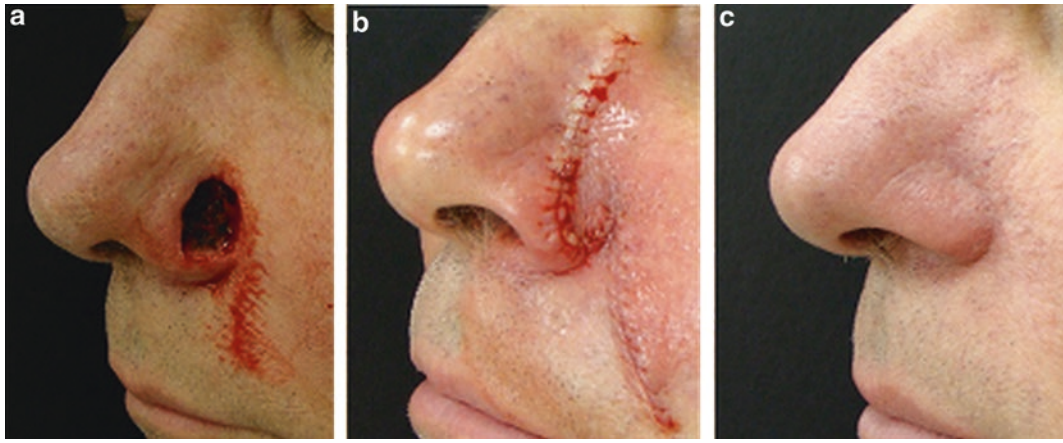

Fig. 32.12 A single-stage nasolabial flap is useful for wounds of the sidewall, including those that may extend onto the ala. (**a**) Defect of the left sidewall and ala in a 59-year-old man. (**b**) Repair with single-stage nasolabial flap. (**c**) Result at 6-month follow-up

Full-thickness alar defects measuring ≥1.5 cm often present the reconstructive surgeon with the option to use an interpolated flap. A two-stage interpolation flap is often used in tandem with cartilage grafts for full-thickness defects limited to the ala (Fig. 32.11) [52]. A recent study of 107 patients with nasal defects did not show a statistically significant difference in flap failure rates between the two-stage interpolated nasolabial flap and the paramedian forehead flap (4% vs. 6%, respectively) [53]. Interestingly, the use of cartilage was not seen to affect failure rates in either flap.

The Spear flap, a modification of the nasolabial flap described by Scott L. Spear, MD in 1987, is an excellent repair option for full-thickness loss of the ala and vestibular lining extending to the alar crease (4) [54]. When executed correctly, this single-stage approach preserves the hemicylindrical convexity of the alar rim. For partial- or full-thickness defects ≤2.5 cm in width, which include the sidewall but extend on the ala, the single-stage nasolabial transposition flap discussed earlier provides favorable outcomes and can be easily executed to minimize trapdoor formation [19] (Fig. 32.12). A case series of 105 patients undergoing alar reconstruction with this single-stage transposition flap reported excellent cosmesis and no flap failures after a minimum of 6 months follow-up

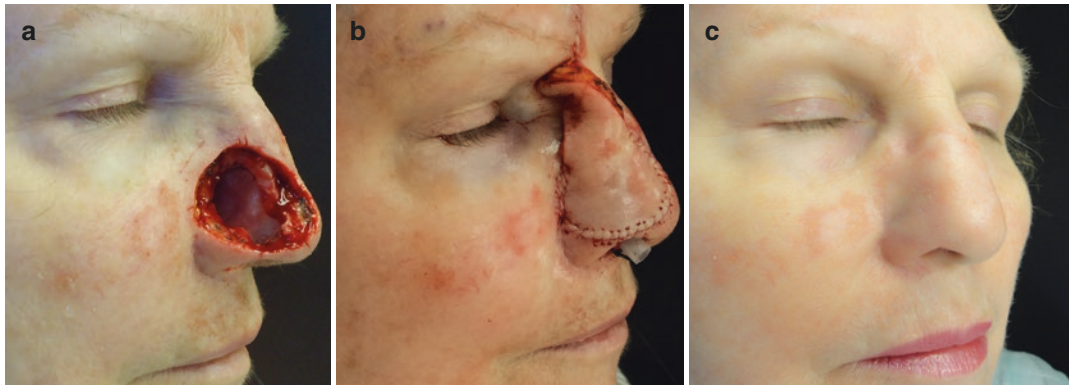

Fig. 32.13 (**a**) Full-thickness loss of the ala, ipsilateral vestibular lining, and lateral half of nasal tip. (**b**) Repair with a fold-under paramidline forehead flap and cartilage strut. (**c**) Result after second-stage inset of flap

(4) [55]. For large alar defects that are not amenable to a single-stage transposition flap, a two-stage interpolation flap or a Spear flap, a forehead flap may provide the best functional and aesthetic outcome (Fig. 32.13). When executed correctly, each of the above options may adequately re-establish the complex architecture of the alar subunit.

Additional Considerations

Structural Reinforcement

The application of suspension sutures and/or cartilage grafting may be necessary in cases where the rigidity of the ala or distal sidewall is compromised after tumor extirpation. Such defects result in functional impairment of the nasal valve(s). Re-establishing nasal contour as a matter of cosmesis may also necessitate structural support. Determining when structural support is necessary is a process informed by a combination of clinical examination and experience.

To date, the available literature does not provide a definitive answer regarding the application of structural support in nasal reconstruction. A large, heterogenous body of literature has demonstrated the feasibility of nasal reconstruction without the use of structural support. In contrast, however, comparative studies were lacking until recently. Ezzat and Liu published a small retrospective review of 38 patients with defects involving the nasal ala and/or sidewall (mean diameter of 2.04 cm) in which they compared reconstruction with and without structural reinforcement (3b) [56]. The authors reported that postoperative nasal obstruction occurred in 16% (3/19) of repairs which utilized only soft tissue (i.e., no cartilage or suspension sutures) versus 0% (0/19) of those that utilized structural support. Importantly, repairs utilizing structural support were substantially larger than those that were not reinforced (2.56 cm vs. 1.53 cm, respectively). This makes it difficult to draw a conclusion regarding reinforcement alone, since the likelihood of functional impairment – and thus the choice to use structural support – is proportional to defect size.

Conclusions

Among reconstructive surgeons, the standards for nasal reconstruction no longer tolerate a compromise between form and function. Patients are equally exacting in their expectations. In fact, prospective study of patients undergoing skin cancer surgery has demonstrated that the perceived quality of care is correlated most strongly with cosmetic outcome (4) [57].

Fundamental to the application of nasal reconstructive techniques is a careful analysis of the defect, including the soft tissue, cartilaginous or bony support and intranasal lining. Architecture,

surrounding skin quality, and defect characteristics (i.e., size, depth, location) combine to facilitate selection of the appropriate reconstructive option. In many cases, simplicity provides the most elegant results.

The reconstructive ladder presented herein is limited in scope to the defects encountered by most dermatologic surgeons and further limited to repair options which provide consistently high-quality results. In our experience, a limited number of reliable repair options for each of the cosmetic subunits may be utilized to achieve consistently superb results. At times, the advantages of one repair option or another are not clear and become a choice informed solely by personal experience. The appropriate use of secondary intention healing was emphasized, especially when underpinned by critical consideration of wound size, depth, and anatomic location (see Table 32.1). Irrespective of study, it is important to remember that the cosmetic results reported from second intention healing are based on subjective evaluation. Finally, evidence-based reconstruction is confounded by the fact that results are very operator dependent.

The use of bone grafts, intranasal flaps, and other complex techniques is beyond the scope of this chapter. The management of more complex defects, such as hemi or subtotal rhinectomy has

Table 32.1 Summary of studies assessing healing by second intention for each nasal cosmetic subunit

Summary of studies of secondary intention healing for defects of the nose by subunit				
Authors	Nasal dorsum	Nasal tip	Nasal sidewall	Nasal ala
Zitelli [2, 3]	Nasal dorsum and tip defects grouped within a single anatomic zone, defined as the "convex surface of the nose." Variable and unpredictable for all but very superficial defects. Full-thickness wounds may result in flat, depressed, or hypertrophic scars		Defects may heal with satisfactory cosmetic results	Excellent cosmetic results for wounds alar crease, irrespective of depth. Defects close to alar rim may cause upward rim retraction
Goldwyn et al. [4]	Series of 20 cases, 7 of which included the nose. Of seven, four were limited to nose alone. Smallest defect measured 2 × 1.5 cm, no indication of depth. Of seven cases involving the nose, three (43%) rated as having "excellent scar"			
Becker et al. [8]	Acceptable cosmesis achieved in only 67% (16/24) defects of all depths (average defect area = 421 mm^2)	Acceptable cosmesis achieved in 32% (24/74) of defects of all depths (average defect area = 298 mm^2)	Acceptable cosmesis achieved in 85% (29/34) of "mostly" partial-thickness defects (average defect area = 308 mm^2)	Satisfactory cosmesis achieved in 41% (28/69) of (average defect area = 237 mm^2). Most defects also involved adjacent cosmetic subunits
Van der Eeden et al. [11]	"Poor-average-good" outcome in the only two nasal dorsum defects evaluated. Depth and size of wound by cosmetic subunit not provided	"Poor-average-good" outcome in the single nasal tip defect evaluated. Depth and size of wound by cosmetic subunit not provided	"Poor-average-good" outcome in 56% (10/18). Excellent" outcome in remaining 8/18 (44%). Depth and size of wound by cosmetic subunit not provided	"Poor-average-good" outcome in 2/4 (50%) alar defects evaluated. Excellent" outcome in remaining 2/4 (50%). Depth and size of wound by cosmetic subunit not provided
Mott et al. [13]	Nasal dorsum and tip defects grouped within a single anatomic zone, defined as the "convex surface of the nose." Acceptable cosmesis achieved in 11/19 (58%) of defects (average defect area = 248 mm^2)		Acceptable cosmesis achieved in 5/5 (100%) of defects (average defect area = 146 mm^2)	Acceptable cosmesis achieved in 29/30 (97%) of "perinasal ala" defects defined as the "concave surface of the nose" (average defect area = 166 mm^2)
Neuhaus et al. [51]	–	–	–	Various defect sizes and depths amenable if adequate alar structural support is present

been presented elsewhere and are typically case reports or small case series outlining particular techniques.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
A paucity of strong evidence precludes definitive guidance for the multitude of scenarios encountered in nasal reconstructive practice	NA
The distinct regional variation existing between the skin of the upper two-thirds and lower third of the nose should guide the application of any repair option	A
Secondary intention healing should be the first option considered as it may provide excellent functional and cosmetic outcomes when applied to the appropriate area of the nose, defect type, and patient	A
Reconstruction algorithms should prioritize simplicity (e.g., primary fusiform repair) and employ changes to the design and surgical technique utilized as means to accomplish this (i.e., lengthening fusiform repair and/or wide undermining)	A

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Self-Assessment Questions

1. Which of the following types of wounds are amenable to secondary intention healing on the nasal dorsum?
   (a) Full-thickness wounds
   (b) Partial-thickness wounds
   (c) Very superficial wounds
   (d) Both full and partial-thickness wounds
   (e) None, all wounds on the nasal dorsum should be repaired
2. Which of the following types of wounds are amenable to second intention healing of the ala?
   (a) Full-thickness wounds
   (b) Partial-thickness wounds
   (c) Very superficial wounds
   (d) All of the above given adequate surrounding structural support of the alar rim
   (e) None of the above; all alar defects should be repaired with a flap or graft.
3. Why may the pedicle of a forehead flap be designed by simply measuring 1.2 cm from the glabellar midline (so-called paramidline)?
   (a) Because the supratrochlear artery is typically found within 1.2 cm from the glabellar midline.
   (b) Because branches of the supraorbital artery are typically found within 1.2 cm from the glabellar midline.
   (c) Because the paramidline designs have been shown to have more arteries within their pedicles than Doppler-based paramedian designs.
   (d) They may not be designed in this manner; the supratrochlear artery must be localized within the pedicle template using Doppler ultrasound.
4. Which of the following factors should be considered in order to optimize the cosmetic outcome of nasal tip defects allowed to heal secondarily?
   (a) Allowing only small, very superficial defects of the nasal tip to heal secondarily
   (b) Immediate or delayed dermabrasion
   (c) Avoiding the use of secondary intention healing in patients with thin, non-sebaceous skin of the nasal tip
   (d) All of the above
   (e) None of the above
5. Skin from which of the following donor sites is most histologically similar to the skin of the lower third of the nose?
   (a) Supraclavicular skin
   (b) Conchal bowl skin
   (c) Pre-auricular skin
   (d) Post-auricular skin
   (e) Upper eyelid skin

Correct Answers

1. c: Superficial wounds on the nasal dorsum may be allowed to heal by second intention. Large and/or full-thickness wounds may result in a depressed scar and distortion of the nasal tip.
2. d: Even full-thickness defects of the ala may be allowed to heal secondarily if the structural support of the alar rim is sufficient to resist the forces of scar contraction and avoid distortion of the free margin.
3. c: Microanatomic study of "paramidline" forehead flap designs had more arteries within their pedicles than Doppler-based paramedian design, suggesting that the blood supply for the paramidline flap is supported by a plexus of arterioles rather than a single artery.
4. d: Superficial defects on the nasal tip can readily be allowed to heal by second intention. Dermabrasion may maximize the cosmetic outcome by softening the transition between the defect and the surrounding skin. Lastly, choosing the right skin type to pursue this approach is critical to achieving the very best possible cosmetic outcome.
5. b: The skin of the conchal bowl provides a reservoir that is similar in color, texture, and quality to the skin of the lower third of the nose. This is underpinned by histologic study demonstrating similar adnexal density.

Topical Anesthesia

33

C. Blake Phillips, Melissa McEnery-Stonelake, and Conway C. Huang

Abstract

Topical anesthetics offer effective, uniform skin anesthesia while avoiding the discomfort and needle anxiety associated with injected local anesthetics. In the context of dermatology, they may be used to provide primary anesthesia or as an adjuvant pretreatment for alternative locoregional anesthesia. Unlike traditional injection anesthetics, two or more agents are typically combined in a vehicle for topical use. Because efficacy, indications, contraindications, and application techniques vary for these combination agents, this chapter aims to review the most common FDA-approved agents with a focus on best available evidence.

Keywords

Topical anesthesia · EMLA · Dermatology anesthesia · Local anesthesia · Topical anesthetic

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Indications for Topical Anesthetics

Topical anesthetics offer effective, uniform skin anesthesia while avoiding the discomfort and needle anxiety associated with injected local anesthetics. To that end, dermatologists have used a variety of agents to minimize the pain of injections, cutaneous laser surgery, cryotherapy, debridement, and various other minor procedures in patients of all ages.

Local anesthetics may be grouped by intermediate chain structure into amide and ester classes. The amide class of anesthetics includes lidocaine, prilocaine, bupivacaine, mepivacaine, and etidocaine among others. Metabolism of amides is via hepatic conversion. Notable ester anesthetics include procaine, cocaine, tetracaine, and benzocaine which are metabolized by plasma cholinesterases.

While single-agent analgesic preparations of lidocaine, benzocaine, and tetracaine are available over the counter, their utility in dermatologic procedures is limited. Compounded and FDA-approved prescription agents are of variable potency and efficacy dependent on drug concentration and delivery vehicle. Selected preparations may be found listed in Table 33.1.

In the context of dermatology procedures, two or more anesthetics are typically combined in a vehicle with or without an added vasoconstricting agent. All FDA-approved agents are

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Table 33.1 Topical anesthetics [1–3]

Topical anesthetic	Active ingredients	Vehicle	Recommended application time	Duration after removal	Maximum dose/ surface area recommended
EMLA	2.5% lidocaine, 2.5% prilocaine	Oil-in-water emulsion	60 min with occlusion for superficial dermal; 120 min with occlusion for deeper dermal; 15 min for mucosa	60–120 min	20 g/200 cm2 for adults
LMX4/ LMX5 (ELA-max/ ELA-max 5)	4%/5% lidocaine	Liposomal cream	15–45 min	60 min	600 cm2 (adults) 100 cm2 (children) Maximum application time 2 h
Pliaglis	7% lidocaine, 7% tetracaine	Cream that hardens into pliable film	30–60 min	11 h	59 g/400 cm2 up to 120 min
Synera	70 g lidocaine, 70 g tetracaine	Patch with heating element	30 min	At least 100 min	Maximum application time 30 min
Topicaine	4 or 5% lidocaine	Gel	30–60 min	60 min	600 cm2 (adults) 100 cm2 (children)
Vapocoolant	Ethyl chloride	Spray	Instant	60 s	
LET	Lidocaine 4%, epinephrine 0.1%, tetracaine 0.5%	Aqueous solution or methylcellulose gel	20–30 min, non-intact skin only	45–60 min	6 cm
TAC	Tetracaine 0.5%, adrenaline or epinephrine 0.05%, cocaine 11.8%	Aqueous solution	20–30 min, non-intact skin only	45–60 min	

indicated for pre-procedural anesthesia on intact skin. Studies support the use of a subset of agents for open wounds as in laceration repair.

Effectiveness of Topical Anesthetics

Anesthetic efficacy is determined by a preparation's active ingredient concentration, delivery vehicle, and time of contact. Head-to-head studies are few with most trials comparing an active drug against placebo.

Eutectic mixture of local anesthetics (EMLA) has been referenced as a gold standard by which other agents may be compared. Its efficacy has been demonstrated in cutaneous laser treatments (4) [4], genital cryotherapy (1b) [5], wound debridement (1b for 3, 4 for 4) [6, 7], and IV insertion [7]. A systematic review, however, identified tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine as equally efficacious or superior to EMLA (1a) [8].

A small prospective trial compared efficacies of EMLA, ELA-Max, 4% tetracaine gel, and Betacaine-LA ointment applied under occlusion for 60 min to adult forearms. EMLA and ELA-Max showed superior anesthesia at removal of occlusion as well as 30 min thereafter (4) [9].

Based on a pediatric study, occluded application of liposomal lidocaine for 30 min is as effective as a 60 min application of EMLA for producing topical anesthesia (2b) [10].

More recently, an FDA-approved preparation of 7% lidocaine/7% tetracaine in a self-occluding cream (Pliaglis) has proven efficacious after 30–60 min of contact time with studies largely focusing on cutaneous laser procedures. Some studies support anesthetic superiority of EMLA (2c for 8, 5 for 9, 1a for 10, 1b for 11, 1b for 12, 1b for 13, 1b for 14, 2c for 15) [11–18].

A systematic review of 22 randomized controlled trials involving >3,000 patients reviewed topical anesthetics for repair of dermal lacerations with the majority of reviewed topical agents demonstrating equal or superior efficacy of anesthesia as compared to intradermal infiltration. There was no significant difference noted in the level of anesthesia achieved between cocaine-containing anesthetic and six cocaine-free topical anesthetic formulations (1a) [19].

Several studies have found that topical and infiltrative anesthesia are equally effective in providing cutaneous anesthesia for harvesting of split-thickness skin grafts, arterial cannulation, and repair of minor dermal lacerations (particularly those located on the head and neck) (1b for 17, 1b for 18, 4 for 19, 1a for 20, 1a for 21) [19–24].

Several studies in the emergency medicine field have reported the efficacy of various topical anesthetics, including EMLA, TAC (tetracaine, adrenaline, and cocaine), amethocaine, prilocaine, and bupivacaine-containing compounds, for repair of lacerations in children and have encouraged these as a less painful and less frightening option to lidocaine infiltration for pediatric patients (4 for 22, 1b for 23, 1b for 24, 2b for 25) [25–28]. A prospective, randomized, double-blind, controlled trial showed that application of topical anesthesia to simple lacerations on pediatric patients during emergency department (ED) triage significantly reduced the total time of ED treatment by 30 min [26]. For the repair of simple lacerations on extremities of pediatric patients, EMLA appears to provide superior anesthesia compared to TAC and less often required supplemental anesthesia during laceration repair [28].

Due to variability of preparations, efficacy of compounded products will not be discussed.

Preoperative Evaluation

FDA package insert guidelines should be followed for any topical anesthetic agent. Given restrictions on applied anesthetic per skin cm^2, determination of targeted skin surface area is necessary to avoid overapplication and potential toxicity. While side-effect profiles are generally minimal, inquiry into the following risk factors may be warranted:

- Contact allergy to PABA (ester anesthetics)
- Cholinesterase deficiency (ester anesthetics)
- Hepatic failure (amide anesthetics)
- Methemoglobinemia (benzocaine)

Best Techniques and Performance

Topical anesthesia may be applied by the patient prior to arriving for their procedure, if they have been provided with proper instructions, or may be applied in office. Prior to application, the skin should be cleansed with mild soap and water, chlorhexidine, acetone, or other effective degreasing agent to remove dirt, oil, make-up, and other contaminants that could impede the absorption and effectiveness of the anesthesia. Washing with benzoyl peroxide should be avoided (4) [29]. A flat-surfaced tool such as a tongue depressor or a gloved finger should be used to apply the topical anesthetic in a thin uniform layer approximately one-eighth-inch thick (2c for 27, 2c for 28) [30, 31]. Depending on the specific topical anesthetic, the agent should remain in place for 30 min–2 h prior to the procedure in order to obtain optimal levels of anesthesia. Occlusion with plastic wrap or a transparent medical dressing such as Tegaderm can promote more rapid onset of cutaneous anesthesia. Prior to the procedure, the anesthetic should be completely wiped off the skin with a dry gauze followed by a water-dampened gauze. This is of heightened importance when the ensuing procedure can produce a spark or flame [31].

The amount of topical anesthetic absorbed depends on drug concentration, vehicle, duration of medication application, and the surface area exposed (2c) [32] (see Table 33.3). A recent review of the literature has shown that damaged or diseased skin, such as in patients with psoriasis or atopic dermatitis, is associated with increased skin permeability and greater chemical absorption (2c) [33].

Selected Agents

Eutectic mixture of local anesthetics (EMLA) is an oil-in-water emulsion cream, comprised of 2.5% lidocaine and 2.5% prilocaine. It is a eutectic mixture, formed from combining the crystalline forms of both lidocaine and prilocaine, causing the mixture to have a lower melting point and greater penetration than either substance alone [19]. EMLA cream may be used for procedures on intact skin or on genital mucosal membranes. For minor dermatological procedures, anesthesia will be achieved in 60 min under an occlusive dressing. For major dermatological procedures, such as split-thickness skin graft harvesting, allow 2 full hours under occlusion to reach peak anesthesia (5) [34]. Anesthesia can be reached in only 5–10 min on genital mucosa. The duration of application correlates to the depth of anesthesia achieved with an average depth of 2.9 mm after 60 min and 4.5 mm after 120 min (4) [35]. Maximum anesthesia in the dermis is reached at 2–3 h of application and persists for 1–2 h after removal of the cream. It is not recommended to apply more than 20 gm over 200 cm^2. EMLA cream may also be used on pediatric patients with the maximum application times and areas shown in Table 33.2 [34].

LMX4 and LMX5 (previously ELA-Max and ELA-Max 5) are 4 or 5% liposomal lidocaine creams. Liposomes are microscopic lipid vesicles that encapsulate lipid- and water-soluble drugs and appear to enhance the absorption and increase protection against rapid metabolism of the compound. Liposomes are readily absorbed into the stratum corneum without penetration to deeper levels of the epidermis or dermis (2c for 33, 2c for 34) [1, 36]. It has been shown that 5% liposomal tetracaine cream has significantly improved anesthetic effect as compared to EMLA cream after 60 min of application (1b) [37]. Cutaneous anesthesia for LMX4 and LMX5 occurs within 15–45 min of application, and occlusion is not needed. The maximum application area for pediatric patients under 20 kg is 100 cm^2 and up to 600 cm^2 for adult patients (2c) [1, 38].

Table 33.2 Pediatric patients: Maximum recommended dosages, application times and areas for EMLA cream [34]

Age and body weight requirement	Maximum total dose of EMLA	Maximum application area	Maximum application time
0–3 months or <5 kg	1 g	10 cm^2	1 h
3–12 months and >5 kg	2 g	20 cm^2	4 h
1–6 years and >10 kg	10 g	100 cm^2	4 h
7–12 years and >20 kg	20 g	200 cm^2	4 h

Pliaglis cream is an emulsion containing 7% lidocaine, an amide local anesthetic, and 7% tetracaine, an ester local anesthetic. It forms a flexible membrane when exposed to air and applied to skin. Pliaglis cream should only be applied to intact skin. Anesthesia can be achieved within 30–60 min of application. No more than 59 g over 400 cm^2 for 120 min should be applied [1, 11, 12].

Four percent tetracaine (amethocaine or Ametop) is an ester and is more lipophilic than amides and better able to penetrate the stratum corneum. It is typically applied under occlusion, achieves anesthesia within 30 min, and lasts approximately 4 h. Maximum recommended application area is 600 cm^2 for adult patients and 100 cm^2 for pediatric patients (5 for 37) [1, 38, 39]. Amethocaine promotes vasodilation and is hypothesized to promote improved venous access for cannulation (2c) [2].

TAC is a combination of 0.5% tetracaine, 0.05% adrenaline, and 11.8% cocaine and was the first topical anesthetic used for repair of head and face lacerations (2c) [40]. Dosing of 1 ml/cm of lacerated tissue is recommended to be applied with firm pressure for 20–40 min. It is ineffective on intact skin. However, due to concerns regarding cost and rare toxicity, largely from systemic absorption of cocaine, this product is rarely used. Complications are notable for seizures and sudden cardiac arrest, and rarely, death has been reported (2c for 40, 5 for 41) [1, 38, 40–42].

LET comprises 4% lidocaine, 0.1% epinephrine, and 0.5% tetracaine and is considered a safer and more affordable alternative to TAC. It is often used for repair of cutaneous lacerations and is ineffective on intact skin. One to 3 mL of gel or

solution may be applied directly into non-mucosal wounds with firm pressure for 15–30 min. Due to the vasoconstriction resulting from epinephrine, avoid applying to end-arteriolar areas on the body such as the digits [1, 38, 40].

Topicaine is a 4% lidocaine gel microemulsion. An application time of 30–60 min is recommended with a surface area maximum of 600 cm^2 for adults and 100 cm^2 for children. Local adverse effects include mild erythema, edema, and blanching (2c for 42) [1, 38, 43]. A randomized, double-blind, controlled trial has shown that Topicaine and LMX5 applied for 30 min produced effective anesthesia for treatment with Q-switched Nd:YAG laser; however, EMLA cream and Topicaine produced the highest level of anesthesia 30 min after removal of the topical anesthetic (4) [3].

Benzocaine is often prepared as a topical anesthetic spray with 10% or 20% benzocaine. A safe spraying time has not yet been determined due to the variability of the compound as it is applied (4 for 44) [41, 44].

Lidoderm (USA) and Versatis (Europe, South America) are slow-release patches containing an adhesive material with 5% lidocaine. The Lidoderm patch size is 10 cm × 14 cm. Each adhesive patch contains 700 mg (50 mg/gm adhesive) of lidocaine in an aqueous base. Up to three patches may be applied for a maximum of 12 h each per 24 h period. Lidoderm is FDA approved for treatment of post-herpetic neuralgia and is intended for use on intact skin only (5 for 45) [1, 2, 45].

Betacaine-LA is a petrolatum-based ointment that contains a combination of lidocaine, prilocaine, dibucaine, and phenylephrine. It is a proprietary anesthetic, and the exact concentrations of each ingredient are not revealed. Topical anesthesia can be achieved within 30–45 min without occlusion, and it should not be applied to a surface area >300 cm^2. It is not recommended for use in children [1, 38, 43].

Adjuvant Strategies

Topical anesthetics may cross the stratum corneum either through the cornified cell itself, through the spaces between cornified cells, or through openings in hair follicles, sweat glands, and sebaceous glands. Conjunctivae and oral and genital mucosa lack a stratum corneum and, therefore, are more easily penetrated by topical anesthetics [1]. There are several methods that can help enhance permeation and promote absorption of topical anesthetics through the stratum corneum and into the dermis. Removal of the stratum corneum by cutaneous tape stripping has been shown to increase transepidermal water loss through mechanical damage and has been shown to accelerate the rate of anesthesia prior to IV catheterization (1b for 46) [33, 46]. Laser-assisted delivery of 5% lidocaine cream through ablation of the stratum corneum with an Er:YAG laser was also found to increase the effectiveness of the topical anesthesia as compared to use of lidocaine cream alone (2b) [47].

Occlusion and heat can facilitate anesthetic penetration into the skin; however, caution must be taken as there is no data supporting standard practice recommendations. Application of EMLA cream with heat provides improved anesthesia at 20 min as compared to EMLA cream alone, although EMLA cream applied for the recommended 60 min remains superior for analgesia (4) [48]. A topical local anesthetic patch containing lidocaine 70 mg and tetracaine 70 mg with an incorporated oxygen-activated heating element (Synera, USA and Rapydan, parts of Europe) has been shown to provide significantly more pain relief prior to IV cannulation than a non-heated patch (1b) [49]. The heated patches are intended for use on intact skin only, and anesthesia may be achieved within 20 min with an average depth of 6.8 mm (5 for 50) [2, 50]. The S-Caine Peel incorporates the same formula as the Synera patch but is applied as a pliable peel that forms a skin-like mask upon exposure to air for easy removal. A recent meta-analysis found that the lidocaine/tetracaine patch or peel consistently and significantly provided more anesthesia than placebo with minimal difference in efficacy and safety. Common adverse effects include transient mild erythema, burning sensation, itching, blistering, and edema, all of which were resolved without intervention [13]. In another study of

heated lidocaine/tetracaine patches, plasma concentrations of lidocaine increased rapidly in the initial 2 h, then remained relatively stable through 12 h; however, the rate of drug delivery reached a peak at 2 h and diminished by 25% by 12 h. No tetracaine was detected in the serum at any time. Serum lidocaine levels were found to be five times higher at 30 min of patch application and three times higher at 60 min of patch application for heated patches as compared to non-heated patches (2b) [51].

There are several methods that physically enhance the ability to permeate through the barrier of the stratum corneum. Iontophoresis is a method of actively delivering a drug under the influence of mild electric current to enhance absorption and penetration across the skin barrier through existing pathways such as hair follicles and sweat glands. Studies have found that effective anesthesia on the skin can be achieved within 10 min for both children and adults, may last up to 15 min, and penetrate to a depth of 1–2 cm (1b for 52, 4 for 53, 4 for 54) [40, 48, 52–54]. Side effects include mild erythema and a burning or stinging sensation and are typically dose dependent. This method can also be cumbersome and complex to administer. Lidosite is an FDA-approved iontophoretic patch containing 10% lidocaine and 0.1% adrenaline for use on intact skin (5) [55].

Electroporation creates temporary aqueous pathways ("pores") across the lipid bilayer membrane through high-voltage electrical impulses and passively transports drug molecules dissolved in solution by diffusion or electrophoretic forces. Between pulses, the skin depolarizes and therefore maintains its native barrier properties. The procedure typically is quick and causes minimal irritation of the skin [53]. Electroincorporation is a similar method of creating transient pores in the stratum corneum, where polarizable particle suspensions, as opposed to solutions, are brought in close contact and transported through to the stratum corneum through pulsed dielectric fields. This procedure is also quick; however, it has increased risk of developing skin irritation depending on the specific particles transported. It has been suggested that iontophoresis, electroporation, and electroincorporation result in a similar level of anesthesia for warm and hot pain sensations, but that iontophoresis is more effective for cool pain sensation and can produce a greater depth of anesthesia into the dermis [53].

Ultrasound can be used to improve the delivery of topical anesthesia into the dermis. Low-frequency ultrasound results in cavitation and formation of transient aqueous channels through the stratum corneum. Treatment of the skin with low-frequency ultrasound prior to application of topical anesthesia has been shown to speed the onset of anesthesia with similar discomfort felt by those receiving ultrasound and topical anesthesia for 5 min as those receiving topical anesthesia alone for 30 min (2b) [56].

Microchannels created through microneedling by force of hand have been found to penetrate through the stratum corneum with a depth of penetration ranging from <100 μm to nearly 150 μm. A recent study showed that after two rounds of microneedling pretreatment, there was up to a 340% increase in topical anesthetic (lidocaine) uptake into the tissue (4) [57].

Needleless jet injection systems use compressed air to transmit topical anesthesia across the skin barrier to help promote a more rapid onset of anesthesia; examples include J-Tip, PowderJect, Dermojet, and PowderMed [2]. A prospective, randomized, controlled trial for children 8–15 years of age compared the anesthetic effectiveness of needle-free jet injection of 1% buffered lidocaine to 4% topical ELA-Max applied for 30 min prior to peripheral intravenous (PIV) catheter insertion and found that the needle-free jet injection method was associated with significantly less pain when assessed immediately after PIV catheter insertion (2b) [58].

Safety

The use of topical anesthetics is generally regarded as safe and well tolerated in appropriate doses; however, localized and systemic reactions may occur. Dermatological procedures that disrupt the epidermis, such as cutaneous laser surgery, may allow for increased absorption of the topical anesthetic and increased risk of toxic effects. Minor adverse effects include mild

erythema, skin irritation, pruritus, pallor if epinephrine is a component, vasoconstriction with EMLA, and vasodilatation with amethocaine (2b for 59) [2, 41, 59].

Amide topical anesthetics are metabolized by hepatic microsomal enzymes, including cytochrome P450 (CYP) 3A4, and should be used in caution in patients with liver dysfunction. Generally, there is minimal systemic absorption of topical anesthetic. Evaluation after application of occluded LMX4 (topical 4% liposomal lidocaine) cream in moderate amounts, 30 gm and 60 gm, did not show any clinical signs of toxicity or serum levels of lidocaine or metabolite monoethylglycinexylidide (MEGX) >0.5 mcg/mL through 24-h post-application [54]. However, when systemic absorption does occur, it can be associated with severe side effects including central nervous system (CNS), respiratory, and cardiopulmonary toxic effects. Lidocaine is associated with dose-dependent toxicity effects, so it is important to adhere to the correct dose as per manufacturer recommendations (Table 33.3). Therapeutic levels for anti-arrhythmia occur at 2–5 mcg/mL, and toxicity range occurs at >5 mcg/mL. A recent review of the literature of systemic toxicity due to EMLA yielded three adult and nine pediatric cases of toxicity. Several factors were noted as possible contributors to the development of systemic toxicity including excessive amount of EMLA over a large application area, prolonged application time, diseased and/or inflamed skin, age <3 months, and concomitant use of a methemoglobin-inducing agent (2c) [60]. EMLA exposure to the eye has resulted in corneal abrasions and ulcerations (5 for 61) [38, 61].

Table 33.3 Signs and symptoms of lidocaine toxicity [31]

Blood lidocaine level (mcg/mL)	Signs and symptoms
1–5	Anxiety, tinnitus, nausea, vomiting, lightheadedness, circumoral numbness, diplopia, metallic taste
5–8	Slurred speech, nystagmus, muscle twitching, tremors
8–12	Seizures (focal activity to generalized tonic-clonic seizures)
20–25	Cardiopulmonary and or respiratory arrest, coma

Methemoglobinemia is another potential serious side effect of topical anesthetics and has been associated with lidocaine, prilocaine, and most significantly, benzocaine. Hemoglobin is oxidized from a ferrous state (Fe^{2+}) to a ferric state (Fe^{3+}), resulting in methemoglobin, and is no longer able to bind oxygen, which lowers the oxygen-carrying capacity of the blood (5 for 62, 5 for 63) [62, 63]. Early symptoms of methemoglobinemia include cyanosis, headache, dyspnea, dizziness, fatigue, and loss of consciousness. An elevated methemoglobin level in arterial blood may result in a chocolate brown discoloration of the blood. With methemoglobin levels >50% (severe methemoglobinemia), symptoms include cardiac dysrhythmias, seizure, coma, and death. A retrospective case-control study revealed that, in general, the overall prevalence of procedure-related (including TEE, EGD, ERCP, bronchoscopy, and NG tube placement) methemoglobinemia is low at 0.035%; however, there was an increased risk noted with benzocaine-related topical anesthetics, with hospitalized patients, as well as with patients taking other methemoglobin-forming medications such as sulfonamides, dapsone, phenytoin, phenobarbital, acetaminophen, and nitrous oxide [2, 63]. Benzocaine has been reported to cause methemoglobinemia with as little as a single spray [1]. A recent study reported eight cases of methemoglobinemia after repeat mucosal exposure to benzocaine within 0–10 days of the initial exposure. In addition, five cases of rebound methemoglobinemia to initial mucosal application of benzocaine occurred up to 18 h after methylene blue administration with values as high as 59.9% [41, 44]. Treatment includes supplemental oxygen, IV methylene blue, and hyperbaric oxygen [1].

Ester anesthetics are metabolized to para-aminobenzoic acid (PABA) by hydrolysis and have rarely been associated with allergic reactions in a small number of patients (5) [64]. Ester topical anesthetics are contraindicated in patients with allergies to PABA, hair dyes, and sulfonamides [38].

The creation of compounded topical anesthetics, including TAC and LET, is not federally regulated or consistent between pharmacies. They are custom-produced for a specific patient by compounding pharmacies per physician prescription

and have been associated with variability in their composition including mixture and strength of topical anesthetics, labeling, and packaging. Dosing recommendations are not standardized, and the maximum recommended dosage is often not known which increases the risks of adverse events and even death (5) [65]. A public health advisory was issued in 2006 regarding the risk of life-threatening side effects associated with compounded topical anesthetics, and warnings were issued to five companies to stop the creation and distribution of compounded topical anesthetics produced for the general public rather than individualized for specific patients [65]. The United States Food and Drug Administration (FDA) has reported the death of two women due to compounded topical anesthetics after the unsupervised application and occlusion of topical lidocaine to their legs prior to laser hair removal (5) [66]. Therefore, it is imperative that topical anesthesia be used correctly and be applied for the shortest duration of application possible and to the smallest surface areas possible to avoid toxicity problems.

There is minimal data regarding the safety of topical anesthesia for pregnant and nursing women. Infiltrative lidocaine anesthetic has been reviewed most thoroughly and is a pregnancy category B medication based on animal studies. However, there have been no well-controlled studies in pregnant women. Per manufacturer recommendations, lidocaine and prilocaine are safe in small amounts for pregnant women. Both medications are excreted in human milk, with a 0.4 milk-to-plasma lidocaine ratio (not yet reported for prilocaine) and should be used with caution in nursing women (2c) [34, 67]. Blood and milk lidocaine levels in 27 epidural cases were found to be low, with no adverse effects noted due to excretion of the anesthetic into breast milk (4) [68]. The American Academy of Pediatrics considers lidocaine as safe for use during lactation (2c for 69, 2c for 70, 2c for 71) [69–71]. However, it is recommended to postpone use of topical anesthesia until after delivery or until the second trimester, at the very earliest, for more urgent procedures [69].

Postoperative Care and Follow-Up

With uncomplicated application, no specific follow-up care is required. Adverse effects should be managed according to their acuity and severity. The most common reactions, irritant or allergic contact dermatitis, may be managed with topical corticosteroids in moderate to severe cases or monitored for resolution in mild cases. Ocular complications should be evaluated by an ophthalmologist.

Systemic toxicity and/or anaphylaxis from topical anesthetics, though exceedingly rare, has/have resulted in death [68]. If signs of toxicity are encountered (Table 33.3), transfer to an emergency facility may be warranted.

Alternative Procedures and Modifications

For procedures requiring prolonged anesthesia, direct injection of local anesthetic agents is a common strategy, either via dermal infiltration or regional nerve blocks. Direct comparison studies are limited, but the use of topical agents was shown to be of equivalent efficacy to intradermal infiltration of anesthetics in harvesting split-thickness skin grafts, arterial cannulation, and repair of minor dermal lacerations [19–24]. Local infiltration of injected agents may be impractical for large surface areas of skin, unless regional blocks or tumescent techniques are utilized. Both techniques are more technically challenging to execute, and tumescent anesthesia requires the use of specialized equipment.

Ethyl chloride spray can provide immediate and transient anesthesia of the skin, which can be helpful in situations when waiting for topical anesthesia to take effect is impractical. The spray vaporizes immediately upon cutaneous contact, briefly dropping the temperature to −10 to −20 °C. It can be associated with mild pain and erythema [39, 41]. A study comparing the application of EMLA cream (45 min prior to procedure) to ethyl chloride spray (4–8 s of spray) prior to botulinum toxin injection showed that patients

experienced significantly less pain with ethyl chloride spray, with all patients in the study preferring this method of topical anesthesia (4) [72]. Review of other studies has shown variability in the efficacy of ethyl chloride in providing reduction of pain during venous cannulation, venipuncture, and skin prick testing, with some finding ethyl chloride as effective and others finding lidocaine infiltration to be superior in achieving anesthesia (4 for 73, 4 for 74, 4 for 75, 2b for76) [73–76].

Transcutaneous electronic nerve stimulation (TENS) is a strategy which uses electricity to provide nerve stimulation and analgesia. A single small randomized, prospective dental trial compared the use of TENS, 20% topical benzocaine (2 min application), and no pretreatment on pain associated with injected inferior dental blocks and lingual blocks. TENS was shown to be superior to both the topical benzocaine and no pretreatment (1b) [77].

At present, no available studies directly compare topical anesthetic agents to skin vibration, vapocoolant sprays, skin rubbing, or distraction techniques.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Topical anesthesia offers a safe and well-tolerated alternative to regional anesthesia when applied appropriately. FDA-approved pharmaceutical agents provide more consistency than compounded agents and are supported by reliable efficacy and safety studies.	D
Cocaine-free formulations should be used preferentially to cocaine-containing formulations.	A
Topical anesthetic agents are safe and effective for repair of skin lacerations in children.	A
Topical anesthetic agents are effective for minor procedures involving instrumentation of the skin.	C
Lidocaine usage should be limited in pregnancy. Insufficient data exists regarding other topical agents, so these should be avoided. Consider delaying procedures requiring topical anesthesia until after delivery.	C
Topical anesthetic agents may be effectively used for cutaneous laser surgery.	C

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Self-Assessment Questions

1. EMLA cream may be safely applied to:
   (a) Open lacerations
   (b) Conjunctiva
   (c) Intact skin
   (d) Genital mucosa
   (e) C and D
2. Which of the following topical agents is contraindicated in patients with known PABA allergy?
   (a) Lidocaine
   (b) Prilocaine
   (c) Benzocaine
   (d) Etiodocaine
   (e) EMLA
3. Initial signs of lidocaine toxicity (blood level 1–5 mcg/mL) include all of the following EXCEPT:
   (a) Circumoral numbness
   (b) Tinnitus
   (c) Metallic taste
   (d) Nystagmus
   (e) All of the above are initial signs of lidocaine toxicity
4. Patients on systemic dapsone therapy are at increased risk of what complication of benzocaine use?
   (a) Contact dermatitis
   (b) Methemoglobinemia
   (c) Anaphylaxis
   (d) Aphthous ulcers
   (e) B and C
5. Topical and infiltrated intradermal anesthesia have been shown to be of equivalent efficacy in each of the following applications EXCEPT:
   (a) Split-thickness skin graft harvesting
   (b) Ablative laser resurfacing
   (c) Arterial cannulation
   (d) Minor dermal laceration repair
   (e) None of the above

Correct Answers

1. e: Per package insert, "EMLA cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on normal intact skin for local analgesia and genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia."
2. c: Ester anesthetics are metabolized to para-aminobenzoic acid (PABA) by hydrolysis and have rarely been associated in allergic reactions in a small number of patients [64]. Ester topical anesthetics are contraindicated in patients with allergies to PABA, hair dyes, and sulfonamides [38].
3. d: See Table 33.3.
4. b: A retrospective case-control study revealed an increased risk of methemoglobinemia with benzocaine-related topical anesthetics and patients taking other methemoglobin-forming medications, such as sulfonamides, dapsone, phenytoin, phenobarbital, acetaminophen, and nitrous oxide [2, 63].
5. b: The use of topical agents was shown to be of equivalent efficacy to intradermal infiltration of anesthetics in harvesting split-thickness skin grafts, arterial cannulation, and repair of minor dermal lacerations [19–24].

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Local and Regional Infiltrated Anesthesia (Excluding Topical Anesthesia)

Meredith Orseth and Divya Srivastava

Abstract

The dermatologic indications for local and regional infiltrated anesthesia are abundant. Local infiltrative anesthesia is considered safe and effective for an array of procedures including excisions, biopsies, wound closures, skin grafting, cauterization, nonablative laser, and ablative skin resurfacing. Few contraindications to local and regional infiltrated anesthesia exist but should be screened for during the preoperative consultation. Numerous techniques for achieving adequate local and regional anesthesia have been described, including practices to lessen the pain associated with injection. Common side effects of local infiltrative anesthesia include pain, erythema, edema, bleeding, and ecchymoses. While overall well tolerated and commonly used, local and regional infiltrative anesthetic procedures do carry risks for toxicity and death. A comprehensive understanding of the pathophysiology, technique, and potential adverse events of various local and regional infiltrated anesthetics is critical to improve patient satisfaction and safety.

Keywords

Local anesthesia · Lidocaine · Injectable Epinephrine · Sodium bicarbonate · Cutaneous surgery · Systemic toxicity

Indications

The number of office-based procedures performed using local anesthesia continues to rise in dermatologic settings. The dermatologic indications for local and regional infiltrated anesthesia are abundant. Evidence-based guidelines from an American Academy of Dermatology (AAD) expert panel published in 2016 included a nonexhaustive list of office-based procedures in dermatology for which local infiltrative anesthesia is safe and recommended, including excisions, biopsies, wound closures, skin grafting, cauterization, nonablative laser, and ablative skin resurfacing (5) [1]. Tumescent local anesthesia, a technique using large volumes of a dilute anesthetic agent to produce swelling of the target areas, is commonly used in tumescent liposuction [2, 3]. A combination of infiltrative anesthesia with tumescent local anesthesia is recommended for follicular unit hair transplantation (5) [1]. Regional anesthesia, most often in the form of peripheral nerve blocks, may be used to anesthetize large areas while minimizing the amount of anesthetic utilized. Peripheral nerve blocks are helpful on the face, digits, and palmoplantar

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surfaces as a way to minimize tissue distortion and patient discomfort [4–6]. Data supports nerve block anesthesia during botulinum toxin injection of the palm (4) [7] and ablative laser resurfacing of the face (5, 4) [8, 9]. Peripheral nerve blocks of the forehead and scalp lead to a considerable reduction in pain during photodynamic therapy (PDT) (1b, 1b, 1b) [10–12]. Local infiltrative anesthesia and peripheral nerve block for ptosis surgery are associated with equal levels of patient satisfaction and are both accepted anesthetic methods for this procedure (1b) [13]. With appropriate technique and few exceptions that are discussed below, local and regional anesthesia may safely be used for localized pain reduction in patients of all ages [14].

Effectiveness

Local infiltrative anesthesia is considered effective for the procedures described above. However, there are few studies comparing the efficacy of local infiltrative anesthesia to other forms of local anesthesia [1].

Depending on the anesthetic agent used, the effect on pain reduction may vary significantly. The potency, duration of anesthesia, and speed of onset of local infiltrative anesthetics are dependent on their structural characteristics: lipid solubility of the aromatic ring, degree of protein binding, and drug dissociation constant, respectively. The closer the drug dissociation constant (pKa) of the medication is to tissue pH, the faster the time to effect [15–17]. With a pKa higher than physiologic pH, local anesthetics will have a faster onset of action when buffered or alkalinized with sodium bicarbonate [17]. Conversely, in tissues that are acidic due to inflammation or infection, the time to effect will be slower (5) [18].

Lidocaine is the most commonly used local anesthetic in dermatology and has a near immediate onset of action and moderate duration of 0.5–2 h [19]. Bupivicaine has a comparatively longer duration of action and may be useful for lengthier procedures such as Mohs micrographic surgery, flaps, and grafts. The onset of action for bupivacaine is 5–8 min and duration of anesthesia is 2–4 h [6, 19]. Anesthesia with either lidocaine or bupivicaine is prolonged by a factor of two with the addition of epinephrine (1b) [20]. Table 34.1 includes characteristics of common anesthetics used for local infiltration.

Table 34.1 Commonly used local anesthetics and their time to onset and duration of action [1, 19]

Name	Onset (min)	Duration without epinephrine (min)	Duration with epinephrine (min)
Amides			
Bupivicaine	5–8	120–240	240–480
Lidocaine	<1	30–120	60–400
Prilocaine	5–6	30–120	60–400
Esters			
Procaine	5	15–90	30–180
Tetracaine	7	120–240	240–480

Of note, the efficacy of local anesthesia may vary depending on patient characteristics. For example, subcutaneous lidocaine has been found to be significantly less effective in red-haired compared to dark-haired women (2b) [21]. Redheads and African Americans appear to be more sensitive to pain in general (2b) [21, 22].

Preoperative Evaluation

Prior to administering local infiltrative anesthesia or regional anesthesia, an appropriate history and physical should be performed as part of the preoperative consultation. Patients should be questioned regarding medication use and past medical history, including history of hypersensitivity to anesthetics as well as liver or cardiac disease. Additionally, the weight of the patient should be obtained prior to the procedure to accurately calculate the maximum recommended dose of infiltrated anesthetic (see Table 34.2). There are few absolute contraindications to local or regional infiltrative anesthesia.

True hypersensitivities are rare, but patients with a known history of hypersensitivity to local anesthetics of the ester (e.g., procaine, tetracaine) or amide (e.g., lidocaine, mepivacaine, bupivacaine, prilocaine) class should not receive

Table 34.2 Maximum recommended dosing of lidocaine and lidocaine with epinephrine per 2016 AAD Guidelines [1]

	Lidocaine	Lidocaine with epinephrine
Adults – single treatment	4.5 mg/kg	7.0 mg/kg
Children – single treatment	1.5–2.0 mg/kg	3.0–4.5 mg/kg
Tumescent liposuction in patients weighing 43.6–81.8 kg		55 mg/kg

medications of that type [1]. If a true allergy is suspected, preoperative allergy testing may be conducted using patch testing (type IV reaction), skin prick testing (type I reaction), or intradermal or subcutaneous challenges [23–26]. Alternatives to amide or ester anesthetics include diphenhydramine 1% and bacteriostatic saline [1]. These alternative medications will be discussed in further detail below.

Amide-type anesthetics such as lidocaine are metabolized by the liver and excreted by the kidneys [18, 27]. Liver disease, therefore, is a relative contraindication to using amide anesthetics as an increased risk for toxicity exists. Studies looking at plasma concentrations of lidocaine following intravenous bolus injection in patients with hepatic dysfunction found the elimination half-life to be prolonged by up to a factor of three [27]. No clear guidelines have been established to direct care.

Lidocaine may prolong cardiac atrioventricular conduction, and caution is advised in patients with impaired cardiovascular function, especially those with heart block [28]. Plasma clearance is reduced by a factor of two in patients with heart failure [27]. While caution is prudent, patients with stable cardiac disease may receive local infiltrative anesthesia with epinephrine (1a) [1, 29, 30]. If concern about a patient's ability to undergo local or regional infiltrative anesthesia exists, a consultation with the patient's cardiologist is recommended [1].

Concurrent use of epinephrine with monoamine oxidase inhibitors, phenothiazines, or tricyclic antidepressants may produce severe hypertension (4) [31]. Although rare, there are reports of severe hypertension developing in patients taking beta-blockers such as propranolol (4) [32]. A review of 114 patients taking beta-blockers undergoing minor surgical procedures with small amounts of epinephrine reported no hypertensive crises or minor cardiovascular episodes (4) [33].

Lidocaine is pregnancy category B. While it does cross the placenta, lidocaine did not demonstrate harm to the fetus in animal reproductive studies. Epinephrine also crosses the placenta and is considered pregnancy category C as one study showed increased risk of malformations in children of mothers exposed to systemic epinephrine during the first trimester (4) [34]. As per recent AAD evidence-based guidelines, small controlled amounts of lidocaine with epinephrine do appear safe for local anesthesia in pregnant women (4). In urgent situations, surgery should be delayed until second trimester if possible and all nonemergent procedures should be delayed until after delivery. Discussion with the patient's obstetrician may be helpful for risk analysis (5) [1].

Anesthetics containing paraben preservatives should be avoided in newborns with jaundice as parabens may displace bilirubin from albumin and worsen the condition (5, 5) [35, 36]. Neonates in general are at increased risk of toxicity due to immature hepatic metabolism and diminished plasma protein binding, and caution is advised (5) [14].

Best Techniques and Performance

There are numerous techniques described to successfully achieve local and regional anesthesia. Furthermore, there are several additives to local anesthesia that can enhance efficacy.

Common routes for local anesthesia administration include a combination of local infiltration in the dermis and subcutaneous tissue, field or ring block, peripheral nerve block, and tumescent infiltration. The specific technique chosen often depends on the procedure performed, anatomic site, and patient factors. The goals include achieving effective anesthesia while minimizing pain of

injection, volume injected, and side effects. Intradermal injection has the advantage of immediate onset and prolonged duration but is associated with increased pain of injection and tissue distortion. Subcutaneous infiltration is associated with less pain and a greater diffusion but has a shorter duration, increased absorption, and requires a greater volume of anesthetic (5) [37]. Commonly, a combination of intradermal and subcutaneous infiltration is used to achieve anesthesia. Field blocks involve injecting anesthesia around the surgical site when direct injection is not optimal, such as in a cyst excision. Nerve blocks have the advantage of prolonged duration and minimal volume injected; however, local infiltration is necessary to achieve hemostasis with the epinephrine effect. Also, there is a risk of nerve damage with nerve blocks [19]. Tumescent anesthesia involves infiltration of the subcutaneous fat with large volumes of dilute lidocaine through spinal needles or cannulas [3].

Whichever technique is utilized, safe patient positioning prior to the procedure is critical. In a large retrospective review, 1.9% of patients experienced presyncope and 0.16% of patients experienced true syncope during in-office procedures involving local anesthesia for simple excisions and shave biopsies (2b) [38]. Vasovagal reactions are characterized by warmth, diaphoresis, and pallor in response to upright posture, emotional stress, pain, or medical settings and may ultimately lead to syncope [39]. Clinicians should be careful to position patients in a way in that if this reaction occurs, neither the patient nor the clinician is injured. Additionally, patients should be positioned in a manner that is comfortable for both the patient and the clinician to complete the procedure. A review of reported sharps injuries in employees at an academic center from 2004 to 2013 revealed a significant increase in sharps injuries associated with local anesthesia over that time period despite a statistically significant decrease in overall sharps injuries (4) [40].

Discomfort associated with local infiltrative anesthesia may be considerable, and numerous studies have examined techniques aimed at reducing pain of injection [41–45]. The addition of sodium bicarbonate to buffer acidic lidocaine solutions has been well established (1b, 1b, 1b) [46–48] and is recommended in local infiltrative anesthesia. Most often, 8.4% sodium bicarbonate is mixed with 1% lidocaine with epinephrine in a 1:9 or 1:10 ratio [1].

Cold air skin cooling prior to injection, slow rate of infiltration, and warming the anesthetic solution to body temperature have been shown to be effective at reducing pain associated with anesthetic injection in single randomized controlled trials (1b, 1b, 1b) [41, 42, 44]. Distraction techniques have been shown to decrease distress behavior in the pediatric population during procedures such as immunization and venipuncture (1b, 1a) [49, 50] and have been suggested as helpful during dermatological procedures (5) [51]. However, there is limited data in the dermatological literature supporting the use of verbal or behavioral distraction techniques during local or regional anesthesia.

Skin-vibrating devices have been studied in upper eyelid surgery and during botulinum toxin and filler injections for cosmesis and were found to lead to a significant reduction in pain during the procedures (1b, 1b, 1b) [52–54]. Repetitive pinching of the skin has been found to be effective at reducing pain of injection of local anesthetic (1b) [43].

Data on the use of cooling the skin with ice prior to injection is limited. A prospective comparison of bicarbonate-buffered lidocaine to preoperative cooling for 2 min with ice prior to unbuffered lidocaine injection showed no significant difference between the two methods (2b) [45]. An ice-saline-xylocaine method has been suggested in which the skin is cooled with ice, then preinjected with normal saline prior to lidocaine injection (5) [55]. Data supporting this is scarce, and currently there is no clinical consensus regarding the use of ice or preinjection with normal saline to lessen pain associated with local anesthetic injection [1].

Commonly epinephrine is added to anesthetic agents for its vasoconstrictive effect and to reduce the dose of anesthetic required, thereby decreasing systemic toxicity [15]. The time to vasoconstriction when using lidocaine with epinephrine is often cited as 7–15 min [37, 56]. However, a

recent prospective, randomized, triple-blind study in 12 volunteers suggests 25 min to be the ideal wait time to begin a procedure after injection of 1% lidocaine with 1:100,000 epinephrine (1b) [57]. The optimal concentration of epinephrine is unclear and using the lowest effective concentration to provide pain control and vasoconstriction is recommended [1]. A comparison of 1% lidocaine with epinephrine in concentrations of 1:100,000, 1:200,000, and 1:400,000 during neck surgery showed no significant difference in blood flow; however, epinephrine 1:800,000 resulted in significantly less vasoconstriction (2b) [58]. Similarly, there was no significant difference in vasoconstriction between 1% lidocaine with 1:100,000 epinephrine and 1% lidocaine with 1:200,000 epinephrine during facial injections (1b) [56]. A randomized, double-blind comparison of 0.5% lidocaine with 1:200,000 epinephrine and traditional 1% lidocaine with 1:100,000 epinephrine demonstrated no significant difference in pain control during Mohs micrographic surgery. The dose of lidocaine administered in the 0.5% lidocaine with 1:200,000 epinephrine group was approximately half that administered in the 1% lidocaine with 1:100,000 epinephrine group (1b) [59]. In dermatologic surgery, epinephrine concentrations of 1:100,000 and 1:200,000 are most commonly used [1]. These concentrations have been shown to increase duration of anesthesia by approximately 200% [20].

While historically there was concern regarding the use of local infiltrative anesthetics with epinephrine on areas such as the ear, nose, penis, hands, feet, and digits, multiple systemic reviews, randomized controlled trials, and retrospective studies have found the addition of epinephrine to local infiltrative anesthesia to be safe for use in these locations [60–63]. There were no reported cases of necrosis and benefits described included improved view and extended effect of anesthesia [60, 63, 64]. Based on this data, the 2016 AAD guidelines state local infiltrative anesthesia with epinephrine is safe and recommended for use on the ear, nose, hand, feet, and digits (1a) and may be considered for use during procedures on the penis (2b) [1].

Buffered lidocaine both with and without epinephrine may be stored in a controlled room or controlled cold temperature environment and be safe for use for up to 4 weeks, although effectiveness of the solution may decrease (5) [65]. A 1989 study showed the addition of bicarbonate to lidocaine with epinephrine leads to a weekly 25% decrease in concentration of epinephrine in the buffered solution [47]. Stewart et al. demonstrated that there is no difference in clinical effectiveness between buffered 1% lidocaine with epinephrine solution prepared within 5 h and solution stored at room temperature for 7 days [46].

More recent data showed lidocaine in buffered solution with epinephrine remained over 95% of its original concentration while stored in a controlled cold temperature environment for up to 4 weeks. Concentration of epinephrine in the solution decreased to 95.9% of original and 61.8% of original at weeks 1 and 4, respectively (5) [66]. In comparison, lidocaine in buffered solution with epinephrine at room temperature showed a respective decrease in lidocaine concentration of 88.73% and 66.11% of original at 1 and 4 weeks, respectively. Epinephrine concentration in the solution stored at room temperature decreased to 72.65% and 1.34% at 1 and 4 weeks, respectively (5) [67]. Therefore, while buffered lidocaine with epinephrine is safe for use for up to 4 weeks, due to concern for diminished effectiveness, some authors recommend use of the solution within 1 week of compounding [47].

Hyaluronidase promotes increased absorption of local anesthetics by digestion of the extracellular matrix. Most often described in ophthalmology and plastic surgery literature, there is limited data regarding its use in dermatological surgery [68–70]. The mixing of hyaluronidase and infiltrative anesthesia did not retard wound healing and was deemed safe in a prospective, double-blind, randomized, placebo-controlled, single-center study (1b) [69]. Hyaluronidase is thought to ease dissection through tissue planes; however, no data supports this, and its role in dermatological surgery is unclear [1, 70]. Patients with a history of bee sting allergy should not receive hyaluronidase as there are reports of cross-

reactivity and type I hypersensitivity with its use (5, 5) [71, 72].

There is a gap in research examining the use of regional anesthesia in dermatology. Despite this, supraorbital, supratrochlear, mental, infraorbital, and digital nerve blocks are commonly used in dermatological surgery [6] and are an accepted alternative to local infiltrative anesthesia for surgeries on the face and digits [1]. Similarly to local infiltrative anesthesia, several anesthetic agents are utilized for peripheral nerve blocks, with 1% lidocaine with epinephrine and sodium bicarbonate being the most common [19]. A randomized control trial examining the duration of anesthesia in digital nerve blocks found bupivacaine 0.5% to have a significantly longer digital anesthesia time (24.9 h) compared to 2% lidocaine with 1:100,000 epinephrine (10.4 h) and 2% lidocaine (average 4.9 h) (1b) [64].

Several techniques for digital nerve blocks have been described including a traditional two-injection (also known as four-sided or "ring") block, subcutaneous block (one or two palmar punctures), transmetacarpal/metatarsal block, or transthecal block (local anesthetic is injected into the flexor tendon sheath) [73]. Traditional two-injection blocks are the form most commonly used in dermatology to block the sensory nerves coursing laterally along the digit [19]. Data specific to dermatology is lacking, with most trials to date published in emergency medicine and plastic surgery literature [73–76]. A randomized control trial comparing traditional two-injection digital block to transthecal digital block found the two techniques to be equivalent based upon associated pain and time to anesthesia (1b) [74]. A comparison of subcutaneous block to traditional digital block found the subcutaneous method to be as effective as the traditional method with outcome measures favoring the former but no significant difference in success of anesthesia or patient distress between the two (1b) [75]. A comparison of subcutaneous block, transthecal block, and transmetacarpal block in healthy volunteers found no significant difference on average pain level between methods, although time to onset was significantly longer for the metacarpal block, and the transthecal block had prolonged discomfort lasting 24–72 h in 40% of the subjects. Therefore the authors of the study favored subcutaneous block (1b) [73]. A trial in patients who had injured two or four fingers and served as their own controls compared transthecal versus subcutaneous digital block techniques and found that while transthecal block was equally efficacious, it was significantly more painful. Subcutaneous block was also preferred in that scenario (1b) [76]. A 2006 meta-analysis found evidence favoring less pain with traditional digital block and subcutaneous injection block techniques compared to transthecal block. No significant difference in associated pain was found between traditional digital block and subcutaneous block (1a) [77].

If a tourniquet is used during the procedure, the clinician should be sure it is removed at termination as forgotten tourniquets have been associated with digital necrosis [78]. Excessive injection volume has also been associated with digital necrosis [1, 78], and while there is no clear safe cutoff, some authors recommend 1.5 ml of volume or less per nerve (5) [79].

Pain and psychological stress associated with digital nerve blocks can be significant. Use of buffered lidocaine and lidocaine warmed to 42°C during digital nerve blocks was examined in single, randomized control trials, and both techniques were found to reduce pain associated with injection (1b, 1b) [80, 81]. Additionally, a two-stage method in which a small amount of infiltrated anesthetic was delivered prior to the main injection during digital blocks was found to be associated with less intense pain compared to the traditional one-stage method (1b) [82].

Tumescent anesthesia with lidocaine and prilocaine is safe and recommended for office-based liposuction (2b) [1, 83]. Other anesthetics such as bupivacaine have not been studied in tumescent liposuction [1]. Epinephrine as an additive has been shown to be safe for use and is recommended in tumescent local anesthesia for liposuction (2b, 2b) [84, 85]. Warm anesthetic solutions and a slow rate of infiltration lead to a significant decrease in pain associated with the administration of anesthetic (1b, 2b) [86, 87].

Safety

Local infiltrative anesthesia, peripheral nerve blocks, and tumescent local anesthesia are considered safe for use in office-based settings [1]. While overall well tolerated and commonly used, local and regional infiltrative anesthetic procedures do carry risks for toxicity and death [88]. Common side effects of local infiltrative anesthesia include pain, erythema, edema, bleeding, and ecchymoses [10, 19, 31]. Certain sites such as the periorbital area carry more risk for bruising and edema. Transient motor nerve paralysis may occur [19]. The addition of epinephrine to lidocaine may lead to tachycardia and an associated sensation of anxiousness [31, 33]. Peripheral nerve blocks carry many of the same risks as local infiltrative anesthesia, including hematoma and local skin infection [10] but are also associated with comparatively higher rates of nerve damage [6]. If a sensory nerve is injured during nerve block, a prolonged sensory nerve paresthesia may develop [19].

Vasovagal reactions are a relatively common adverse event associated with injectable local anesthesia [38] and must be distinguished from anesthetic toxicity, epinephrine effect, or an anaphylactic reaction [31]. Less than 1% of all adverse reactions to local anesthetics are due to a true IgE-mediated immunologic reaction [23, 31]. Historically, reactions to ester anesthetics appeared to be more common than reactions to amide anesthetics [23]. A recent review demonstrated amide anesthetics are associated with the most reported true cases of local anesthetic immediate hypersensitivity (4) [31]. This may be due to the preponderance of use of amide over ester anesthetics in current practice. Cross-reactivity exists within the amide group and patients with a true allergy to one amide anesthetic should not be given other anesthetics from that group [23]. Both ester and amide local anesthetics may contain methylparaben, a preservative agent that is metabolized to para-aminobenzoic acid (PABA) and may contribute to a significant number of adverse reactions [23, 89]. Allergic contact dermatitis (type IV hypersensitivity) reactions to local anesthetics appear to be increasing (2b) [90], with one retrospective study estimating a 2.4% prevalence based on patients who had undergone patch testing (2b) [91]. Suspected allergy to an anesthetic agent may be investigated with skin prick testing as well as intradermal and subcutaneous challenges; however, no firm guidelines have been established [23–25]. Patch testing is useful to identify type IV hypersensitivities [23, 26].

Toxicity with local anesthetics may occur due to underlying impaired metabolism, inadvertent overdose, or intravascular injection [36, 88, 92]. Local anesthetics differ in regard to their central nervous system and cardiovascular toxicity, with bupivacaine associated with a higher risk of cardiac toxicity compared to other agents [93]. Toxicity with lidocaine has been well studied [see Table 34.3] with dose-dependent effects typically starting at serum levels of 1–6 μg/ml [36]. As serum levels increase, side effects span nonspecific dizziness to peri-oral and digital paresthesias and tinnitus to seizures and cardiac arrest [36, 92]. In the 2010 American Society of Regional Anesthesia and Pain Medicine Practice Advisory, the expert panel notes that in their overall analysis and review of the literature, less than 20% of cases of local anesthetic systemic toxicity involved "classic" prodromal symptoms such as metallic

Table 34.3 Serum lidocaine levels, associated signs and symptoms, and management of toxicity [19, 36, 92]

Serum lidocaine levels (μg/ml)	Signs and symptoms	Management
1–6	Circumoral and digital paresthesias, metallic taste, lightheadedness, euphoria	Observation, supplemental oxygen
6–9	Nausea, vomiting, tremors, slurred speech, localized muscle twitching, tinnitus, psychosis	Diazepam, airway maintenance, EMS activation
9–12	Seizures, respiratory and cardiopulmonary depression	Respiratory support
>12	Respiratory and cardiac arrest, coma, death	Cardiopulmonary resuscitation and life support

taste and auditory changes. Seizure was the most common presenting symptom of local anesthetic toxicity, occurring in two-thirds of cases [88, 92]. If toxicity is suspected, vital signs should be immediately obtained and supplemental oxygen should be administered. Airway management and prevention of hypoxia and acidosis may prevent cardiovascular collapse [94]. Seizures should be treated with benzodiazepines [88].

Various precautions are recommended to decrease the risk of local anesthetic toxicity. These include using the lowest effective dose of local anesthetic needed and continually assessing and communicating with the patient for early recognition of potential toxicity. Additionally, intravessel injections may be avoided by aspirating the needle or catheter prior to each injection [1, 88].

Recent recommendations from the AAD for maximal safe dosing of lidocaine with and without epinephrine is summarized in Table 34.2 [1]. During multistage procedures that span several hours such as Mohs micrographic surgery, the maximum recommended dose of local infiltrative anesthesia is 50 ml of 1% lidocaine solution (500 mg) based upon a 2010 prospective cohort study (2b) [95]. Tumescent local anesthesia for office-based liposuction is a safer alternative to liposuction under general anesthesia [2] with no reports of death [83] and a total complication rate in one review of 9478 cases of less than 1% (2b) [96].

As discussed above, epinephrine is recommended and considered safe for use in procedures involving the digits [1]. In a large retrospective review, cases of digital necrosis associated with local anesthetic use were reported in the setting of previously damaged tissue in patients with diabetes mellitus, arteriosclerosis, or thromboangiitis obliterans (4) [97], and careful attention is recommended in patients with these comorbidities. There is an association with the use of large amounts of epinephrine and exacerbations of severe hypertension or severe cardiovascular disease [29, 30, 98]. This effect is rare, however, and recent reviews and consensus guidelines accept the use of local infiltrative anesthesia with epinephrine in patients with stable cardiac disease [1, 29]. Patients with a history of hyperthyroidism, severe hypertension, or pheochromocytoma may be more sensitive to epinephrine's effects, and caution is advised [31, 78].

Postoperative Care and Follow-Up

There is minimal follow-up required after local or regional infiltrated anesthesia. Reviewing common side effects with patients, including bruising, discoloration, and swelling around injection sites, may help relieve patient concern. Additionally, reminding patients that sensory nerves may return to normal several hours before motor nerve paralysis resolves may help reduce anxiety [19].

Alternative Procedures and Modifications

It is unknown if local infiltrated anesthesia is more effective than other forms of local anesthesia [1]. Studies comparing topical and infiltrated anesthesia in a variety of clinical situations including split-thickness skin graft harvest (1b) [99] and minor laceration repair (1a) [100] found topical anesthesia at least as effective as infiltrated anesthesia. Peripheral nerve blocks have been found to have superior pain reduction compared to cold air skin cooling alone in the setting of frontotemporal scalp photodynamic therapy [7, 12].

The use of ethyl chloride in dermatological procedures has not been well studied, and there is contradictory evidence about its effectiveness. Several reports examining ethyl chloride during venipuncture did find it effective for reducing pain of the procedure (1b, 1b) [101, 102]. In one study, while ethyl chloride did induce statistically significant anesthesia, it was comparatively less effective than anesthesia with intradermal 1% lidocaine [101]. A randomized control trial examining injection pain in children found significantly less pain with the use of a topical refrigerant spray and placebo aerosol spray as compared to no spray use at all. There was no significant difference in pain reduction between the topical refrigerant and placebo sprays (1b)

[103]. Given the limited data, use of ethyl chloride as a sole anesthetic agent for dermatological procedures is not recommended [1].

In patients with a true hypersensitivity reaction to lidocaine, bacteriostatic normal saline (0.9% benzyl alcohol in normal saline) or 1% diphenhydramine are alternatives for local infiltrative anesthesia in addition to ester-type local anesthetics [1]. In a study comparing 0.9% buffered lidocaine, 1% diphenhydramine, and 0.9% benzyl alcohol with epinephrine, the investigators found no difference in duration of anesthesia between diphenhydramine and benzyl alcohol with epinephrine. Buffered lidocaine revealed a significantly longer duration of anesthesia compared to the other two local infiltrated anesthetics. Additionally, the injection of diphenhydramine was significantly more painful compared to buffered lidocaine and benzyl alcohol with epinephrine (1b) [80]. Another prospective, randomized, double-blind comparison found 0.5% diphenhydramine with epinephrine to be both less effective anesthetically and more painful compared to buffered 1% lidocaine with epinephrine and unbuffered lidocaine 1% with epinephrine (1b) [104]. A comparison of the effectiveness of 1% diphenhydramine, 1% buffered lidocaine, 1% lidocaine, and normal saline found diphenhydramine reached a significantly larger diameter of analgesia compared to placebo (normal saline) by 5 min after injection. By 30 min after injection, the diphenhydramine diameter of anesthesia was equivalent to placebo while buffered 1% lidocaine and 1% lidocaine diameter of anesthesia remained significantly larger than placebo (1b) [105]. Based on this data, bacteriostatic normal saline and 1% diphenhydramine may be considered for minor dermatological procedures in patients unable to tolerate lidocaine [1].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Indications:	
1. Local infiltrative anesthesia is safe and recommended for excisions, cauterization, obtaining biopsy specimens, nonablative laser, skin grafting, tissue rearrangement, and ablative skin resurfacing	C
2. Lidocaine and prilocaine are safe for use during tumescent local anesthesia for liposuction	A
3. In patients with a true allergy to lidocaine, accepted alternatives include bacteriostatic normal saline, diphenhydramine, and ester-type local anesthetics	C
Dosage and administration:	
4. For a single treatment, the maximum recommended dose of lidocaine with epinephrine in adults is 7.0 mg/kg, without epinephrine is 4.5 mg/kg	C
5. For a single treatment, the maximum recommended dose of lidocaine with epinephrine in children is 3.0–4.5 mg/kg, without epinephrine is 1.5–2.0 mg/kg	C
6. For multistage procedures such as Mohs micrographic surgery, the maximum recommended dose of lidocaine is 500 mg	B
7. For tumescent liposuction, the maximum recommended dose of lidocaine with epinephrine is 55 mg/kg for patients weighing 43.6–81.8 kg	A
8. The addition of sodium bicarbonate to local anesthetics is recommended to reduce pain associated with injection of the anesthetic	A
9. Techniques shown to decrease pain associated with delivery of local infiltrative anesthetics include vibration, cold air skin cooling, use of a warm solution, and slow rate of infiltration	B
Safety of local infiltrated anesthetics and additives:	
10. True IgE-mediated hypersensitivity to lidocaine is very rare	B
11. Buffered lidocaine with epinephrine stored at room temperature is effective and safe for use at 1 week after compounding	B

Findings	GRADE score: quality of evidence
12. Local anesthetics with epinephrine are safe for use on the ear, nose, and digits	A
13. Local anesthetics with epinephrine may be used during procedures on the penis	B
14. Lidocaine with epinephrine is safe for use during tumescent local anesthesia for liposuction	A
15. Small amounts of lidocaine with epinephrine may be used in pregnant women	C
Nerve block anesthesia:	
16. Nerve block anesthesia is recommended for botulinum toxin injection of the palm, ablative laser resurfacing of the face, and upper lid ptosis surgery	B
17. Digital nerve blocks performed in a traditional two-injection or subcutaneous manner are associated with less pain compared to transthecal digital blocks	C

Note: recommendations 1–9, 12–16 are reproduced with permission from the 2016 AAD guidelines

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Self-Assessment Questions

1. What is the maximum recommended dose of 1% lidocaine with 1:100,000 epinephrine for a 55-kg woman?
   (a) 8 ml
   (b) 16 ml
   (c) 24 ml
   (d) 38 ml
   (e) 300 ml
2. Which agent is NOT recommended for use in tumescent anesthesia?
   (a) epinephrine
   (b) lidocaine
   (c) bupivacaine
   (d) prilocaine
   (e) sodium bicarbonate
3. A patient reports a history of anaphylaxis to a bee sting. What medication is contraindicated?
   (a) epinephrine
   (b) lidocaine
   (c) sodium bicarbonate
   (d) hyaluronidase
   (e) prilocaine
4. The following have been shown to reduce pain associated with infiltration of local anesthesia *except*:
   (a) Buffering lidocaine with sodium bicarbonate
   (b) Rapid infiltration of lidocaine
   (c) Warming the anesthetic prior to injection
   (d) Vibration
   (e) Cold air cooling
5. A 70 kg patient is undergoing Mohs micrographic surgery. What is the maximum dose of 1% lidocaine with 1:200,000 epinephrine he can be given over several hours?
   (a) 10 ml
   (b) 30 ml
   (c) 50 ml
   (d) 100 ml
   (e) No limit

Correct Answers

1. d: The correct answer is 38 ml. 55 kg (weight of patient) multiplied by 7 mg/kg (maximum recommended dose) divided by 10 mg/ml (1% lidocaine) = 38.5 ml. The other answers are incorrect. Answer c (24 ml) is the maximum recommended dose for plain lidocaine without epinephrine. Answer e (300 ml) is the recommended dose for tumescent anesthesia using a 1% solution.
2. c: All agents listed above except for bupivacaine have been studied and found safe for use in tumescent local anesthesia. There is no data regarding bupivacaine.
3. d: Hyaluronidase is contraindicated in patients with a history of bee sting allergy given reports of cross-reactivity and type I hypersensitivity with its use.
4. b: All of the above, except for answer b (rapid infiltration of lidocaine), have been shown to reduce pain associated with infiltration of local anesthesia. Slow (not rapid) infiltration of lidocaine is associated with reduced pain.
5. c: During multistage procedures that span several hours, the maximum recommended dose of lidocaine is 500 mg. 500 mg divided by 10 mg/ml (1% lidocaine) = 50 ml of 1% lidocaine solution.

Nail Procedures

35

Daniel R. Knabel, Nathaniel J. Jellinek, and Thomas J. Knackstedt

Abstract

The evidence-based treatment of nail disease remains a challenge. Unlike in the skin, the nails are slow growing and many interventions will not be readily apparent for several months. Many practitioners do not feel comfortable with invasive nail procedures and, relative to the remaining skin, nail biopsies are done by fewer practitioners. Indeed, most residents perform less than ten nail procedures in their training, and 30% of residents do not feel competent in nail diseases at the conclusion of their residency (4) (Clark et al. Dermatol Surg 42:696–698, 2016). Experts have noted significant knowledge gaps among practitioners for nail procedures (5) (Hare and Rich, Dermatol Clin 34:269–73, 2016). Especially in the procedural realm, high-level evidence in the form of randomized trials and prospective cohorts is rarely available. Oftentimes, case reports, case series, and expert opinion dictate the standard of care for nail procedures.

Keywords

Nail procedures · Nail disease · Nail plate avulsion · Nail bed biopsy · Matrix biopsy Mohs micrographic surgery · En bloc excisions

Introduction and Perioperative Considerations

Evidence-Based Treatment of Nail Disease

The evidence-based treatment of nail disease remains a challenge. Unlike in the skin, the nails are slow growing and many interventions will not be readily apparent for several months. Many practitioners do not feel comfortable with invasive nail procedures and, relative to the remaining skin, nail biopsies are done by fewer practitioners. Indeed, most residents perform less than ten nail procedures in their training, and 30% of residents do not feel competent in nail diseases at the conclusion of their residency (4) [1]. Experts have noted significant knowledge gaps among practitioners for nail procedures (5) [2]. Especially in the procedural realm,

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high-level evidence in the form of randomized trials and prospective cohorts is rarely available. Oftentimes, case reports, case series, and expert opinion dictate the standard of care for nail procedures.

Patient Evaluation

As with any surgical procedure, preoperative considerations in nail surgery include a detailed history and physical exam; review of systems; a discussion of the risks and benefits of the procedure with the patient (illustrations are often helpful); a sound understanding of the anatomy, physiology, and pathology of the nail unit; and competent surgical skills. Smoking is discouraged. Immunosuppression may increase the risk of postoperative infection but is not normally a contraindication. Imaging studies may occasionally be indicated—for example, to better delineate and localize space-occupying defects or to assess underlying soft tissue or bony abnormalities (5) [3]. Such perioperative considerations apply to all nail procedures including nail bed and matrix surgeries and en bloc excisions. Examination of nail plate pigment under dermoscopy may assist the clinician in decision to biopsy and aid further procedure planning. For instance, nail apparatus melanoma has been associated with irregular spacing, thickness, and coloring of longitudinal nail lines within a brown background on dermoscopy (3b) [4]. Furthermore, end-on dermoscopy of the free edge of the nail plate allows for localization of pigment in the proximal (dorsal nail plate) or distal (ventral nail plate) matrix (5) [5]. Although proximal nail matrix pigmented lesions are less common, proximal matrix disruption is associated with higher rates of postoperative dystrophy; thus, knowledge of the location of a lesion within the matrix assists with preoperative counseling and setting appropriate patient expectations (5) [6].

Cleanliness/Preparation

Acral sites are prone to contamination and a number of antimicrobial preparations have been advocated in nail surgery. A prospective, randomized trial of 127 patients found chlorhexidine scrub and isopropyl alcohol superior to povidone iodine in reducing the rate of post-preparation positive bacterial cultures in foot and ankle surgery (1b) [7]. Use of a sterile glove with fingertip removed, and then rolled back, exposing only the affected finger provides an elegant sterile field and reliable tourniquet and has been promoted virtually unanimously by nail surgeons [3]. Soaking the affected digit in tepid water or in a combination of water and chlorhexidine may soften the nail and facilitate procedures, especially on the toes.

Instruments

Few special instruments are required for nail surgery [3]. In fact, many procedures can be performed with a standard surgical tray. A comprehensive list of instruments appropriate for nail surgery is not within the scope of this publication. As there are no evidence-based criteria for most nail instruments, the reader is referred to additional references for a more thorough discussion of nail instruments (5) [8]. However, it is generally agreed that fine instruments in addition to the nail elevator, dual action nail clippers, and English anvil-action nail splitter are among the most important equipment unique to nail surgery [8]. Fine sutures, such as 5-0 or 6-0 nylon, coated polyglactin 910, or chromic gut sutures, are most appropriate for repair of fine anatomical structures of the nail apparatus.

Effective Anesthesia

When approaching anesthesia of the nail apparatus, the surgeon must consider choice of anesthetic agent, the technique of anesthetizing, as well as various comfort measures. The most commonly used local anesthetics in nail surgery are lidocaine, bupivacaine, and ropivacaine. Due to its availability, low toxicity, and quick onset of action, many nail surgeons use lidocaine. Although it has a slightly slower onset of action, ropivacaine is preferred by

some due to its inherent vasoconstrictive activity and prolonged duration of anesthesia when compared with lidocaine (5)(2b) [3, 9, 10]. A prospective study comparing ropivacaine to lidocaine in 70 patients receiving digital nerve blocks demonstrated that lidocaine had a faster onset of anesthesia (mean time 1.3 min [range 1–2.7 min]) than ropivacaine (mean time 4.5 min [range 3.5–5.5 min]). However, the duration of postoperative anesthesia was significantly higher in ropivacaine digital nerve blocks (mean 21.5 h) than in lidocaine nerve blocks (mean 2.4 h) [10]. These findings were further substantiated in a small prospective, double-blinded, randomized study with 20 volunteers (2b) [11] and in a systematic review of 6 studies with 335 nerve blocks (1a) [12]. It should be noted that most of these studies were conducted in the emergency room or hand surgery arena and apply directly to traditional digital blocks rather than other methods of nail unit anesthesia (see below).

The two most commonly used techniques for anesthetizing the nail apparatus are the wing block—a method of infiltrating anesthesia targeting the distal digit—and the traditional digital block, a nerve block targeting the volar and dorsal digital nerves (5) [13]. A wing block can provide additional hemostasis of the nail apparatus by virtue of its local tumescent effect. These techniques have been recently reviewed [13].

Refrigerant spray, ice application, psychological distractions (conversation, music), tactile vibrational stimuli, and topical anesthetics have been employed to diminish pain associated with local anesthetic injection (4) [13, 14]. In addition, local anesthetic warmed to body temperature, buffered to physiologic or near-physiologic pH, and injected with a 30-gauge needle has been proven to reduce pain associated with injection in a meta-analysis and systematic review (2b)(1a) [15, 16].

Obtaining Hemostasis

Hemostasis during nail surgery is reliably obtained with a tourniquet or tourniquet-like device. The rolled sterile glove technique (described above) or use of a Penrose drain provides reliable and easily reversible exsanguination of the fingertip. Several proprietary tourniquets are also available. Notably, tourniquets not only apply pressure on the vasculature but may concomitantly traumatize the underlying skin, muscle, and neurovascular structures either via excessive pressure, shearing forces, or long periods of tourniquet application (5) [17]. A simulation measuring pressure gradients applied by Toe-niquet™ (Orthotic-Lab Limited, Middlesex, UK), T-ring™ (Precision Medical Devices LLC, San Clemente, USA), and Biogel™ (Mölnlycke Health Care, Gothenburg, Sweden) surgical gloves demonstrated that the lowest mean pressures were produced by larger glove sizes (size 8) (25 mmHg), while the highest pressures were produced by Toe-niquet (1560 mmHg). Small size and large size T-ring pressures were 146 mmHg and 427 mmHg, respectively (2b) [18]. A prospective study completed in 2016 surveying users of T-ring digital tourniquets in emergency hand surgery reported simple application, good quality exsanguination, easy finger positioning, and easy tourniquet removal (4) [19].

Although not necessary in most cases, in the absence of contraindications, epinephrine in dilute concentrations has been repeatedly shown to be safe and effective in achieving digital hemostasis and prolonging the effect of short acting local anesthetic (5)(1b)(3a) [20–22]. Most recently, a retrospective review of 1111 cases reported no complications with the use of 1% lidocaine with epinephrine (1:100,000) in a dose range of 0.5–10 cc (mean dose of 4.33 cc) in digital nerve blocks (3b) [23]. This study added to a previous more broad multicenter prospective study of 3110 consecutive cases of elective epinephrine (1:100,000 or less) use in the fingers and hand which demonstrated no cases of digital tissue loss [21].

Nail Plate Avulsion

The goal of nail avulsion is usually to optimize exposure of the nail bed and distal matrix while minimizing trauma and postoperative

complications and only occasionally is the treatment of choice (4) [24]. Traditional nail plate avulsion involves the complete separation of the nail plate from the nail unit. Many recently described, targeted, and elegant partial nail avulsion techniques have made the traditional nail plate avulsion obsolete when performing most nail procedures (4) [8, 25, 26]. Many nail surgeons advocate partial nail avulsion due to an observed lower risk of postoperative dystrophy, decreased pain, and improved healing (4) [3, 27]. In nail unit trauma, post repair splinting of the nail fold and bed with the native nail plate has been associated with lower rates of nail deformity when compared to artificial splints in a retrospective study (2b) [28]. Overall, total nail avulsion should be avoided and partial nail avulsion is preferred whenever possible.

Nail Bed Biopsy

Nail bed biopsies are nearly as simple as at other skin sites and may provide valuable information to diagnose inflammatory conditions (e.g., psoriasis) and nail tumors, differentiate mycotic from inflammatory disease, or demonstrate the pathogenicity and invasiveness of fungal organisms. Generally speaking, reconstruction after nail bed biopsy is deferred for healing by second intention. The tight and friable epithelium of the nail bed is difficult to mobilize and suture and heals with minimal dystrophy and only occasionally results in onycholysis.

A nail bed biopsy may be performed with or without nail plate avulsion. Alternatively, a longitudinal ellipse biopsy can be performed after a partial plate avulsion.

Matrix Biopsies

Several techniques for nail matrix biopsy have been reported including nail matrix punch biopsy, tangential matrix shave biopsy, and lateral or midline longitudinal excisional biopsy. Throughout this chapter, perioperative considerations including patient evaluation, appropriate anesthesia, and management of hemostasis remain the same regardless of the technique employed.

Nail Matrix Punch Biopsy

Indications

Punch biopsies may be performed to aid in the diagnosis of nail bed or nail matrix pathology.

Effectiveness

Traditional teachings suggest that matrix punch biopsies, 3 mm or less, are unlikely to cause a permanent dystrophy and avoid dystrophic nail plate scarring. In practice, however, only small, full thickness biopsies from the distal matrix are considered low risk in terms of causing permanent nail dystrophy; the proximal matrix, responsible for a majority of the nail plate production as well as the superficial nail plate, is more susceptible to scarring or developing a split nail, even with a 3-mm punch. In the absence of direct matrix visualization with partial or complete nail avulsion and proximal nail fold reflection as needed, punch biopsies are susceptible to a sampling bias with false-negative results as well as incomplete lesion extirpation.

In addition to obtaining tissue histology, the punch tool has also been utilized to remove the nail plate to facilitate drainage of subungual hematomas (4)(5) [29, 30] and diagnose proximal subungual onychomycosis.

Best Techniques and Performance

After appropriate anesthesia has been obtained, the patient is prepped and draped in the standard fashion. A tourniquet may or may not be utilized, depending on the complexity/duration of the procedure. Practitioners may choose to biopsy through the nail plate in a single punch, with a double-punch technique, utilizing a larger punch to remove the nail plate and a second smaller punch to sample the lesion (4)(5) [31, 32], or may perform a partial or complete nail avulsion first to appropriately visualize the lesion. If a standard punch biopsy of 3 mm or

smaller is used, the surgical site does not need to be closed and is allowed to heal by secondary intention.

Tangential Matrix Shave Biopsy

Indications

The tangential matrix shave biopsy is a surgical technique designed for the sampling of clinical entities affecting the nail matrix. It is valuable in establishing a diagnosis in longitudinal melanonychia of any width but in particular lesions greater than 3–4 mm in width, as it serves to minimize nail plate dystrophy (5)(3b) [33, 34]. Longitudinal melanonychia has a differential diagnosis that includes melanocytic activation (from drugs, systemic conditions, ethnic predisposition, and trauma, among other causes), nevi, lentigines, infection, blood, and melanoma. This broad differential combined with the risk of nail dystrophy with traditional biopsy techniques poses a dilemma for many practitioners. A delay in biopsy can be catastrophic (3b) [35]. A cross-sectional cohort study of 148 cases of adult longitudinal melanonychia found 20 to be melanoma (13.5%) upon biopsy [4]. Another retrospective observational study found 25 of 82 adult cases of longitudinal melanonychia to be melanoma (30.5%) upon biopsy (2b) [36]. While certain physical exam characteristics and dermatoscopic findings are more suggestive of malignancy, histopathologic analysis remains essential in the diagnosis of nail apparatus melanoma (5) [37]. In the appropriate clinical context, any new, atypical, or evolving pigmented band in adults should be evaluated and potentially biopsied.

Effectiveness

The goal of the tangential matrix shave biopsy is to obtain a broad and adequate sample of a pigmented lesion of the nail matrix while minimizing unnecessary damage to the nail apparatus. As a diagnostic tool, the procedure has demonstrated its ability to provide adequate tissue depth for establishing a histological diagnosis. A retrospective study of 22 patients with longitudinal melanonychia involving the matrix, biopsied via tangential shave, found a mean specimen depth of over 7 times thicker than the lesion of concern, allowing histological diagnosis in all cases (3b) [38]. In a retrospective study of 23 cases of longitudinal melanonychia sampled via tangential matrix shave, a diagnosis was possible in all cases [34]. Furthermore, follow-up of at least 6 months (median follow-up of 19.7 months) demonstrated that 17 of the 23 patients (74%) had no postoperative nail dystrophy. However, 16 of 23 patients (70%) did have recurrence of pigmentation.

Best Techniques and Performance

A complete discussion of this biopsy technique is beyond the scope of this chapter. Haneke and Baran first described the tangential matrix shave biopsy and it has since been described in depth by others [33, 34, 37]. Following appropriate preoperative evaluation, disinfection, and anesthesia, incisions are made with a #15 blade scalpel at the junction of the proximal and lateral nail fold. With an elevator or hemostat the proximal nail fold is dissected gently from the underlying nail plate and reflected proximally until the origin of the longitudinal pigment is fully identified. At the proximal third to 50% of the nail plate, an English anvil action nail splitter is inserted perpendicularly into the lateral nail fold and advanced beneath the nail plate to cut the nail plate transversely. This freed portion of the proximal nail plate is then reflected laterally with a hemostat exposing the nail matrix and proximal nail bed. Using a new, sharp (Teflon or silicone coated) scalpel blade, the origin of the longitudinal band of pigment is scored at a depth of approximately 1 mm with 1–2-mm margins. The blade is then turned parallel to the scored lesion and a tangential shave of the lesion is delicately performed. The matrix specimen should be less than 1 mm thick in most instances. The specimen should be raised with the blade (without using forceps) and placed carefully on a piece of cardboard or paper (to prevent curling) and covered with filter paper or moist gauze. A map of the nail apparatus and corresponding location of the sample is helpful in orienting the lesion (available for download at: https://www.cta-lab.com/pdfs/CTALab_Nail_Cutouts.pdf). The sample is then immersed in

formalin and sent to pathology. Repair involves trimming the elevated free edge of the laterally reflected nail plate and returning it to the nail bed. The proximal nail fold is returned to its original position and may be sutured. Securing the reconstructed proximal nail apparatus with suture, adhesive wound dressing, and/or a postoperative pressure dressing is also helpful.

Safety

When performed by an experienced nail surgeon, the tangential matrix shave biopsy is an extremely safe, well-tolerated, and effective procedure for sampling and diagnosing pigmented lesions of the nail matrix. As with any procedure involving the matrix, nail dystrophy is of primary concern. The risk of dystrophy is increased if the lesion of interest involves the proximal matrix [6]. Current literature is scarce; however, Haneke and Baran reported no postoperative dystrophy in the 12 cases in the original description of the procedure [3]. A subsequent retrospective study including 23 patients undergoing tangential matrix shave biopsy demonstrated a 26% rate of dystrophy at follow-up, 13% being classified as severe. However, in this study, no postoperative dystrophy was observed with tangential shave of the distal matrix, even when sampling over 50% of the distal matrix [34]. Other experienced nail surgeons report similar findings of minimal long-term dystrophy [27, 37]. A valuable photographic series documenting the healing process in one patient over 12 months has been published and may be a helpful tool to align patient and physician expectations [27].

Postoperative Care and Follow-Up

Follow-up is dictated by the histological diagnosis obtained in each case. In cases of histological atypia or melanoma, complete nail apparatus ablation (see later) can be performed within days following biopsy [3]. For benign lesions, patients are typically seen at 1 month for wound check and 4–6 months to monitor nail growth and recovery. Malignancies are followed up at the intervals recommended for the respective disease (3,6, or 12 months). The rate of nail growth varies by digit, age, nutritional status, patient comorbidities, and systemic medications. Healthy fingernail growth at monthly rates of 2.94–3.47 mm and toenail growth at monthly rates of 1.65–2.09 mm has been reported (2b) [39]. After complete surgical nail avulsion, complete nail regrowth within 4–5 months and 10–18 months for fingernails and toenails, respectively, has been reported (3b) [40]. It should be noted that re-pigmentation of the nail bed has been reported in up to 70% of patients undergoing tangential matrix shave biopsy in one study [34]. This may require patient reassurance.

Alternative Procedures and Modifications

Alternative procedures include matrix punch biopsy for lesions 3 mm or less, lateral longitudinal excision for pigmented lesions of the lateral nail, or en-bloc excision of the entire nail apparatus for cases of melanonychia involving a large portion of the nail. The tangential matrix shave biopsy is superior to these alternatives in cases involving longitudinal melanonychia larger than 3–4 mm due to lower risk of post-procedural nail dystrophy [3, 33, 37]. In the absence of high-level clinical trials comparing various biopsy techniques, a valuable, single-author expert-opinion diagnostic algorithm for nail matrix biopsy of longitudinal melanonychia has been published [37] (Fig. 35.1).

Lateral and Paramedian/Midline Longitudinal Excisional Biopsy

Indications

The longitudinal biopsy encompasses tissue sampling extending anywhere from the most proximal aspect of the nail matrix to the digit pulp. In comparison to the punch biopsy, this full thickness excision specimen maintains fixed anatomic reference points and visualizes the anatomic relationship of all nail structures.

Longitudinal excisions can be performed anywhere along the nail but are frequently considered as lateral or midline/paramedian in location. Lateral longitudinal excisions are preferentially

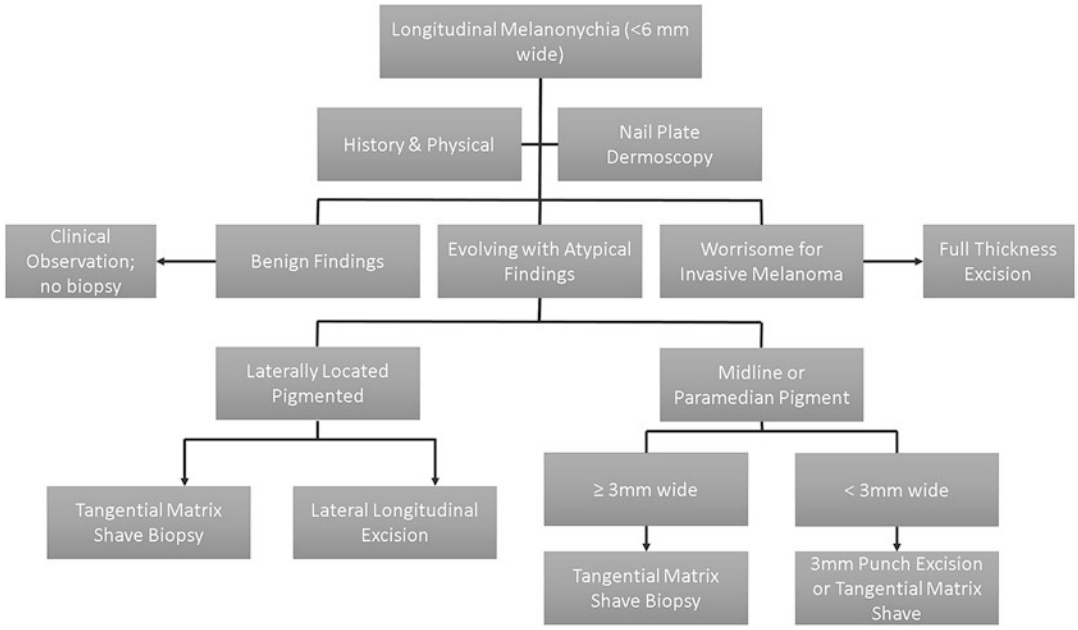

Fig. 35.1 Algorithm for the approach to biopsy of longitudinal melanonychia. (Adapted from Jellinek [37])

used in the setting of generalized nail dystrophy without a diagnosis or a localized abnormality of one digit involving the lateral nail margin. More medial longitudinal nail biopsies that divide the matrix into two parts may lead to permanent deformity of the nail plate or a split nail. Historically, an excision width of <3 mm has been deemed safe anywhere on the nail. However, the authors have observed permanent splitting when midline or paramedian longitudinal defects involving the mid- or proximal matrix are left to granulate. Reconstruction with alignment of the epithelium may prevent this complication.

Effectiveness

High-level comparative studies between various nail biopsy techniques have not been performed. In the setting of inflammatory nail dystrophy, longitudinal biopsy confirmed the clinically suspected diagnosis in 8 of 20 clinically suspicious lichen planus cases and in 4 of 6 psoriasis (3b) [41]. The authors note that the diagnostic yield may be higher *without prior nail avulsion.* They have since altered this practice to avoid disrupting the nail bed epithelium secondary to traumatic plate avulsion. Grover and colleagues reported longitudinal nail biopsies to be diagnostic by providing confirmatory evidence of the underlying nail disease in 11 of 21 patients with 20 nail dystrophies (3b) [42].

Best Techniques and Performance

Following appropriate preoperative evaluation, disinfection, and anesthesia, an elliptical excision is designed incorporating the nail plate, nail bed, nail matrix, and relevant nail folds. The incisions are carried out to the bone. This wedge shape ellipse should be long and narrow, paralleling the longitudinal ridges of the nail. After successful tissue extirpation, the wound may be left to heal via granulation by second intention or closed primarily. At times, lateral relaxing incisions or undermining may be useful to achieve closure. Detailed teachings have been published (5)(4) [43, 44].

Safety

A lateral longitudinal excision predictably heals with a more narrowed nail. The excision defect is either allowed to heal by second intention with granulation or reapproximated with sutures. Full thickness midline excisions have the potential for

nail dystrophy including a permanently split nail. Collins et al. suggest matrix reconstruction with nail matrix advancement flaps to mitigate this risk (4) [45]. The advanced proceduralist may wish to explore additional reviews on nail flap reconstruction (4) [46].

Therapeutic Interventions

Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) has several applications in nail surgery. The primary advantage of MMS is the tissue (and thus often digit)-sparing nature and achievement of histologically clear margins. Keratinocytic tumors and melanocytic neoplasms have been successfully treated with MMS. In general, the conceptual technique remains unchanged when operating on or near the nail. A complete discussion of Mohs surgery is beyond the scope of this chapter. However, there are nuances that should be kept in mind for successful work around the nail unit.

Historically, a complete nail avulsion was performed prior to MMS. Although improving visualization, this approach is hampered by nail bed epithelium occasionally missing from the frozen section slides given the adherence to the overlying nail plate. Experts suggest that avulsion prior to surgery is not necessary and indeed, the plate can be maintained in an anatomic position and easily cut (after presoaking with a mixture of warm water and chlorhexidine), yielding high-quality histologic specimens with preserved epithelium over the entire cut surgical margin [26]. This technique is not used by all (5) [47].

The treatment of nail apparatus squamous cell carcinoma (SCC) with MMS is well established. Several retrospective case series demonstrate its utility in achieving clear margins and long-term surgical cure. Dika et al. described the successful use of MMS in 57 SCC cases with a 3.5% 10-year recurrence rate (2b) [48]. Earlier, Jellinek et al. reported the use of MMS in 35 SCC with an 8.5% recurrence rate (2b) [49]. Recurring tumors had a history of prior recurrence or aggressive nodular tumor growth at presentation. The use of a bone rongeur or dual action nail nipper has been proposed by some to further achieve clearance of the deep MMS margin [49]. Periungual basal cell carcinoma is rare and its treatment with MMS has only been documented in case reports (4) [50–52].

The use of MMS for the treatment of in situ and invasive cutaneous melanoma is increasingly well-established but infrequently reported specifically for nail apparatus melanoma. The difficulty in visualizing nail matrix melanocytes on routine frozen hematoxylin and eosin sections is enhanced through the use of Melanoma antigen recognized by T cells (MART-1) immunostains (2b)(4) [53, 54]. Several authors have successfully used MMS for the treatment of nail apparatus melanoma in situ but this technique has only been documented in case series, albeit with slowly increasing case numbers (3b)(4)(2b) [55–57]. On the basis of the published data MMS does not appear to have cosmetic, oncologic, or cost benefits over en bloc excision (see later) with traditional serial sectioning.

En Bloc Excision of All Nail Tissues

Indications

En bloc excisions refer to the complete removal of the entire nail apparatus including matrix, nail bed, nail plate, proximal nail fold, lateral nail folds, and hyponychium, oftentimes to the level of the tendon and periosteum. This technique is primarily indicated for the management of nail apparatus melanoma in situ and superficially invasive melanoma and squamous cell carcinoma. The technique has been described in detail (5) [58] and utilized in several nail apparatus melanoma studies.

Effectiveness

Several retrospective case series have reported on the treatment of nail apparatus melanoma in situ and early invasive melanoma with en bloc excision. In this setting the treatment efficacy is compared to digital amputation at various anatomic levels (which was historically the treatment of choice).

Randomized studies comparing the treatment of nail apparatus melanoma and/or nail apparatus melanoma in situ with en bloc excision versus amputation are lacking. Moehrle et al. compared results of 31 patients with invasive nail apparatus melanoma treated with en bloc excision plus removal of the ungual process (termed "functional surgery") and 31 patients treated with amputation at or proximal to the distal interphalangeal joint (2b) [59]. This comparative study was limited by its retrospective design and lack of randomization; however, no difference in recurrence-free survival and overall survival between the two techniques was identified. Others have shown that recurrence rates for invasive nail apparatus melanoma do not improve with more proximal or more radical amputations (2b) [60–62]. Neczyporenko et al. treated 11 patients with biopsy-proven melanoma in situ by en bloc excision (3b) [63]. The authors highlight the late presentation of the two known local recurrences (7 and 11 years) and the importance of long-term patient follow-up. Nukamura, et al. published data on 48 patients with nail apparatus melanoma in situ treated with wide local excision, with only two instances of incomplete excision, four recurrences, and no upstaging or development of subsequent metastasis (2b) [64]. Similar results have been published by others: Duarte et al. recently presented six cases of nail apparatus melanoma in situ treated with en bloc excision with no recurrences noted at a mean of 25 months (3b) [65]. Sureda et al. performed en bloc excisions in seven nail apparatus melanomas in situ and superficially invasive nail apparatus melanoma (3b) [66]. No recurrences were noted after a mean of 45 months. The data in favor of en bloc excision for nail apparatus melanoma in situ and early invasive disease are increasing. Nevertheless, significant technical variability remains among proceduralists performing this surgery, and technical details and margin width and status are inconsistently reported in the literature.

Preoperative Evaluation

Specific testing beyond a routine history and physical exam is not indicated for en bloc excisions. A musculoskeletal examination of the digit prior to surgery may reveal any preexisting changes to the joints proximal to the surgical site or (in the setting of invasive melanoma or other subungual tumors) may reveal invasion into the bone or extensor tendon. Should imaging be necessary, x-ray allows for evaluation of bony structures, and magnetic resonance imaging (MRI) appropriately studies the soft tissue of the nail apparatus and digital pulp to identify any mass lesion. Criteria for sentinel lymph node biopsy and adjuvant therapy remain the same as on the skin. Perioperative considerations established for other surgical sites should otherwise be followed. Review of medications, anticoagulation, infection risk is key for successful and complication-free surgery.

Best Techniques and Performance

Following appropriate preoperative evaluation, disinfection, and anesthesia, the excision is designed proximally by a transverse line overlying the distal interphalangeal joint (DIPJ) crease and continued to the midlateral line bilaterally, with a right angle turn at the midlateral line onto the lateral nail fold. The two lines are extended and joined, 3–4 mm distal to the hyponychium onto the distal digital tip skin. Appropriate tumor margins established for malignancies in other skin sites of 5–9 mm are incorporated into this design. The nail apparatus extirpation is performed directly over the distal phalanx, with care to avoid transecting the tissue when dissecting distally over the ungual process (due to the adherent periosteum) and proximally at the cul-de-sac (due to the anatomic constraints of nail anatomy). This process is continued distal to proximal over the waist (often but not always including periosteum on this narrow bony section), with the deep proximal extent of dissection ending at the insertion of the extensor tendon, taking care to maintain the integrity of the tendon. Detailed teachings have been published [58].

Safety

En bloc excisions require a thorough understanding of digital and nail anatomy. As such, they should be performed by proceduralists well versed in nail procedures to avoid complications.

Complications after en bloc excision are similar to those at other sites including bleeding, infection, and damage to deeper structures. Exposed tendon and bone pose an increased risk for deeper infections including osteomyelitis, and patients should be treated with appropriate antibiotic prophylaxis although this has not been further studied to our knowledge. Few publications have addressed surgical complications after nail surgery and more specifically en bloc excision. Unique complications after en bloc excision include nail spicule formation and cyst formation. Spicule formation represents incomplete excision of the nail matrix. In the setting of a malignancy, this requires re-excision. Lazar et al. retrospectively studied epidermal cyst formation in 5 of 13 patients. Cysts may represent traumatic implantation of epidermis at the time of suturing or with needle trauma, rather than remnant matrix epithelium. Some have reported cysts to be the most common complication following nail unit excision (3b) [67], although this is not the authors' experience. Surgery overlying the tendon predisposes to tendon injury. To our knowledge, this injury, termed mallet finger deformity, has only been presented in one conference abstract and is a rare complication requiring splinting and immobilization as the first-line approach for treatment.

Postoperative Care and Follow-Up

Patients are routinely seen at 1- and 3-week follow-up periods. After successful healing by second intention or skin grafting, patients are seen at intervals appropriate for the underlying malignancy (i.e., 3-, 6-, or 12-month intervals).

Alternative Procedures and Modifications

When en bloc excisions are not desired or possible, amputation is the treatment of choice [66, 67]. In cases of advanced malignancy, amputation may be the only feasible treatment. According to the American Medical Association Guide to the Evaluation of Permanent Impairment, proximal (metacarpophalangeal joint) or distal (interphalangeal joint) amputation of the thumb corresponds to 50% or 100% impairment of the digit. On the other fingers, amputation at the DIPJ, proximal interphalangeal joint, and metacarpophalangeal joint corresponds to 45%, 80%, and 100% impairment, respectively (2b) [68]. After the surgical recovery period, en bloc excisions would appear to have less morbidity when compared to amputation but this has not been published in the literature. Mohs micrographic surgery is a treatment alternative that primarily differs in the method of margin assessment (complete margin assessment with frozen tissue rather than serial longitudinal sections through the en bloc specimen). The nail unit is ultimately still removed with margins in its entirety.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: Quality of Evidence
Diagnostic and therapeutic nail procedures rely largely on expert opinion and retrospective case series	D
Dermoscopy may aid in the visualization and localization of pigment and surgical planning	C
Local anesthesia with lidocaine or ropivacaine	A
With or without epinephrine can be safely administered during nail procedures	A
Complete nail avulsion is not necessary for most nail procedures	C
Available evidence supports the tangential matrix shave biopsy as an elegant, safe, and effective method for sampling lesions of the nail, especially for longitudinal melanonychia. This technique avoids total nail avulsion, provides adequate tissue for histological diagnosis, and limits post-procedural nail dystrophy	B
Biopsy techniques must be tailored to the anatomic location harboring the pathology and may include nail punch biopsy, matrix shave biopsy, and longitudinal excisions	B
More definitive treatments for malignancies include Mohs micrographic surgery, en bloc nail unit excisions, and amputation	B

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Self-Assessment Questions

1. What biopsy technique is most appropriate for sampling a 4-mm pigmented lesion of the central nail matrix?
   (a) Nail avulsion followed by 4-mm punch biopsy of the matrix
   (b) Lateral longitudinal excision
   (c) Tangential matrix shave biopsy
   (d) En bloc excision
   (e) 4-mm punch biopsy through nail plate and nail matrix
2. According to current evidence, patients are at most risk of which of the following after tangential matrix shave biopsy of a pigmented lesion of the distal matrix?
   (a) Dystrophy of the nail plate
   (b) Re-pigmentation of the nail bed
   (c) Digital ischemia and necrosis due to use of epinephrine
   (d) Osteomyelitis
   (e) Pterygium
3. Which of the following has been shown to most reduce positive bacteria cultures following antimicrobial preparation of the surgical site?
   (a) Povidone iodine scrub and paint
   (b) Chlorhexidine scrub and isopropyl alcohol paint
   (c) Chlorhexidine scrub
   (d) Isopropyl alcohol paint
   (e) Hexachlorophene
4. Which of the following techniques is not an appropriate diagnostic tool for the diagnosis of longitudinal melanonychia and presumed nail apparatus melanoma in situ?
   (a) Nail matrix punch biopsy
   (b) Nail bed punch biopsy
   (c) Longitudinal excision
   (d) Tangential matrix shave biopsy
   (e) En bloc excision of the nail apparatus
5. Full thickness biopsy in which anatomic area of the nail unit is most likely to cause permanent nail dystrophy?
   (a) Proximal nail matrix
   (b) Distal nail matrix
   (c) Proximal nail fold
   (d) Nail bed
   (e) Hyponychium

Correct Answers

1. d: The correct answer is tangential matrix shave biopsy. Especially for broad pigmented lesions, this is the procedure of choice. Larger-diameter punch biopsies create full thickness defects that have a higher risk of nail dystrophy, especially with more proximal biopsy sites. En bloc excisions are occasionally used for very broad pigmented lesions but are otherwise reserved as a therapeutic treatment following initial diagnosis by biopsy.
2. b: The correct answer is re-pigmentation of the nail bed. The cause for this is unclear but may be due to melanocytes adherent to the nail plate which is routinely partially avulsed, reflected, and then returned to its native anatomic position. Patient education and reassurance is valuable. In the absence of contraindications, with appropriate concentrations of epinephrine, and reasonable volumes of local anesthesia, digital ischemia and necrosis due to epinephrine is not seen. Pterygium refers to scarring of the nail matrix to the overlying proximal nail fold, oftentimes in the setting of scarring inflammatory nail conditions (e.g., lichen planus) or as an iatrogenic complication with biopsies involving the matrix, proximal nail fold, and complete nail plate avulsion. Osteomyelitis remains as a theoretical concern with any digital surgery via deeper extension from a primary superficial wound infection. This complication is exceedingly rare.
3. b: According to the current level of evidence, chlorhexidine scrub and isopropyl alcohol are the most effective preparations to reduce positive bacteria cultures following application.
4. b: The correct answer is nail bed punch biopsy. Longitudinal melanonychia originates in the nail matrix and thus, a biopsy of only the nail bed is unlikely to provide valuable diagnostic information.
5. a: The correct answer is the proximal nail matrix. The proximal nail matrix is responsible for producing the majority of the nail plate, including the more visible dorsal nail plate. Despite this, melanocytic lesions of the proximal nail matrix are much less common than melanocytic lesions of the distal matrix. Scarring in the proximal nail plate may produce nail dystrophy and ridging whereas any injury to the distal nail matrix more frequently results in thinning along the ventral (underside) of the nail plate.

Superficial/Soft Radiation Therapy for Nonmelanoma Skin Cancer

36

Christopher M. Wolfe and Armand B. Cognetta

Abstract

Similar to surgical modalities such as excision or Mohs micrographic surgery, the bulk of research forming the foundation for radiation therapy has come from retrospective analyses over the past 100 years of patients chosen for radiation therapy. Superficial radiation therapy is a viable and effective treatment option for patients over the age of 60 who are not ideal candidates for surgery. Superficial radiation therapy is curative for 90–95% of primarily treated nonaggressive basal cell and squamous cell carcinomas of the skin.

Keywords

Superficial radiation treatment · Superficial radiotherapy · Dermatologic radiotherapy Nonmelanoma skin cancer · Basal cell carcinoma · Squamous cell carcinoma

Preamble to *Evidence-Based Procedural Dermatology*: Superficial Radiation Therapy

The inclusion of superficial radiation therapy (SRT) in a textbook on *Evidence-Based Procedural Dermatology* appropriately underscores that radiation therapy is a physical procedure just as laser and ultraviolet therapy are and that clinical experience, best evidence, and patient preference all play a role in the selection of the most appropriate procedure for each individual and unique patient.

Evidence-based practice involves three essential components: evidence, clinical expertise, and patient values, preferences, and characteristics [1]. It has been described as a three-legged stool, wherein a bottom-up approach supports evidence-based practice to optimize patient care. As clinicians we are in the practice of giving and obtaining informed consent for surgical procedures, a process which has its basis in legal doctrine going back to 1914 where Justice Cardozo ruled "every human being of adult years and sound mind has a right to determine what shall be done with his own body" and "the surgeon who performs an operation without (his) patients consent commits an assault." This has been refined by case law and summarized more recently by the American Medical Association (AMA) defining informed consent as a "dialogue between patient and physician in which both parties exchange information and questions culminating in the patient's agreement to a specific medical or surgical intervention." Recently, some have gone as far as to state that "as practiced, informed consent has become a ritualistic signature on a form that does not reflect bidirectional communication between provider and patient about relative risks, benefits and limitations." [2] There is a move

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afoot to supplant informed consent as we know it with a modern model termed shared decision-making (SDM) which can be viewed as informed preference versus informed consent.

Briefly let us explore what SDM means and how it can be used as an adjunct to informed consent and help fulfill the patient value and preference portion of evidence-based practice. Mulley [3] states that "no decision should be made in a state of a avoidable ignorance on the part of the patient about what is possible based on evidence, or on the part of the clinician what would be valued most" (by the patient).

He goes on to say that "the personal harm caused by a clinician's failure to accurately diagnose a patient preference can be just as severe as that caused by failure to accurately diagnose the disease itself." In 2012 Mulley [4] goes so far as to state that "preference misdiagnosis is medical error." What may not be obvious, in the case of a patient referred by another colleague for Mohs surgery, is that even though the referring physician has discussed treatment options with the patient, in order to qualify as evidence-based medicine, the patient must be thoroughly educated and versed on other treatment options in addition to Mohs surgery.

A good starting point is to discuss the fact that patients all have a choice. Once they understand this, the discussion can proceed to include all reasonable options with them and their caregivers to include surgical, nonsurgical, or no treatment, along with the pros and cons of each of these avenues. While many patients may not at first appear to want a choice, universally all feel empowered by having been given adequate attempts to look at various choices and what they entail. Once we have given them choice and knowledge of options, a "decision talk" with the patient will solidify their choice. All of the above describes the shared decision-making model of Elwyn and colleagues [5], where three talks are described and detailed.

1. Choice talk: the step of making sure that patients know that reasonable options are available.
2. Option talk: providing more detailed information about options.
3. Decision talk: supporting the work of considering preferences and deciding what is best.

In the literature, it is intimated that these talks should be on separate days with multiple inputs and second opinions. From a practical standpoint, this expanded informed consent or what has been termed informed preference can be done on the day of surgery. When discussing the pros and cons of various surgical and nonsurgical treatments, it is important that the physician be nondirective. Patients have a natural tendency to want to please the provider and "be a good patient," and some may feel awkward asking questions. Allowing family members to discuss options in the absence of the physician will allow expression of questions that could be suppressed otherwise.

Tools are available to aid in all of the above steps. One such tool is the "making GRADE the irresistible choice" (MAGIC) project which makes use of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines to improve SDM. It urges patients to "ASK THREE QUESTIONS": (1) What are my options? (2) What are the possible benefits and harms of those options? (3) How likely are each of these benefits and harms to happen to me? This "Ask, Share, Know" (ASK) puts the onus on the patient to start the dialogue and allows the physician to continue it. Both the option talk and decision talk can be aided by patient decision aids (PDAs). We have these in our offices and specialties, and state societies have gone on to certify these after review. The option talk and the choice talk can start with the scheduling nurse's first phone call and include mailing informational packets containing patient decision aids to the patient. On arrival, all members of the healthcare team can be utilized to assure that the patient understands their option to choose Mohs surgery or another procedure.

Factors influencing a patient's choice are what we must strive to understand. As Mohs surgeons, we often see treatment failures from previous procedures elsewhere and are very keen to avoid this on our watch. We tend to feel most comfortable, especially in the framework of appropriate

use criteria (AUC) as a justification, to recommend Mohs. In doing so, we may be imposing our values on the patient and not following the spirit of the AUC process. When determining fitness for surgery, we evaluate the patient's overall health, comorbid medical conditions, coagulation status, and age when deciding whether Mohs surgery is appropriate. We must also give adequate weight to patient values and preference when prescribing Mohs versus non-Mohs modalities even if the cure rate is not equal to Mohs surgery.

Clinical experience is another leg of the three-legged EBM stool that plays into our recommendation, but lack of experience with other modalities should not limit what we recommend. Ignorance of a procedure or treatment, or local unavailability of that option, does not absolve our duty to explore its usage during the option talk. In the case of SRT, a whole generation of dermatologists have been educated in an era when dermatology has been transformed from a medical specialty to a highly surgical specialty. During this time, dermatologists, standing on the shoulders of pioneers such as Leon Goldman and Ellet Drake, have developed a vast array of powerful yet specific laser systems and light-based therapeutic systems that target specific disorders selectively. Likewise, dermatologists have developed a very sophisticated and comprehensive set of procedures to deal with skin cancer based on the early adaptation of Mohs surgery from a fixed to a frozen tissue technique gaining universal acceptance through the leadership of Perry Robbins, Theodore Tromovitch, Sam Stegman, and others. Data for SRT goes back to the early 1900s with heavy continued use of this modality by dermatologists through the age of Phillip Mackee, the head of New York Skin and Cancer in the 1970s. Despite a temporary decline in the usage of superficial radiation therapy, our specialty developed, refined, and produced a vast amount of data that over the first half of the last century was transformed from empirical to practical and reproducible formulations to determine first the nominal skin dose, a reproducible number that could compare multiple fractionation schemas to the time-dose-fractionation (TDF) factors which allowed one to flexibly tailor dosage and fractionation schedules and compare and match their biological equivalency. No group played a greater role or had more clinical expertise in radiation than dermatologists and their treatment of innumerable skin cancers over the last century. As we will show in this chapter, multiple studies document its effectiveness and widespread usage by our predecessors.

The last leg of the three-legged EBM stool is "best available evidence." An assumption exists that best evidence means the exclusive use of randomized clinical trials. Since the aforementioned clinical experience has taught us that radiation should be used selectively, the use of a clinical trial which randomizes patients with severe medical comorbidities to surgery or young patients to radiation therapy and its long-term sequelae would be unethical. EBM specifically asks for the "best available" not "only the best" evidence, and there is a multitude of suitable studies to draw conclusions from.

Introduction

Superficial/soft radiotherapy (SRT) has over 106 years of research and development by dermatologists. Just 8 years after the discovery of X-rays by Wilhelm Conrad Roentgen on November 8, 1895, the first reported results using radiotherapy came from dermatologists in what was the precursor to the annual AAD meeting, "Rationale of and the Indications for Therapeutic Use of Rontgen Rays," 27th Annual Meeting of the American Dermatology Association, Washington, May 13 and 14, 1903. Today the procedure and technology have evolved with the manufacture and development of new SRT platforms that contain multiple built-in safety features and daily automatic calibration. Proper patient and tumor selection, tumor location, patient set-up, shielding, and histologic review of the tumor are critical for obtaining excellent outcomes and cannot be overemphasized.

Procedure Performance

The focus of this text is on the evidence involving the use of SRT for nonmelanoma skin cancer (NMSC); it is not intended to be a detailed tutorial on treatment delivery; nonetheless, two important concepts warrant further discussion. The half-dose depth (D1/2) concept and the time-dose-fractionation (TDF) factor have been used in dermatologic radiotherapy for selecting appropriate radiation qualities. For a detailed tutorial, we refer the reader to the book *Radiation Therapy for Skin Cancer*, chapter entitled "Superficial Radiation Therapy Treatment Planning" by Springer [6].

Half-Value Depth (D ½) Concept

The half-value depth (D ½) concept has served as an invaluable guideline in dermatologic radiotherapy and has been used for over 50 years in the treatment of skin cancer [7–10]. In lieu of confusing arithmetic computations based on depth dose charts with varying combinations of radiation factors, the dermatologic radiotherapist takes advantage of pre-set calibrations based on the D ½ (Fig. 36.1). The D ½ is the tissue depth in millimeters at which the dose is 50% of the surface dose. In treating NMSC, the goal is to deliver at least 50% of the surface dose to the tumors' deepest portion.

Time-Dose-Fractionation (TDF) Factor

In 1973, Orton and Ellis [11] developed the time-dose-fractionation (TDF) factor, building upon prior work of the nominal standard dose (NSD) concept. The TDF factor takes into account the time, dose, fractions, and the interval between fractions [7, 11–17].

$$\begin{aligned} TDF &= 10^{-3} \times NSD^{1.538} \\ &= Nd^{1.538} \left(T/N\right)^{-0.17} \times 10^{-3} \end{aligned}$$

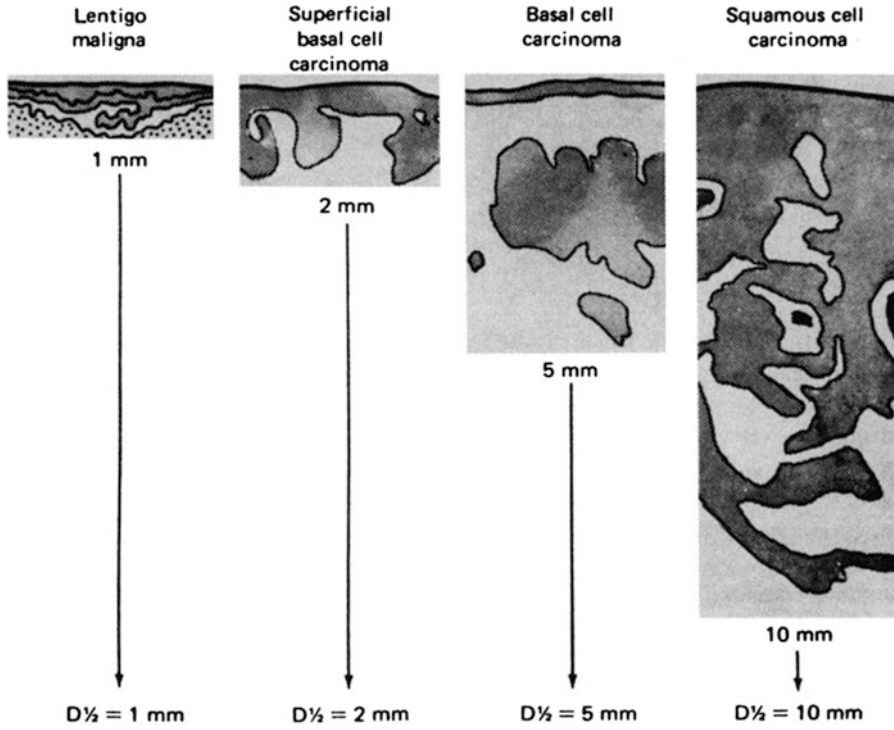

Fig. 36.1 Selection of D ½ for skin cancer treatment. (With permission from [87])

(NSD = nominal standard dose, N = number of fractions, d = dose per fraction, T = overall treatment time in days)

The culmination of their work are TDF factor tables which have been pre-calculated based upon the number of fractions/doses given per week. Treatment schedules comprise 1,2,3,4, and 5 fractions per week with the TDF factors based on dose (cGy) and total number of fractions. By using the TDF factor tables in treatment planning, it is possible to predict treatment outcome for cure, skin necrosis, and other effects. The optimal TDF factor for cure of epithelial skin cancer lies between 90 and 110 (Fig. 36.2) [8, 11–13, 15–17]. TDF factors less than 90 may result in underdosing, and greater than 110 increases the risk of complications such as skin necrosis.

Utilization of the TDF tables:

Step 1: The number of fractions delivered each week is selected (1, 2, 3, 4, or 5); we have selected the 3 fraction per week TDF table in this example.

Step 2: Select the total number of fractions for the overall treatment course.

Step 3: Locate the TDF factor between 90 and 100.

Step 4: Determine the dose in centigrays (cGy) of radiation to give with each fraction that correlates with the chosen TDF factor.

Note: New SRT platforms automatically calculate the TDF factor based on parameters entered into the software for the patient.

The number of fractions can be increased (lower dose per fraction) to decrease the late sequelae such as hypotrophic scarring, telangiectasias, and necrosis. Alternatively, the number of fractions can be decreased to deliver more radiation per dose if the patient is less concerned with cosmesis and wishes to have less treatments and travel.

In contrast to the TDF factor tables, radiation oncologists began using the linear-quadratic (LQ) model and biological effective dose (BED) as it was an easy way to convert dose-time frac-

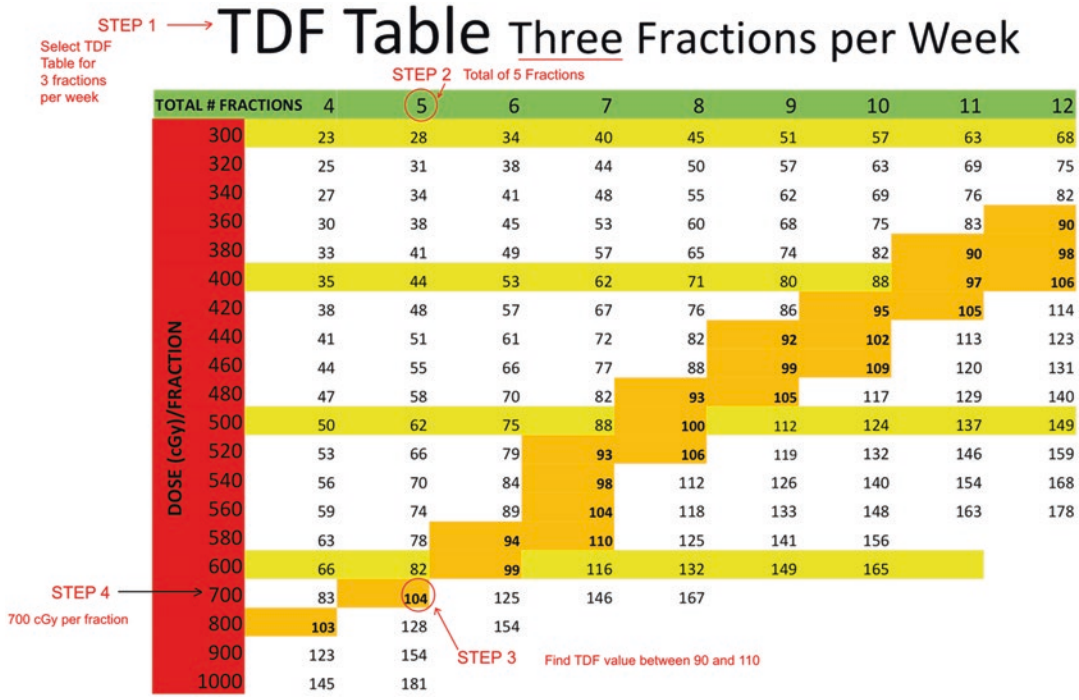

Fig. 36.2 TDF table utilization example. (Source: Modified from [11])

tionation schedules into a biologically effective dose, allowing for comparison between different radiation treatment schedules. This LQ/BED model depends upon α/β ratios obtained from experiments involving irradiated tissues in animal models.

An increase in dose per fraction relative to 2 Gy is termed hypofractionation and a decrease is hyperfractionation [18]. Most radiation oncology treatment schedules use hyperfractionated schedules of 2 Gy per fraction for 30 or more total fractions. Bentzen and Joiner [19] report that the LQ/BED model is only supported by data in the 1.0–5 Gy dose per fraction range, which is less than many dermatologic NMSC treatment schedules, making BED less reliable for comparison. They go on to note that even when dose ranges of 1–5 Gy are used, there is a lack of appropriate parameter estimates, or the available estimates have wide 95% confidence limits and that parameter estimates for clinical endpoints remain scarce [18, 19].

We feel that the NSD concept and TDF factors are most appropriate for comparing efficacy of different treatment regimens for NMSC in the dermatologic setting. As long as treatment schedules fall into the data range for which the TDF factor tables were originally calculated, they will be accurate in comparing treatment schedules. The TDF factors were derived from the following data ranges: dose per fraction 200–1000 cGy (2–10Gy), total number of fractions 4–40, and number of treatments per week 1–5. Treatment schedules for NMSC reported in the literature fall within these parameters [7, 20, 21].

Once SRT has been decided upon, appropriate lead shielding is placed to include eye shields, a thyroid shield, and the lead cutout for treatment of the tumor (Fig. 36.3). The lead cutout for the NMSC includes visible tumor plus a margin of at least 5 mm of surrounding normal tissue (Fig 36.4a,b). The patient is immobilized and the dose of radiation is delivered which takes approximately 60–120 s. In certain instances, intraoral and intraocular shielding is necessary depending on the treatment area (Fig. 36.5a, b).

Indications

The most critical aspect of SRT use is appropriate patient/tumor selection.

Though no formal appropriate use criteria (AUC) exist for SRT, the following indications and contraindications are generally accepted by experienced dermatology radiotherapists in the past and present for the treatment of basal cell carcinoma (BCC)/squamous cell carcinoma (SCC):

1. Location: central face, including the eyelids, nasal tip, nasal ala, ears, and lips [22–54].
2. Age ≥ 60 years: to minimize the synergistic effects of ultraviolet radiation [55–60].

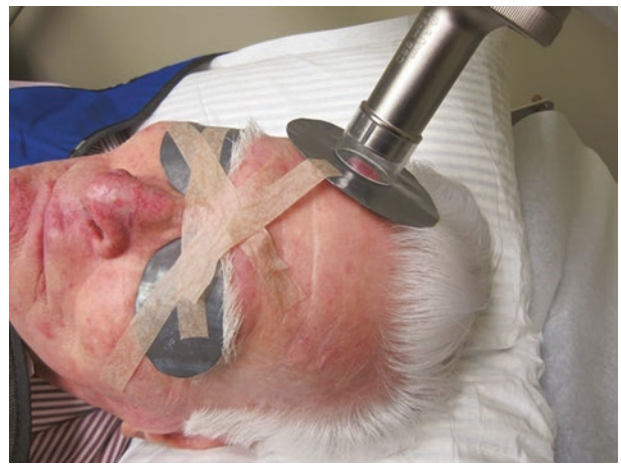

Fig. 36.3 Lead shielding and patient set-up

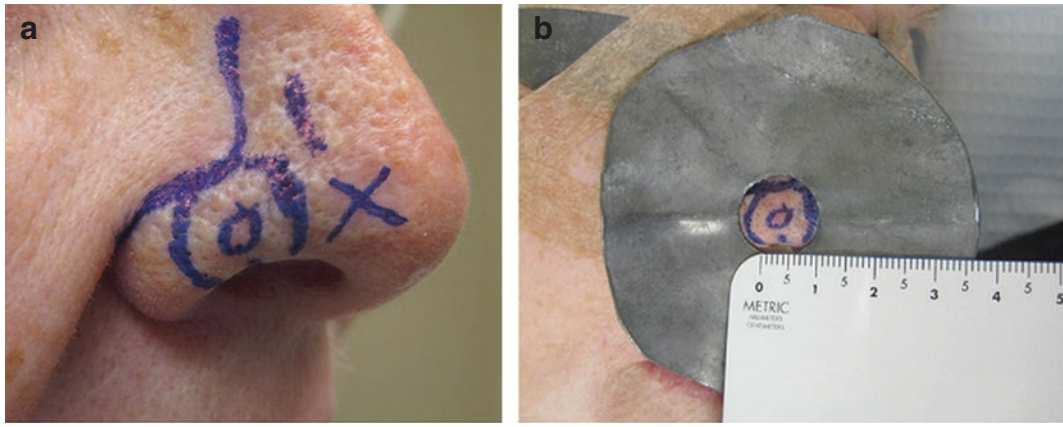

Fig. 36.4 (**a**, **b**) Lead cut out with 5-mm margin around NMSC

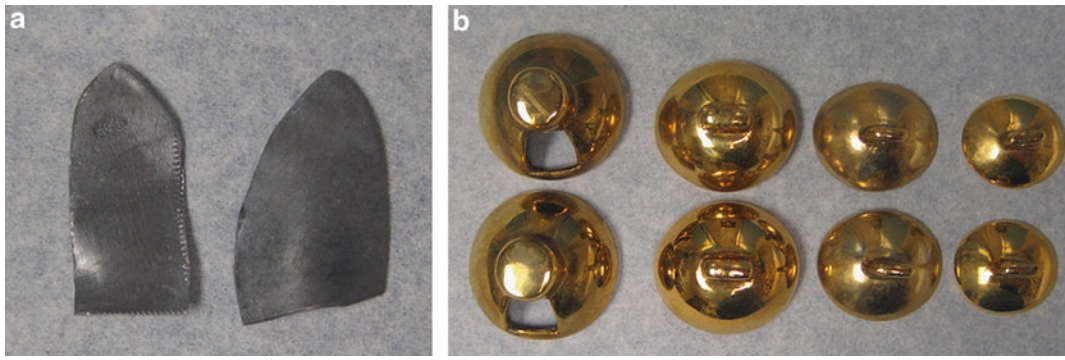

Fig. 36.5 (**a**, **b**) Intraoral and intraocular shielding

3. Tumor size. Medium-sized tumors up to 5 cm in diameter may be adequately treated with SRT [30, 61–65].
4. Tumor type/depth of invasion. Superficial and nodular BCCs, SCC in situ (SCCIS), and SCC that are nonaggressive are amenable to SRT [26, 62, 63, 66].
5. Frailty and medical status. Inability to tolerate surgery due to poor health, multiple comorbidities, or those on anticoagulant therapy may have a higher risk of adverse events. Eastern Cooperative Oncology Group (ECOG) performance status [67] (Table 36.1) may be used to document selection of radiotherapy over surgery.
6. Patient preference to avoid surgery may be a consideration and in cases where surgery will lead to skin graft or complex flap closure.

Table 36.1 ECOG performance status

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

From Oken et al. [67]

Absolute (1–4) and relative (5, 6) contraindications for SRT:

1. Aggressive tumor histology: BCCs (sclerosing, morpheaform, infiltrative), SCC (perineural invasion, arising in previous sites of RT, burn scars, chronic ulcers, spindle cell carcinoma, poorly/ undifferentiated, or those secondary to osteomyelitis) [26, 62, 63, 66, 68–71].
2. Deep tumor invasion. Tumors that invade bone, cartilage, or arise within the mucosal surfaces (intranasal/intraoral) [72, 73].
3. Previously irradiated site. Increases incidence of late-term sequelae (ulcer, radionecrosis of cartilage and bone), results in unsatisfactory cosmesis, recurrence, and second primary tumors [68, 69, 74, 75].
4. Genetic anomalies. Nevoid basal cell carcinoma syndrome (NBCCS), xeroderma pigmentosum (XP), Garner's syndrome, Li-Fraumeni syndrome, and others with increased radiosensitivity or where radiation may induce new malignancies [76–83].
5. Organ transplant recipients (OTR). The mainstay of treatment is surgical excision or Mohs surgery.
6. Location trunk/extremities. Early pioneers of SRT recommended against the use of radiotherapy on the trunk and extremities due to late-sequelae changes (telangiectasias and pigmentary changes), lower oxygen saturation leading to potential decreased efficacy and wound healing issues, and the general ease and expediency of surgical removal. Recent studies also demonstrate the increased risk of non-healing ulcers of the lower extremities using RT[64, 84–90].

Additional considerations:

1. History of methicillin-resistant *Staphylococcus aureus* (MRSA) or other invasive infections.
2. Implantable pacemaker, defibrillator, intravascular device, artificial joint prosthesis that may serve as a nidus for bacterial or fungal colonization.
3. Current anticoagulant or antiplatelet use that cannot be discontinued prior to surgery.

Superficial/Soft Radiation Therapy for Basal Cell Carcinoma and Squamous Cell Carcinoma

Consensus Documents

National Cancer Comprehensive Network Guidelines (2a)

The National Cancer Comprehensive Network (NCCN) state their recommendations are category 2A unless otherwise noted, defined as "uniform NCCN consensus, based on lower-level evidence including clinical experience." NCCN guidelines recommend radiation therapy for non-surgical candidates in the form of megavoltage electron beam radiation therapy (RT), performed by radiation oncologists, a much more costly form of radiation therapy than SRT that requires the use of a linear accelerator in the treatment of BCC [68, 69]. Wolfe and Cognetta [91] performed a cost comparison of the various radiotherapy (RT) modalities used for skin cancer and found SRT in the outpatient setting performed by dermatologists to be the least expensive form of RT, $512 for SRT versus $7100 for electron beam RT. Recommendations for RT of SCC are the same as for BCC, with the recommendation to consider the addition of systemic therapy in conjunction with RT for local SCC with high-risk features (Table 36.2. Risk factors for local recurrence or metastasis SCC).

These guidelines fail to mention of SRT as a modality to treat NMSC. Of the 28 panel members that developed the NMSC NCCN guidelines, 16 are dermatologists (10 Mohs surgeons), 5 are medical oncologists, 5 are surgical oncologists, 1 is a pathology-trained dermatopathologist, and 1 is a radiation oncologist. To prevent perpetuating underlying bias introduced by members of original guideline panels, it has been suggested that periodic review by experts not involved with development of the initial guidelines be conducted [92]. Inclusion of dermatologists who utilize SRT as a treatment option may help prevent the exclusion of SRT as a treatment modality from future NCCN guidelines.

Table 36.2 NCCN risk factors for local recurrence or metastases SCC [69]

H & P	Low risk	High risk
Location/size	Area L <20 mm Area M <10 mm	Area L ≥20 mm Area M ≥10 mm Area H
Borders	Well defined	Poorly defined
Primary vs recurrent	–	+
Immunosuppression	–	+
Site of prior RT or chronic inflammatory process	–	+
Rapidly growing tumor	–	+
Neurologic symptoms	–	+
Pathology		
Degree of differentiation	Well or moderate	Poor
Adenoid (acantholytic), adenosquamous (mucin producing), desmoplastic, or metaplastic (carcinosarcomatous)	–	+
Depth: Thickness or Clark level	<2 mm or I,II,III	≥2 mm or IV, V
Perineural, lymphatic, or vascular involvement	–	+

Area H: "Mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, feet
Area M: Cheeks, forehead, scalp, neck, and pre-tibia
Area L: Trunk and extremities (excluding pretibial, hands, feet, nail units, and ankles

British Association of Dermatologists Guidelines

Basal Cell Carcinoma (2a) [93]

In 2008, British Association of Dermatologists (BAD) guidelines reported by Telfer et al. [93] state that RT is effective in the treatment of primary BCC, surgically recurrent BCC, as adjuvant therapy, and is probably the treatment of choice for high-risk disease in patients who are unwilling or unable to tolerate surgery. The authors assign the following quality of evidence I: evidence obtained from at least one properly designed, randomized controlled trial; strength of recommendation A: there is good evidence to support the use of the procedure.

The authors also note that poor long-term cosmetic results are much less likely following treatment using modern techniques. Fractionated treatment regimens generally produce superior cosmetic outcomes compared with single-fraction treatment. In the elderly, infirm patient, single-fraction regimens are still used, as the long-term cosmetic result of treatment is less of a concern. RT can be used successfully on many facial sites, and studies have reported good outcomes following treatment of BCC on the nose, lip, ear, and periorbital skin.

SCC (2a) [94]

Unpublished BAD guidelines for the treatment of SCC by RT reported by Motley et al. in 2009 [94] state that RT is generally contraindicated in the younger patient due to late effects in irradiated skin; in some circumstances RT will give a better cosmetic effect such as the lower eyelid, the inner canthus of the eye, the lip, the tip of the nose, and in some cases the ear. Areas that tolerate RT poorly include the back of the hand, the abdominal wall, and the lower limb, and surgical excision is preferable at these sites. The authors note that no long-term randomized trials have been conducted for the treatment of SCC and give no recommendation based on the level of evidence or strength of recommendation that was done with RT in the treatment of BCC and SCCIS; an update is in progress.

SCCIS (2a) [95]

BAD guidelines for the treatment of SCCIS by RT reported by Morton et al. in 2014 state that RT can be used to treat SCCIS in areas where surgical modalities are difficult. Level of Evidence 2+: extrapolated from well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance; strength of recommendation D: a moderate probability that the relationship is causal.

Canadian Nonmelanoma Skin Cancer Guidelines Committee

Basal Cell Carcinoma (2a)

In 2015, Zloty et al. [96] published Canadian guidelines for the management of BCC with the recommendation that radiation therapy may be used in selected cases for treatment of high-risk primary BCCs when surgery is contraindicated or could be disfiguring. The authors define high-risk BCC as those arising on the eyelids, nose, lips, ears, fingers, toes, periorbital, and periauricular locations; size >2 cm all sites or ≥1 cm on cheeks/forehead/temples/scalp/neck/chin; histology morpheaform/sclerosing, infiltrative, micronodular, basosquamous, mixed subtype BCCs (should be treated as the highest-risk form); recurrent, perineural involvement, and poorly defined (level of evidence moderate, strength of recommendation weak).

Squamous Cell Carcinoma (2a)

In 2015, Sapijaszko and colleagues [97] published Canadian guidelines for the management of recurrent or high-risk SCC and primary low-risk SCC, including SCC in situ and keratoacanthomas with the recommendation that they may be treated with radiation therapy in selected patients with contraindications to surgery, when surgery would be disfiguring, or when radiation therapy is needed for palliation (level of evidence moderate, strength of recommendation strong).

Adjuvant radiation therapy may be added to the surgical treatment of high-risk SCCs, such as those with perineural invasion (level of evidence moderate, strength of recommendation weak).

High-risk SCC was defined as those arising on the external ears, lips, and scalp; size ≥2 cm, depth ≥0.2 cm or Clark level IV–V; poorly differentiated, Broder grade 3–4; etiology other than ultraviolet radiation, immunosuppression, perineural involvement, recurrent, rapid growth, and those originating from a wound or scar. The Canadian guidelines used for classifying and rating evidence are found in Tables 36.3 and 36.4.

Table 36.3 Canadian guidelines: Level of evidence classification system used

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for classifying quality of evidence	
Level of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Table 36.4 Canadian guidelines: Definitions for rating the strength of recommendations

Strength of recommendation	Definition
Strong	Desirable effects Outweigh undesirable effects
Weak	Desirable effects Probably outweigh undesirable effects

American Academy of Dermatology Position Statement

The American Academy of Dermatology (AAD) March 2014 Position Statement on SRT for BCC and SCC is that surgical management remains the most effective treatment, providing the highest cure rates. The Academy supports consideration of superficial radiation therapy as a secondary option for the treatment of BCC and SCC, for use in special circumstances, such as when surgical intervention is contraindicated or refused and after the benefits and risks of treatment alternatives have been discussed with the patient. Unfortunately, the AAD still maintains the position that SRT is in need of research on long-term outcomes despite the numerous reports and research dating back to the late 1900s.

Dermatologists were the first radiation oncologists applying SRT to treat skin disease as early as 1897, shortly after the discovery of X-rays by Wilhelm C. Roentgen in 1895 and decades before the specialties of radiology and radiation oncology emerged and then diverged. Pioneers in radiotherapy, dermatologists authored, and more recently coauthored with radiation oncologists, textbooks that have been in continuous publication since 1921 on the use of SRT and radium in skin disease [6, 87, 98–102]. The first reported results using radiotherapy came from dermatologists in what was the precursor to the annual AAD meeting, "Rationale of and the Indications for Therapeutic Use of Rontgen Rays," 27th Annual Meeting of the American Dermatology Association, Washington, May 13 and 14, 1903.

Defining Radiation Modalities

Before commencing a review of the evidence for RT, it is important to define what constitutes SRT. By definition, SRT involves the emission of photon radiation from an X-ray machine cathode and classically involves kV energies ranging from 10 kV to 150 kV and less than 250 kV, with a source to surface distance (SSD) of ≤30 cm and a D1/2 of 1–30 mm. For the purpose of this text, energies ≥250 kV range (utilized by radiation oncologists) are not SRT and fall into the range of orthovoltage RT. We have not included Grenz ray therapy as newer SRT machines are just now being developed to deliver RT with these parameters but may do so in future editions of this text. Table 36.5 classifies RT based on several param-

Table 36.5 Radiation therapy methods

Classification of radiotherapy methods based on energy/voltage/generator						
Type	Sources & synonyms	Type of generator	kV	SSD[a] (cm)	$D^1/_2$ mm tissue	Surface dose (%)[b]
Megavoltage electron therapy	Electron beam Radiation	Linear accelerator (LINAC)	>1000 (6000–9000)	80	90% Isodose method used for electrons[c]	78–86
Megavoltage photon therapy (not routinely used to treat NMSC)	Megavoltage X-ray	Linear accelerator (LINAC), Betatron	>1000	80	150–200	6–30
Supervoltage therapy	Gamma (γ)-ray	Isotope teletherapy machines (60Cobalt)	400–800	50–80	80–110	40–90
Orthovoltage therapy	Deep X-ray	X-ray machine cathode	250–400	50–80	50–80	100
Intermediate therapy	*Half-deep therapy*	*X-ray machine cathode*	*110–249*	*30*	*30*	*100*
Contact therapy	*Ultrashort distance (Chaoul)*	*X-ray machine cathode*	*50–60*	*1.5–3.0*	*4–30*	*100*
Superficial X-ray therapy[d]	*Pyrex (glass) window (older units),*	*X-ray machine cathode*	*60–100*	*15–30*	*7–20*	*100*
Soft X-ray therapy[d]	*Beryllium window (modern units)*	*X-ray machine cathode*	*20–100*	*10–30*	*1–20*	*100*
Grenz therapy	Ultrasoft therapy, Supersoft therapy	X-ray machine cathode	5–20	10–15	0.2–1.2	100

Adapted from Goldschmidt et al. [21]
Bold = SRT range included in review
[a]SSD: Source to surface distance
[b]Surface dose is the percent of radiation dose delivered to the skin surface
[c]90% Isodose method is used by radiation oncologists for electron beam radiotherapy
[d]Superficial/soft X-ray therapy is the type most often utilized in dermatology office-based radiotherapy for SCC, SCCIS, and BCC

eters and identifies the types that fall within the realm of SRT.

Systematic Review of Randomized Controlled Trials (1a)

In 2004, Bath-Hextall (1a) [103] and colleagues conducted a systematic review (SR) of randomized controlled trials (RCT) on interventions for BCC. The authors searched the Cochrane Library and used standardized search engines to search Medline (from 1996 to December 2003), Embase (from 1980 to December 2003), the Cochrane Skin Group (December 2003), and the Cochrane Library (2004, issue 1) and manually searched cited references from identified trials and recent review articles. Twenty-five studies were identified, two studies involving RT. The authors conclude that little good-quality research has been done on the treatments used to treat BCC and that surgery and RT seem to be the most effective treatments.

Avril and colleagues (1b) [104] compared RT (n = 173) to surgery with frozen section margin control (n = 174) for the treatment of primary BCC of the face measuring less than 4 cm. The primary endpoint was failure rate (persistent or recurrent disease) at 4 years of follow-up. Of the RT group of 173 patients, 95 were treated with brachytherapy (implanted radioisotopes), 57 with 50 kV close-contact SRT, and 20 with 85–250 kV SRT. Brachytherapy was used for the smallest lesions (8.4 mm), close-contact 50 kV SRT for medium-sized lesions (12.9 mm), and 85–250 kV SRT for the largest lesions (15.5 mm). Failure rates were the highest for brachytherapy (8.8%), and lowest for the SRT subgroups, 6.6% for 50 kV close-contact SRT, and 5.0% for 85–250 kV SRT (Table 36.6. RT subgroup analysis). The 4-year failure rates for combined RT were 7.5% and surgery 0.7%. Actuarial failure rates were estimated with the Kaplan-Meier method.

Table 36.6 RT subgroup analysis

Method of RT	Number	BCC size mm	4-year failure rate (%)
Interstitial brachytherapy	95	8.4	8.8
Contact SRT (50 kV)	57	12.9	6.6
SRT (85–250 kV)	20	15.5	5.0

Data extracted from Avril et al. [104]

The second RT study included in this SR was a small study of 93 patients with BCC, comparing SRT to cryotherapy by Hall and colleagues (2b) [105]. RT was applied using 130 kV X-rays; tumors less than 1 cm were treated with 5 fractions of 700 cGy in 5 days or with 3 fractions of 650 cGy Monday, Wednesday, Friday for week 1 followed by 4 weekly fractions of 700 cGy. Lesions >1 cm were treated with 375 cGy in ten treatments over 12 days. Cryotherapy procedure involved using a thermocouple to record target temperatures of −25 °C and −30 °C beneath the tumors for two 1-min freeze-thaw cycles. At 2 years, 93/105 (89%) were available for follow-up; 47/49 (96%) of the SRT group and 27/44 (61%) of the cryotherapy group were disease-free.

Randomized Controlled Trials

Similar to Mohs micrographic surgery, the vast majority of research that has formed the foundation of dermatologic radiotherapy has come from retrospective analysis of patients chosen for SRT. From these studies we have gained an in-depth understanding of optimal dosimetry based on tumor characteristics and patient factors [22–29, 31, 32, 34–54, 65, 84, 88, 101, 106–128].

Randomized trials for the treatment of skin cancer are near impossible to undertake. To blindly assign patients to various modalities today would significantly increase the risk of recurrence, morbidity, and even mortality. For NMSC invading bone and orbital structures, it would be unethical to randomize a cohort of patients to Mohs surgery and another to RT; neither would be an appropriate choice based on the knowledge we have today, most of it from retrospective studies. As such selection bias is a factor in much of the literature.

In addition to the two studies in the prior section by Avril [104] and Hall [105], one additional

Table 36.7 RCT: TDF factor comparison

High dose (TDF 123)	Number treated	Recurred	Cure rate (%)
BCC	144	14	90
SCC	24	4	85
Overall	168	18	89
Low dose (TDF 106)			
BCC	148	12	92
SCC	20	1	96
Overall	168	13	92

Data extracted from Landthaler and Braun-Falco [15]

RCT was uncovered which involved the comparison of two TDF factors in SRT by Landthaler and Braun-Falco in 1988 (2b) [15] involving 319 patients with 142 BCC and 24 SCC placed in the high-dose (TDF 123) group and 148 BCC and 20 SCC in the low-dose (TDF 106) group, all followed up for 3 years. The results are shown in Table 36.7. The authors note that the age distribution of patients was identical in both treatment groups with the peak age of 70 years, the majority of tumors were located in sun-exposed areas in both groups with no significant differences in local distribution, and that 70% were located on the forehead, periocular region, nose, and lips. It is important to note the design is that of a randomized trial; however, the publication preceded recommendations outlined in Consolidated Standards Of Reporting Trials (CONSORT) first published in 1996 [129].

Systematic Review of Cohort Studies (2a)

A systematic review (SR) by Thissen and colleagues (2a) [130] included cohort studies reporting 5-year recurrence rates for seven treatment modalities for primary BCC. The study was limited to prospective cohorts completed after 1970 that included at least 50 lesions. Eighteen of 298 studies met the authors' inclusion criteria with 9930 primary BCC. This SR included one study of SRT by Silverman and colleagues (2b) [107] of 1288 biopsy-proven BCC treated by X-ray therapy between 1955 and 1982, including 862 primary BCC and 211 recurrent BCC. SRT was delivered using 29–50 kV with a D ½ between 2 mm and17 mm for a total of 5 fractions of 680 cGy. The 5-year recurrence rates were calculated using the modified life table method; for primary BCC the recurrence rate was 7.4% (64/862) and for recurrent BCC 9.5% (20/211).

Prospective Cohort Studies (2b)

In addition to the prospective cohort studies including Silverman and colleagues(2b) [107], one additional prospective cohort study by Avila and colleagues (2b) [23] reporting 3-year cure rates comparing surgery to RT for carcinoma of the ear (pinna) was identified. The surgery group included 50 patients, 5 treated with electrocoagulation, 39 treated with "V" excision, and 6 with partial amputation. The RT group included 44 treated with SRT 40–200 kV range and 1 patient with Cobalt RT (400–800 kV range). The 3-year cure rate was 96% (48/50) for the surgery group and 86.7% (39/45) for the RT group.

Classical Analytic Retrospective Cohort Study (2b)

Pampena and colleagues (2b) [131] compared two different treatment schedules for orthovoltage RT which included kilovolt levels in the SRT range, 50 kV up to 300 kV. The authors compared a one fraction per week (weekly) hypofractionated regimen to a standard daily regimen with the primary aim to compare overall survival, disease-free survival, and cosmetic outcome using life table analysis, Kaplan-Meier survival analysis, and multivariate Cox regression model to determine whether the one fraction per week schedule would be appropriate for elderly disabled patients.

The authors retrospectively enrolled 385 consecutive patients with 436 tumors. Group A consisted of those treated with one 525 cGy fraction per week for 7 weeks. Group B was treated with the standard daily 300 cGy/fraction for 15 consecutive daily fractions. Mean age for Group A (one weekly fraction) was 81.3 years and included

181 BCC, 93 SCC, and 1 mixed tumor; recurrence rate at 32 months was 5.5% (15/275). Group B mean age was 73.3 and included 128 BCC, 31 SCC, and 2 mixed tumors; recurrence rate at 32 months was 3.7% (6/161). The authors conclude that the one fraction per week regime seemed more appropriate for the elderly disabled patients in their cohort.

Distinguishing Case Series from Descriptive Cohort Studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative was developed to improve the quality of reporting in observational studies, specifically cohort studies, case-control studies, and cross-sectional studies [132, 133]. These study types are classically defined according to epidemiological analytical principles where the aim is to determine the incidence or natural history of a disease together with the risk factors for the disease or outcome of interest [134]. While these descriptions are useful in epidemiological studies where the aim is to determine disease associations and risk factors, these descriptions fall short when attempting to classify studies involving therapeutic interventions which can lead to difficulty differentiating case series from cohort studies [135, 136].

Nijsten and colleagues [134] provide a basic definition for cohort studies and case series which are in agreement with basic texts on the subject. Cohort studies are defined as analytical, observational studies, based on data, from a follow-up period of a group in which some have had or will have the exposure of interest, to determine the association between that exposure and an outcome. Case series were defined as descriptive observational study of a series of cases, typically describing the manifestations, clinical course, and prognosis of a condition [134]. Furthermore, a comparison group is not a necessary or defining feature of a cohort study [135–141].

A cohort study is a research design where a group of subjects is identified on the basis of exposure (intervention) and followed over time for the occurrence of the outcome of interest (recurrence). As a comparison group is not a defining feature of a cohort study, when it is absent the design is more accurately described as a "descriptive" cohort study and like classical analytic cohort studies they can be retrospective, prospective, or both [136, 141]. A central feature of cohort studies is that they enable an absolute risk estimate for the outcome, or incident rate calculation. For descriptive cohort studies, the exposure is the intervention, and the outcome of interest is recurrence, from which an absolute risk estimate (recurrence rate) can be calculated and in the absence of a comparison group can be likened to "exposed" arm of analytic epidemiology cohort studies (Fig. 36.6. 2 × 2 Table for etiologic research, retrospective descriptive cohort absolute risk calculation) [135].

Dekker and colleagues [135] have proposed guidelines for distinguishing cohort studies from case series stating that a cohort study is one in which sampling is based on exposure (intervention), follow-up is part of the study, and absolute risks can be calculated. A case series is described as a study in which only patients with the outcome of interest are sampled (disease or recurrence) without regard to exposure (intervention), which does not permit calculation of an absolute risk. The Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence in which a case series may be considered a collection of individual case reports which contain detailed information about the individual patients. An absolute risk estimate (recurrence rate) cannot be obtained from a case report or group of case reports (Fig. 36.7. 2 × 2 Table for etiologic research, case series).

Much of the dermatologic literature on therapeutic interventions, to include Mohs micrographic surgery, radiation therapy, destructive modalities, and targeted therapies, should be labeled descriptive retrospective cohort studies level of evidence 2b according to the Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence, rather than relegated to level 4 evidence, the reflex reaction when a comparison group is not reported. According to STROBE guidelines [132, 133] and epidemiologic text-

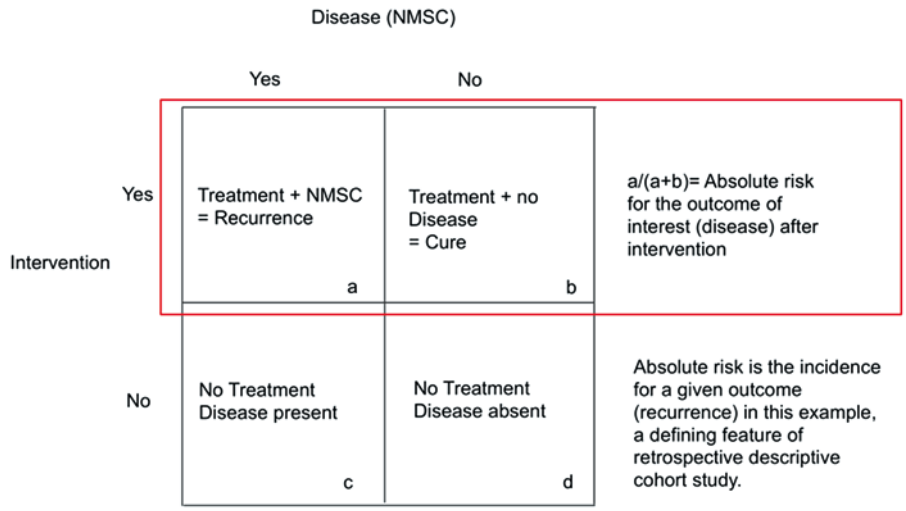

Fig. 36.6 2 × 2 Table for etiologic research, retrospective descriptive cohort absolute risk calculation

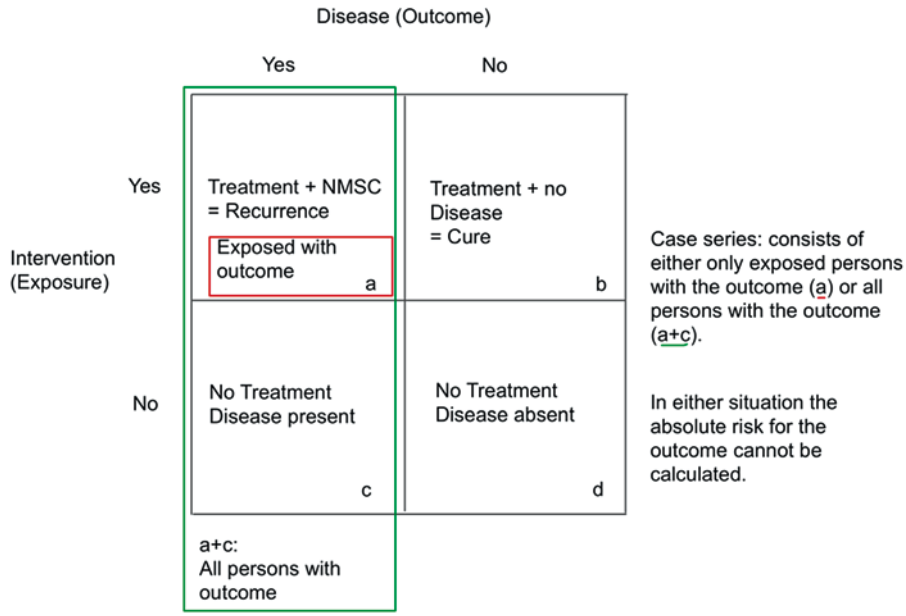

Fig. 36.7 2 × 2 Table for etiologic research, case series

books [137–140], these studies are indeed cohort studies because patients with a common exposure (intervention) are followed over time from a well-described inception point, which can be retrospective, for the outcome of interest (presence of disease or recurrence) and they need not have a comparison group. We have assigned a level of evidence of 2b "descriptive cohort study" when sampling is from exposure (intervention) to outcome (recurrence).

Conflicting definitions of what constitutes a case series are reported in the literature. We will report studies as case series as suggested by Dekkers and colleagues [135] when sampling is on the basis of both exposure and the presence of the outcome, for example, only patients who

undergo Mohs surgery (exposure) that have myocardial infarction (outcome) are described. The second type of case series involves the patients being sampled by the outcome under study (myocardial infarction) regardless of exposure characteristics (see Fig. 36.7).

Retrospective Descriptive Cohort Studies (2b)

A veritable mountain of research exists in the form retrospective descriptive cohort studies in dermatology involving SRT. For the purpose of summarizing the data, we have included tables for which data on SRT have been extracted based on the number of NMSC treated with SRT (Tables 36.8, 36.9, 36.10, 36.11, 36.12 and 36.13). Where research was conducted in the early years of medical literature where the widespread use of statistical analyses to account for patients lost to follow-up was not commonplace, we have included those studies that have accounted for all patients in the specified follow-up period with direct observation and have reported less than 5% lost to follow-up as retrospective descriptive cohorts (level 2b); those that report more than 5% lost to follow-up and do not include statistical analyses to account for them will be categorized as level 4 evidence (poor quality cohorts, poor quality case controls, case series), although this is not the only reason such studies will be labeled as "poor quality."

Poor Quality Cohort Studies and Case Series (4)

A retrospective cohort study by Griep and colleagues (4) [153] examined the recurrence rates and cosmetic outcome of 389 histologically confirmed NMSC either treated with SRT or electron beam RT from a single institution from 1980 to 1989. SRT was delivered at 600–1000 cGy/fraction for 6–10 fractions with a margin of 0.5–1.0 cm around the tumor. Recurrence rate for SRT was 6.9% with average follow-up of 32 months and 15.3% for electron beam RT with 24 months average follow-up (Table 36.14. SRT vs Electron beam RT).

In another retrospective cohort study of patients from a single center in Finland from 1963 to 1973, Nordman and Nordman (4) [154] examined the cure rates for BCC of the eyelid comparing SRT to radical excision. All patients were followed up for a minimum of 2 years, cure rate for SRT was 82% (65/79), and radical excision was 90% (27/30). The authors used a 1-mm margin around the tumor site, whereas it is common practice to use a minimum of 5 mm today which may account for the lower cure rate during this time period. A summary of the remaining level 4 studies is found in Tables 36.15, 36.16 and 36.17.

Safety of Superficial/Soft Radiotherapy

Safety issues were once a concern in the early years after the discovery of radiation as a potential treatment for various ailments. Realizing the need to protect the public and environment from unrestricted and unlicensed sources of ionizing radiation, the United States (US) government created the Energy Act of 1954 and later the Energy Reorganization Act of 1974. Since that time, federal and state regulatory requirements have continued to address safety concerns associated with the use of RT. Modern radiation platforms are manufactured with numerous safety mechanisms and systems of redundancy to minimize radiation accidents. All X-ray machines require annual calibration and certification providing ongoing oversight usually conducted at the state level.

In the 1940–1950s, ionizing radiation was used to treat benign conditions such as tinea capitis and acne resulting in radiogenic carcinoma development, on average 30 years later, likely from the combined effects of ultraviolet radiation (UV) as reported by Shore and colleagues [55, 56]. The total doses used to treat these conditions were in the order of 800–900 cGy [55, 56, 165], whereas the total dosages used to treat skin cancer are much larger, 3500–6000 cGy. Radiogenic

Table 36.8 Level 2b studies up to 125 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
62	70, 100, or 140 kV	Single fraction 1500 cGy (5), 2000 cGy (2); Weekly fractions 2600 cGy × 2 (5), 3000 cGy × 3 (2); Daily fractions 32–54Gy × 5–12 (62)	Lim JT. Irradiation of the pinna with superficial kilovoltage radiotherapy. Clin Oncol (R Coll Radiol). 1992;4(4):236–239 [36]	Single center January 1983 to June 1989. Ear NMSC. All accounted for, 62 patients at start, 15 died of unrelated causes, 47 available for follow-up. TDF factors 92–137	96%			2	Direct follow-up, raw data
94	75 kV (10), 100 kV (56), 225 kV (24)	3500–5000 cGy divided in 5–20 daily fractions	Krema H, Herrmann E, Albert-Green A, Payne D, Laperriere N, Chung C. Orthovoltage radiotherapy in the management of medial canthal basal cell carcinoma. Br J Ophthalmol. 2013;97(6):730–734 [142]	Single center 1998 to 2010. Medial Canthal BCC. Primary BCC 56% (50), recurrent BCC 28% (26), adjuvant treatment in 16% (14). Treatment outcomes 10-year cure rate: SRT as primary treatment 95%, adjuvant treatment 100%, recurrent after excision 91%. Median follow-up 80 months		94%		10	Kaplan–Meier actuarial local control
104	50–100 kV	300 cGy/fraction, 5 fractions/week, 14 fractions	Olschewski T, Bajor K, Lang B, Lang E, Seegenschmiedt MH. Radiotherapy of basal cell carcinoma of the face and head: Importance of low dose per fraction on long-term outcome. J Dtsch Dermatol Ges. 2006;4(2):124–130 [143]	Single center data from 1998 to 2002. BCC face/head. SRT 50–100 kV (101). All followed for 2 years minimum, median follow-up 37 months		100		2	Direct follow-up, raw data

(continued)

Table 36.8 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
109	80 kV, 250 kV	450 cGy × 10 fractions (near eyes); 300 cGy × 18 fractions (all other sites)	Duinkerken CW, Lohuis PJ, Heemsbergen WD, et al. Orthovoltage for basal cell carcinoma of the head and neck: excellent local control and low toxicity profile. Laryngoscope. 2016;126(8):1796–1802 [144]	Single center from 2000 to 2015. Total 253 BCC. SRT 80 kV for 109 BCCs smaller than 4 cm and depth <5 mm, 1 recurrence (99.1% 5-year cure rate). Orthovoltage 250 kV for 120 BCC >4 cm & >5 mm deep, 4 recurred (96.6% 5-year cure rate). Voltage used unknown in 24 BCC		99.1		5	Kaplan-Meier
115	Contact SRT 55–60 kV (110), SRT 55 kV (2), SRT + contact SRT 80–120 kV/55 kV (3)	500 cGy/fraction, 2 fractions/week, 4500–10,500 cGy total dose, D 1/2 2–30 mm	Caccialanza M, Piccinno R, Kolesnikova L, Gnecchi L. Radiotherapy of skin carcinomas of the pinna: a study of 115 lesions in 108 patients. Int J Dermatol. 2005;44(6):513–517 [29]	Single center data from 1990 to 2002. Total 115 NMSC, 99 BCC, 16 SCC. Mean follow-up 28.8 months. Contact SRT SSD = 1.5–5.0 cm. Contact SRT may be less efficacious than SRT for tumors of the ear	78%			5	Life table method

Table 36.9 Level 2b studies 125–200 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
127	55–60 kV (99), 50 kV (26), 100–120 kV (2)	Contact SRT 55–60 kV: 500 cGy/fraction, 2 fractions/week, 4500–6500 cGy total dose (125); SRT: 200 cGy/fraction, 5 fractions/week, total dose 4000–5500 cGy (2); D 1/2 = 2–30 mm	Caccialanza M, Piccinno R, Cuka E, Alberti Violetti S, Rozza M. Radiotherapy of morphea-type basal cell carcinoma: results in 127 cases. J Eur Acad Dermatol Venereol. 2014;28(12):1751–-1755[145]	Single center data from 1982 to 2013. Morpheaform BCC. Contact SRT SSD 1.5–5 cm. Numbers treated with each modality = CSRT (99), SRT (26), HDSRT (2)		81		5	Life table method, actuarial cure rate
128	90 kV	680 cGy/fraction, 5 total fractions daily, 3400 cGy total dose	Rodriguez JM, Deutsch GP. The treatment of periocular basal cell carcinomas by radiotherapy. Br J Ophthalmol. 1992;76(4):195–197 [146]	Single center data from 1974 to 1988. Eyelid and canthal BCC, 128 BCC. All minimum 3 years of follow-up		100		3	Direct follow-up, raw data
158	45 kV (1), 100 kV (138), 140–200 kV (19)	45 kV: 4000 cGy/fraction/week, 2 fractions; 100 kV: 1000 cGy/fraction, 4–5 fractions over 8–12 days, total dose 4000–5000 cGy (61), 300–500 cGy/fraction, daily for 9–18 total fractions; 140–200 kV: 300 cGy/fraction given daily, 18 fractions, 5400Gy	Traenkle HL, Stoll HL, Jr., Lonkar A. Results of roentgen therapy of carcinoma of the lip. Arch Dermatol. 1962;85:488–489 [54]	Single center data from 1947 to 1955. Primary lip carcinoma, 145 lower lip, 7 upper lip, 1 commissure. Histologic type not reported. Diameter ≤ 1 cm (94), 1–2 cm (52), > 2 cm (12)	95.0			3	Standard life table
175	20–50 kV	Not reported	Zagrodnik B, Kempf W, Seifert B, et al. Superficial radiotherapy for patients with basal cell carcinoma: recurrence rates, histologic subtypes, and expression of p53 and Bcl-2. Cancer. 2003;98(12):2708–2714 [147]	Single center data from 1981 to 1991. Subtype recurrence rates: Sclerosing BCC 21% (10/47), superficial multifocal BCC 16% (4/25), nodular BCC 7.8% (8/103). Median follow-up 48 months		87.4		5	Kaplan-Meier

(continued)

Table 36.9 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
180	30–60 kV	Mean 460 cGy/fraction, 11.2 fractions, total dose 4820 cGy, D 1/2 = 7.2 mm, SSD 3–20 cm	Barysch MJ, Eggmann N, Beyeler M, Panizzon RG, Seifert B, Dummer R. Long-term recurrence rate of large and difficult to treat cutaneous squamous cell carcinomas after superficial radiotherapy. Dermatology. 2012;224(1):59–65 [148]	Single center data from 1960 to 2004. Mean tumor size 3.5 cm. Two-year relapse-free survival was 94.8% for good, 88.9% for moderate and 85.7% for poor differentiated tumors. Five-year relapse-free survival was highest in cSCCs located around the eyes (100%) and cheeks (90.9%), lowest with cSCCs on scalp (69.2%) and ears (72.2%)			86.4 (5 year); 80.4 (10 year)	10	Kaplan-Meier
189	SRT kV not given	Not reported	Lovett RD, Perez CA, Shapiro SJ, Garcia DM. External irradiation of epithelial skin cancer. Int J Radiat Oncol, Biol, Phys. 1990;19(2):235–242 [149]	Single center data from 1966 to 1986. SRT (192), electron beam RT (59), megavoltage photon RT (18), combination (70). Cure rates: SRT 95%, Electron beam RT 74%, megavoltage photon 72%, combination 74%	95.3	95.2	95.8	2	Life table method, actuarial cure rate

Table 36.10 Level 2b studies 200–500 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
249	55–60 kV contact SRT (237), 55 kV SRT (10), 120 kV HDSRT (1)	Contact SRT: 500 cGy/fraction, 2 fractions/week, 4500–7000 cGy total dose, D1/2 = 2–12 mm; SRT: 500 cGy/fraction, 2 fractions/week, 5000–6000 cGy total dose, D1/2 = 15 mm; HDSRT: 250 cGy/fraction, 3 fractions/week, 5000 cGy total dose, D1/2 = 30 mm	Caccialanza M, Piccinno R, Grammatica A. Radiotherapy of recurrent basal and squamous cell skin carcinomas: a study of 249 re-treated carcinomas in 229 patients. Eur J Dermatol. 2001;11(1):25–28 [30]	Single center data from 1982 to 1989. Recurrent BCC. Prior treatments: surgery (116), 5-flourouracil (22), cryotherapy (48), electrodessication (49), laser (13, intralesional interferon (1)		83.6		5	Life table method
338	100 kV, 45 kV, 140–200 kV	100 kV: 1000 cGy/fraction, 4 fractions over 8–10 days, (53) necrosis was an issue regimen altered; 100 kV: 500 cGy/fraction, 9 fractions in 11 days or 400 cGy/fraction, 13 fractions in 17–19 days or 300 cGy/fraction, 18 fractions in 24–26 days (246); 45 kV: 4000 cGy/fraction, 2 weekly fractions (36); 140–200 kV: 300 cGy/fraction, 18–20 daily fractions	Stoll HL, Jr., Milgrom H, Traenkle HL. Results of roentgen therapy of carcinoma of the nose. Arch Dermatol. 1964;90:577–580 [108]	Data single center between 1947 and 1957. BCC of the nose. SRT 299 (100 kV), contact SRT 26 (45 kV), SRT 13 (140–200 kV)	90.5	89.5	94.5	5	Standard life table
454	SRT kV not given	1800 cGy single fraction; 800 cGy/fraction, 4 weekly fractions, total dose 2400 cGy; 700 cGy/fraction, 3 weekly fractions, total dose 2100 cGy; 300 cGy/fraction, 5 fractions/week, 12 fractions, total dose 3500 cGy	Ashby MA, Smith J, Ainslie J, McEwan L. Treatment of nonmelanoma skin cancer at a large Australian center. Cancer. 1989;63(9):1863–1871 [123]	Data from single center 1980 to 1981 for 1090 NMSC. SRT (434), other RT (28), surgery (614), 5-FU (2), cryotherapy (12). Five-year cure rates: SRT 90%, surgery 96%, other RT 70%, 5-FU & cryotherapy 84%. Histology: 901 BCC, 242 SCC, 11 mixed	90			5	Kaplan-Meier

(continued)

Table 36.10 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
500	100 kV	680 cGy/fraction, 5 fractions total, 2–3 days between fractions, total dose 3400 cGy	Bart RS, Kopf AW, Petratos MA. X-ray therapy of skin cancer: evaluation of a "standardized" method for treating basal cell epitheliomas. Proc Natl Cancer Conf. 1970;6:559–569 [26]	Single center 1955–1964. Modified life table, recurrence rates: 5-year = 7.9%, 10-year = 12.6%		7.9		5	Modified life table method

Table 36.11 Level 2b studies 500–700 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
603	26 kV	240 cGy/min, total doses 3000–7000 cGy. SSD 10 cm, D 1/2 = 1.6 mm	Mosekilde E. Results of treatment of skin cancer with ultrasoft roentgen rays given in a single dose. Acta radiologica. 1951;36(1):28–34 [150]	Single center 1937–1942. All biopsy-proven, primary NMSC only. At 5 years of 603 NMSC, 420 evaluable, 183 NMSC not (patients died), 28 recurred = 93.3% cure rate. Statistical analyses used to account for deaths and 5-year recurrence rate by Magnusson circa 1935 was 90.4% (545/603)	90.4			5	Method used by Magnusson, W.: Skin Cancer, Acta radiol. Suppl XXII (1935)
620	60 kV, 180 kV	Contact SRT 60 kV: 425–500 cGy/fraction, 3 fractions/week, 10–11 fractions, total dose 4600–5200 cGy, SSD = 2 or 5 cm; SRT 180 kV: 300 cGy/fraction, 3 fractions/week, 15–21 fractions, total dose 4500–5500 cGy	Schlienger P, Brunin F, Desjardins L, Laurent M, Haye C, Vilcoq JR. External radiotherapy for carcinoma of the eyelid: report of 850 cases treated. Int J Radiat Oncol, Biol, Phys. 1996;34(2):277–287 [151]	Data from single center 1970 to 1980. Eyelid carcinoma. Treatment: SRT 60Kv (507), SRT 180Kv (314), electron beam RT (29). Histology: 694 BCC, 41 SCC, 80 mixed, 18 adenocarcinoma. Results at year 5 for 60 kV: 394 alive NED, 6 alive with disease, 78 died from other disease, 29 lost to follow-up, total 507. Results at year 5 for 180 kV: 203 alive NED, 13 alive with disease, 4 died from cancer, 78 died from other causes, 15 lost to follow-up, Total 314. Results at year 5 for electron beam RT: 16 alive NED, 1 alive with disease, 1 died from cancer, 10 died from other causes, 1 lost to follow-up, Total 29. Total 5% (45) of patients lost to follow-up at year 5	96.3			5	Direct follow-up, raw data

(continued)

Table 36.11 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
671	55–60 kV, 80–120 kV	Contact SRT: 500 cGy/fraction, 2 fractions/week, 3000–7500 cGy total dose, D1/2 = 2–12 mm (668); HDSRT: 250 cGy/fraction, 3 fractions/week, 6000 cGy total dose, D1/2 = 30 mm (3)	Caccialanza M, Piccinno R, Percivalle S, Rozza M. radiotherapy of carcinomas of the skin overlying the cartilage of the nose: our experience in 671 lesions. J Eur Acad Dermatol Venereol. 2009;23(9):1044–1049 [27]	Single center 1972–2007. 671 carcinoma overlying cartilage of the nose. Mean follow-up 38 months, cosmesis good in 75%, acceptable in 23%	88.1			5	Actuarial rate by life table method
675	100 kV	1020 cGy/fraction, 3 total fractions over 14 days	Abbatucci JS, Boulier N, Laforge T, Lozier JC. Radiation therapy of skin carcinomas: results of a hypofractionated irradiation schedule in 675 cases followed more than 2 years. Radiother Oncol. 1989;14(2):113–119 [152]	Single center 1974–1983. Used Muller RT100 (SRT machine up to 100 kV). Minimum follow-up 2 years. 675 cases of primary NMSC of the face (excluding lips, ears, eyelids)	4.15	4.8	2.8	2	Direct follow-up, raw data

Table 36.12 Level 2b studies 700–1000 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
710	14–50 kV	400 cGy/fraction, 3 fractions/week, total 45–5500 cGy; 900 cGy/fraction once weekly for 4 weeks, 3600 cGy	Hernandez-Machin B, Borrego L, Gil-Garcia M, Hernandez BH. Office-based radiation therapy for cutaneous carcinoma: evaluation of 710 treatments. Int J Dermatol. 2007;46(5):453–459 [65]	Single center 1971–1996. Histology: BCC (604), SCC (102). Statistical analysis: recurrence rate/1000 patient years assuming Poisson distribution of events, Kaplan-Meier survival curves plotted for each tumor		94.4	92.7	5	Kaplan-Meier
781	100kv	1020 cGy/fraction in 3 fractions over 14 days, 3060 cGy total; 500 cGy/fraction in 11 fractions over 35 days, 5500 cGy total; 330 cGy/fraction in 18 fractions over 40 days, 6000 cGy total; 200 cGy/fraction in 35 fractions over 47 days, 7000 cGy total	Mazeron JJ, Chassagne D, Crook J, et al. Radiation therapy of carcinomas of the skin of nose and nasal vestibule: a report of 1676 cases by the Groupe Europeen de Curietherapie. Radiother Oncol. 1988;13(3):165–173 [22]	Nose and nasal vestibule. Multicenter analysis (18 sites) by the Groupe Europeen de Curietherapie conducted May 1986. 781 patients (47%) treated with SRT = 693 (up to 100 kV, 88 above 100 kV) = 47%. Brachytherapy in 762 = 45%. Megavoltage in 133 = 8%. All 1676 followed up for minimum of 2 years, 1102 > 5 years, 279 > 10 years. Overall histology BCC 1397 (83%), SCC 279 (17%). Local control rate for SRT 738/781 = 95%	95			2	Direct follow-up, raw data
985	Contact SRT 55–60 kV, SRT 80–120 kV	Contact SRT: 500 cGy/fraction, 2 fractions/week, 3000–7500 cGy total dose, D1/2 = 2–12 mm (668); HDSRT: 250 cGy/fraction, 3 fractions/week, 6000 cGy total dose, D1/2 = 30 mm (3)	Caccialanza M, Piccinno R, Gaiani F, Contini D. Relevance of dermatologic radiotherapy in the therapeutic strategy of skin epithelial neoplasms: excellent results in the treatment of lesions localized on eyelids and skin overlying the cartilage of the nose. G Ital Dermatol Venereol. 2013;148(1):83–88 [31]	Single center SRT 1972–2011 Nose & 1976–2011 eyelid. Nose overlying cartilage histology: 835 BCC, 20 SCC, 1 mixed. Eyelid histology: 125 BCC, 3 SCC, 1 mixed. Mean follow-up eyelid 48 months, nose cartilage 42 months	Eyelid 96.3/ Nose 92.4			5	Life table method

Table 36.13 Level 2b studies 1000 to >2000 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Citation	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
1005	45 kV, 100 kV	Total doses 1800–2200 cGy, SSD 10 cm.	Chan S, Dhadda AS, Swindell R. Single-fraction radiotherapy for small superficial carcinoma of the skin. Clin Oncol (R Coll Radiol). 2007;19(4):256–259 [126]	Single center data all patients from 1976, review conducted in 1986. Total 1005 head & neck NMSC, histology: BCC 986, SCC 19	90			5	Kaplan–Meier disease-free survival
1267	45,70,100 kV	BCC: 500 cGy/fraction × 9 fractions; SCC: 500 cGy/fraction × 12 fractions. Additional fractions given 1–2/week if complete tumor involution not apparent at end of SRT. D1/2: 45 kV: 5.7 mm, 70 kV: 11.5 mm, 100 kV: 15.7 mm	Schulte KW, Lippold A, Auras C, et al. Soft X-ray therapy for cutaneous basal cell and squamous cell carcinomas. J Am Acad Dermatol. 2005;53(6):993–1001 [34]	Single center 1988–1992. 1267 NMSC, 77 month avg. follow-up, 88% followed up for minimum 5 years. Used D 1/2 to deposit 80% of dose to base of tumor Titrated response SRT- continued to deliver additional fractions if no tumor involution or erosive reaction noted on physical exam. 5-year cure rates 93.8% for all tumors, 94.8% BCC, 90.4% SCC	4.7	4.2	6.0	5	Modified life table
1715	80 kV	700 cGy/fraction, 3 fractions/week, 5–7 fractions, 3500–4500 cGy total dose	Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial X-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. J Am Acad Dermatol. 2012;67(6):1235–1241 [33]	Single center data from 2000 to 2010. Median follow-up 31.5 months, all NMSC histologically confirmed and reviewed nonaggressive BCC/SCC treated with SRT. Histology: Nodular BCC 631, superficial BCC 81, invasive SCC 133, SCCIS 861, mixed 9. Hazard ratio for recurrence: Size >2 cm 3.94–4.18 (p value 0.02).	5	4.2	5.8	5	Kaplan-Meier
2002	50 kV (125); SRT 100–120 kV (22); contact SRT 55–60 kV (1855)	Contact SRT & SRT 50–60 kV: 500 cGy/fraction, 2 fractions/week, 8–14 fractions, total dose 4000–7000 cGy	Caccialanza M, Piccinno R, Beretta M, Gnecchi L. Results and side effects of dermatologic radiotherapy: a retrospective study of irradiated cutaneous epithelial neoplasms. J Am Acad Dermatol. 1999;41(4):589–594 [119]	Single center from 1982 to 1995. SRT 50 kV (125); SRT 100–120 kV (22), contact SRT 55–60 kV (1855). Mean follow-up 33.11 months. Raw cure rate by histology: BCC 96.5% (1702/1763); SCC 98.2% (225/229), mixed 100% (9/9)	90.7			5	Life table method

Table 36.14 SRT vs electron beam RT

	SRT, n (%)	Electron beam RT, n (%)
Male	69 (69.7)	182 (62.8)
Female	30 (30.3)	108 (37.2)
Average age (years)	71.4	71.5
Average follow-up (weeks)	127 (31.75 months)	95 (23.75 months)
BCC	83 (83.8)	212 (73.1)
SCC	16 (16.2)	78 (26.9)
Number previously untreated	73 (73.7)	215 (74)
Number previously treated (recurrent)	26 (26.3)	75 (26)
Average age	71.4	71.5
Recurrences (no prior treatment)	2.7%	3.3%
Recurrences (prior treatment)	4.2%	12.0%
Total percent recurrences	6.9%	15.3%

Data from Griep and colleagues [153]

carcinomas in these settings likely developed from smaller non-lethal, yet mutagenic, anti-inflammatory doses of radiation combined with the effects of UV radiation. In a follow-up study by Shore and colleagues [166] (3b), 2224 children receiving RT for tinea capitis were followed up for up to 50 years to determine cancer incidence compared to a control group of 1380 patients receiving only topical medication. The relative risk (RR) for BCC was 3.6 (95% confidence interval 2.3–5.9) among irradiated Caucasians (124 RT cases, 21 control cases) in response to a scalp dose of 475 cGy, no melanomas, and only a few SCC occurred. The authors note that 25% of both the treatment group and control group were African-American, with only 3 BCC in the RT group highlighting the importance of UV radiation as a cofactor.

In contrast to these reports, Lindelof and Ekklund [167] analyzed information from the Swedish Cancer Registry, Stockholm (1958–1981) for radiogenic carcinoma formation following Grenz ray therapy for benign conditions such as psoriasis, tinea, and hand dermatitis. In all 14,140 patients had received Grenz ray therapy, and only 8 radiation-induced SCC were uncovered at the Grenz RT sites using a latency period of ≥5 years from RT to tumor development as criteria for radiogenic carcinoma. Grenz ray is less penetrating, with an average D ½ penetration into skin of 0.2–1.3 mm, whereas SRT used for treating tinea in the studies by Shore and colleagues penetrated deeper, 7–20 mm, which in addition to other factors may account for the difference between these studies.

Ehring and Gattwinkel [116] in a study of 2005 patients irradiated for BCC report only one second tumor occurring 40 years after initial RT. Bart and colleagues [26] in a series of 500 patients treated with RT for skin cancer report only three possible radiogenic carcinomas. Landthaler and colleagues [168] examined the records of 2746 patients undergoing RT and uncovered 612 RT sites receiving a minimum dose of 1200 cGy with follow-up period of at least 10 years. The authors considered radiogenic carcinoma those that arose after a lag time of 10 years and uncovered 12 BCC and 9 SCC arising in RT sites (3.5%). Caccialanza and Cuka [169] examined the records of 5875 patients treated with SRT by dermatologists from 1970 to 2007 and discovered no radiogenic carcinoma (0%) using a latency period of 5 years from RT onset. Halpern [170] reports the incidence of radiogenic carcinoma using dosages to treat skin cancer to be less than 0.3% and attributes this to refinement in radiation and calibration techniques and the availability of more efficacious radiation modalities. Nevertheless, the recommendation of the NCCN guidelines and general consensus of most dermatologic radiotherapists is to use RT in those ≥60 years of age to minimize late sequelae.

Cost Comparisons

Previous cost comparisons of RT for the treatment of NMSC in the dermatologic literature have not differentiated dermatologic office-based RT (SRT) from radiation delivered by radiation oncologists in the hospital setting. Rogers and Coldiron [171], Kauvar and colleagues [172], and Zitelli and Cook [173] all report RT to cost between $2591 and

Table 36.15 Level 4 studies <100 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
50	100 kV	680 cGy/fraction, 5 fractions, interval 2–3 days between fractions	Green R, Kopf A, Bart R. X-irradiation of basal cell epitheliomas of the eyelids and canthi. Proceedings of the International Cancer Conference. 1972:333–342 [25]	Single center data from 1955 to 1966. Eyelid and Canthal BCC. 74% followed for 2 years, 40% >5 year.		96		2	Direct follow-up, raw data
50	100–150 kV	Not reported	Del Regato JA, Vuksanovic M. Radiotherapy of carcinomas of the skin overlying the cartilages of the nose and ear. Radiology. 1962;79:203–208 [32]	Single center data from 1949 to 1958. NMSC overlying the cartilage of the Nose and Ear. Total 56 NMSC, 5 died of other causes, 3 recurrences, 1 died of cancer, all accounted for at 3 years. Cure rate 90.2% (46/51)	90			3	Direct follow-up, raw data
73	SRT no kV listed	600–1000 cGy/ fraction, 6–10 fractions	Griep C, Davelaar J, Scholten AN, Chin A, leer JW. Electron beam therapy is not inferior to superficial X-ray therapy in the treatment of skin carcinoma. Int J Radiat Oncol, Biol, Phys. 1995;32(5):1347–1350 [153]	Single center data from 1980 to 1989. Superficial RT 99 patients 6.9% recurrence rate, 83 BCC, 16 SCC, avg. follow-up 32 months. Electron beam RT 290 with a 15.3% recurrence rate, 212 BCC, 78 SCC, avg. follow-up 24 months	93			2	Kaplan-Meier actuarial control rate
74	SRT no kV listed	3600–4200 cGy divided into 6–10 fractions, 4 fractions/week	Biro L, Price E, MacWilliams P. Basal cell carcinoma in office practice. N Y State J Med. 1975;75(9):1427–1433 [155]	Single center data from 1966 to 1971. Lists follow-up by groups: Group A follow-up 6–18 months (99 SRT) not included; Group B: 159 patients 3–8 years of follow-up 73 SRT, 4 recurrences		94.5		3–8	Direct follow-up, raw data
79	45–100 kV	500–600 cGy/ fraction, 5 fractions/week, 2800–6500 cGy total dose	Nordman EM, Nordman LE. Treatment of basal cell carcinoma of the eyelid. Acta Ophthalmol (Copenh). 1978;56(3):349–356 [154]	Single center 1963 to 1973 comparing SRT to excision. All followed for 2 years, cure rate 82% (65/79) for SRT and 90% (27/30) for excision. Only used 1 mm margin around tumor site, today we use at least a 5 mm border of uninvolved skin. Follow-up at year 5 was 56%. Cure rates for tumors <1 cm 98% (45/46) 2-year, 92% (22/24) 5–year		82 (2 year); 69 (5 year)		2 & 5	Direct follow-up, raw data

Table 36.16 Level 4 studies 100–400 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
129	80 kV	400–500 cGy/fraction. 5 fractions/week, 10–12 total fractions, total dose 4000–5000 cGy	Nevrkla E, Newton KA. A survey of the treatment of 200 cases of basal cell carcinoma (1959–1966 inclusive). Br J Dermatol. 1974;91(4):429–433 [156]	Data from a single center from 1959 to 1966. Total of 200 cases of BCC treated with the following: Excision (35), brachytherapy (36), SRT (129). Average age 60 years. Lesion size 0.5–10 cm, 82% ≤ 2.0 cm. Data not presented clearly; gives 92% cure rate for 126 patients using one SRT regimen and 94% cure rate for another regimen used in 26 patients using actuarial method. Total number of recurrences from raw data 8/129 = 6%		94		5	Actuarial method
178	45–55 kV	500 cGy/fraction, 6 daily fractions/week, 14 total fractions, 7000 cGy total dose	Rubisz-Brzezinska J, Musialowicz D, Zebracka T. Treatment of basal cell epitheliomas. Dermatol Digest. 1976(9):10–15 [109]	Single center data from 1965 to 1969. BCC in 270 patients, 230 followed for at least 3 years, all 3–5 years, 40 not included in analysis = 15% lost to follow-up unaccounted for. Women (128), men (102), age range 24–88 years, 95% BCC on head, lesion diameter 0.5–2 cm. Total patients 230, SRT in 178 patients (95% cure), electrocoagulation 26 patients (53.8% cure), 17 surgery (88.1% cure), 9 chemotherapy = podophyllin or stilbesterol (0% cure)		95		3	Direct follow-up, raw data
199	85–120 kV	Total dose 3000–5000 cGy	Cobb GM, Thompson GA, Allt WE. Treatment of basal cell carcinoma of the eyelids by radiotherapy. Can Med Assoc J. 1964;91:743–748 [157]	Single center data from 1953 to 1958. BCC eyelid. Total 199 BCC, 60% followed for at least 4 years, cure rate 93.3% (111/119). No statistical analyses to account for lost to follow-up or death		93.3		4	Direct follow-up, raw data

(continued)

Table 36.16 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
208	12–26 kV	34 underdosed cases 12 kV, 8000–15,000 cGy single dose, D 1/2 = 0.33 mm; 174 cases 20,000 cGy, 12 kV, D1/2 = 0.33 mm or 5600–6000 cGy, 26 kV, D1/2 = 1.6 mm	Ebbehoj E. Experiences in the treatment of skin cancer with ultrasoft roentgen rays, 1933–1936. Acta Radiologica. 1951;36(1):17–27 [158]	Data from single center from 1933 to 1936. Used Ebbehoj method = lesion biopsied, curetted prior to SRT. Histology: SCC 84, BCC 97, Epithelioma unspecified 26. Authors experimenting with proper dosage (early years of RT) 34 underdosed, 22/34 (65% cure) recurred or failed therapy. Proper dosage 168/174 (96.6%) clear at 5 years (4 SCC, 2 BCC recurred)	91.3			5	Direct follow-up, raw data
354	26 kV	26 kV: 4200 cGy/fraction, single dose for BCC, 5000 cGy/fraction, single dose for SCC, SSD 10 cm, D 1/2 = 1.6 mm	Jensen TS, Vetner MO. Treatment of 443 cases of skin carcinoma with curettage and soft roentgen rays by the Ebbehoj method. Acta Radiol Ther Phys Biol. 1973;12(5):369–377 [159]	Data from single center 1948–1950. Used the Ebbehoj method of curetting first, delivering single dose of 26 kV, 10 cm SSD. 5 year cure rate in 306/354 (86.4%), those recurrences were treated with 1 more fraction = 94.6% 5-year recurrence-free rate. Follow-up of 354 for 5 years, 89 < 5 years. Histology: BCC (268), SCC (160)	86.4			5	Direct follow-up, raw data

Table 36.17 Level 4 studies 400 to >2000 NMSC treated with SRT

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
430	120 kV, 140 kV	First regimen: 300–400 cGy/fraction, daily fractions, total dose 2500–5000 cGy; second regimen: 200 cGy/fraction × 8 daily fractions, 300 cGy/fraction × 4 daily fractions, then 400 cGy/fraction × 2 daily fractions, total dose 3600 cGy	Eberhard TP. Treatment of epitheliomas of the skin. Radiology. 1947;49(5):620–626 [160]	Data from single center September 1939 to September 1942. Compares SRT (430), brachytherapy (235), and surgery (77). Recurrence rates SRT: BCC 5.1% (17/333), SCC 4.1% (4/97); brachytherapy: BCC 4.9% (8/163), SCC 4.2% (3/72); surgery: BCC 2.0% (1/49), SCC 10.7% (3/28). Patients lost to follow-up: BCC 5.2%, SCC 5.8%, does not account for the number of NMSC in this group lost to follow-up. Direct follow-up for 5 years in 354/443		5.1	4.1	3	Direct follow-up, raw data
454	29–43 kV	29 kV: 500 cGy/fraction, 10 fractions, (226); 29 kV: 1000 cGy/fraction, 3–5 fractions, (33); 29 kV: 3000–5000 cGy/fraction, single fraction, (15); 43 kV: Not given (55)	Reymann F, Kopp H. Treatment of basal cell carcinoma of the skin with ultrasoft X-rays. Dermatologica. 1978;156(1):40–47 [161]	Single center from 1965 to 1969. 226 females, 228 males. Follow-up conducted from 1975 to 1976, 154 females 149 males. 454 treated, 303 with follow-up, 273 followed between 5–9 years, 30 followed 1–5 years, 151 died = all 454 accounted for		91.5		See notes	Direct follow-up, raw data

(continued)

Table 36.17 (continued)

# Treated	Voltage, (n) = number treated with listed voltage	RT parameters, (n) = number treated with parameters	Manuscript	Notes	% Cure or recurrence			Follow-up time period (years)	Method to calculate recurrence
					Total	BCC	SCC		
483	100 kV	680 cGy/fraction, 5 fractions, 2–3 day interval between fractions, total dose 3400 cGy, D 1/2 = 15 mm	Kopf AW. Computer analysis of 3531 basal cell carcinomas of the skin. J Dermatol. 1979;6(5):267–281 [162]	Single center 1955–1969. Treatments: Curettage & electrodessicaton 1781, SRT 748, excision 505. Recurrence rates: ED&C 19.8% (206/1043), SRT 9.3% (45/483), excision 8.9% (26/292). No statistical analyses to account for lost to follow-up or died from other causes. 38% lost to follow-up in SRT group. 65% available for follow-up at year 5.		90.6		5	Direct follow-up, raw data
703	60 kV (595), 45–220 kV (108)	Single fraction 2000–3000 cGy (171); 1–2 fractions/week over 1–3 weeks, total 3500–5000 cGy (150); 3–5 fractions/week over 1–3 weeks, total 4500–6000 cGy (394)	Churchill-Davidson I, Johnson E. Rodent ulcers: an analysis of 711 lesions treated by radiotherapy. Br Med J. 1954;1(4877):1465–1468 [84].	Single center 1939–1950. Biopsy in 228/711 (28%), felt to be unnecessary for "rodent ulcers." Reported cure rates: 2.5–3 years (93.6%), > 3 years (95.7%), > 5 years (92.6%) but did not count treatment failures as recurrences. Corrected for treatment failures: 2.5–3 years (91.3%), >3 years (93.4%), > 5 years (89.2%).		89.2		5	Direct follow-up, raw data
1790	100 kV	100 kV: 2250 cGy single fraction; 45 kV:1800–2000 cGy single dose.	Orton CI. The treatment of basal cell carcinoma by radiotherapy. Clin Oncol. 1978;4(4):317–322 [163]	Single center data from 1966 to 1967. No statistical analyses or mention of patients lost to follow-up.		6.1		10	Direct follow-up, raw data
2219	50–60 kV	BCC: 400 cGy/fraction, 5 fractions/week, 14 total fractions, 5200–6000 cGy total dose; SCC: 400 cGy/fraction, 5 fractions/week, 14–16 fractions, 5600–6000 cGy total dose	Finizio L, Vidali C, Calacione R, Beorchia A, Trevisan G. What is the current role of radiation therapy in the treatment of skin carcinomas? Tumori. 2002;88(1):48–52 [164]	Single center data from 1986 to 1999. Authors do not list follow-up, recurrence rates are to be assumed to be those that developed during the 14 year period. 2161 SRT (50–60 kV), 58 electrons. Histology: BCC 1863, SCC 276, mixed 80. Recurrence rates: Total 4.3% (96/2219), BCC 3.8% (72/1863), SCC 7.9% (22/276).	4.3	3.8	7.9	14 year chart review	Direct follow-up, raw data

Table 36.18 Cost comparison of RT modalities

Treatment method	2015 CPT/APC codes	Total cost to treat one lesion in US$
Dermatologic office-based superficial radiation (*5 fractions*)	77,261,77,300,77,332,77,427,77,401 × 5	512.38
Dermatologic office-based superficial radiation (*12 fractions*)	77,261,77,300,77,332,77,427 × 2, 77,401 × 12	844.20
Outpatient high-dose rate electronic brachytherapy (*8 fractions*)	77,261,77,290, 77,316, 77,334, 77,470, 77,789 × 8, 0182 T × 8	7871.86
Radiation oncologist hospital-based orthovoltage radiation (*20 fractions*)	77,261,77,300,77,332,77,427 × 4, 77,401 × 20 (CPT + APC)	3714.80
Radiation Oncologist hospital-based megavoltage electron beam radiation (*20 fractions*)	77,261,77,306,77,332,77,280,77,336, 77,427 × 4, 77,402/G6003 × 20 (CPT + APC)	7106.79

With permission from Wolfe and Cognetta [91]
CPT Common Procedural Terminology, *APC* Ambulatory Payment Classification

$4558 at the time of their publication. We calculated and reported the costs of RT delivered in the outpatient dermatologic setting with SRT, the hospital setting using orthovoltage (250 kV) or megavoltage RT, as well as electronic brachytherapy using 2015 Medicare fee schedule national payment amount for physician services and the national Ambulatory Payment Classification rates paid to hospitals (Table 36.18. Cost comparison of RT modalities). RT delivered by dermatologists in the outpatient setting is the least costly form of RT in treating NMSC. Large-scale studies with more complex analyses are warranted that specifically examine SRT in the outpatient dermatologic setting; to date none exist.

Conclusion

SRT has over 106 years of research and development by dermatologists. One of the first reports on the use of radiotherapy came from dermatologists. Randomized trials, innumerable retrospective cohort, and several prospective cohort studies support the use of SRT in the treatment of NMSC. Calling on more than 70 specialty society partners including the AAD and ASTRO, the American Board of Internal Medicine (ABIM) Foundation launched "Choosing Wisely," a campaign to prevent unnecessary medical tests, treatments, and procedures through the promotion of conversations between clinicians and patients. The campaign is based on four tenets to help patients choose care that is (1) supported by evidence, (2) not duplicative of other tests or procedures already received, (3) free from harm, and (4) truly necessary. The key to "choosing wisely" with SRT is to select therapy based on patient age, infirmity, comorbidities, tumor type/depth, and patient choice. In line with choosing wisely, prospect theory is a concept applied to health values which considers a patient's baseline functionality when determining risk-to-benefit for an intervention, acknowledges uncertainty, reflects patient's values, and allows for treatment which may not necessarily achieve the highest cure rate but an acceptable one.

Chhabra and colleagues [174] in a viewpoint piece in the Journal of the American Medical Association (JAMA) entitled "Surgical Decision Making: Challenging Dogma and Incorporating Patient Preferences" discuss three recently published randomized trials which questioned the primacy of surgical management. These three randomized trials compared the established surgical gold standard to less aggressive operations or nonoperative alternatives. In all three trials, neither treatment was superior across "all outcomes." An example used by the authors to illustrate this point involves diverticulitis; colectomy was more effective in preventing the outcome of reoperation, whereas laparoscopic lavage was more effective in preventing the outcome of

stoma formation. Within the patient-centered framework, the modality that is "best" is determined by which outcome the patient values most. Informed consent represents an opportunity to understand a patient's values; the onus rests on us to understand which outcomes are most important to them and communicate the risks and benefits of each potential treatment option and the associated trade-offs, as Chhabra and colleagues state "patients are the ones who must live with the consequences."

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: Quality of evidence
SRT is indicated for the treatment of NMSC of the central face, nose, periorbital, ear, periauricular, periorbital locations	A
SRT should be limited to patients over 60 years of age	B
NMSC up to 5 cm in diameter may be treated with SRT	B
Better cure rates may be obtained by limiting SRT to the treatment of nonaggressive SCC, BCC (Tis-T2, N0, M0, TNM classification)	A
Aggressive histologic subtypes of BCC are a risk factor for recurrence	A
Aggressive SCC are a risk factor for recurrence: T3, T4, depth >2 mm, Clark level ≥IV, poorly differentiated, undifferentiated, perineural, lymphatic, or vascular invasion	A
SRT should not be used at sites of prior RT, chronic ulcers, or burn scars	A
SRT is associated with poorer cosmetic outcomes on the trunk and extremities	B
Frailty and poor overall health are reasons to consider SRT over surgery	B
Genetic anomalies associated with radiosensitivity are a contraindication to RT	A
Anticoagulant or antiplatelet use that cannot be discontinued prior to surgery is a consideration for SRT over surgery	B
SRT is associated with better cure rates than interstitial brachytherapy for the treatment of BCC	A
SRT has significantly higher cure rates than cryotherapy for BCC	A
SRT can be efficacious in the treatment of recurrent BCC	B
Hypofractionated once weekly fractions of SRT may be as effective as daily fractions of SRT for the elderly and disabled	B
Optimal TDF factors for the treatment of NMSC are between 90 and 110	B
The appropriate parameters should be chosen so that at least 50% of the depth dose (D ½) is at the base of the NMSC	B
Morpheaform BCC may be treated with SRT if surgery cannot be done	B
SRT is more effective than electron beam RT and megavoltage photon RT in the treatment of NMSC	B
SRT may be used for recurrent BCC (other than prior RT) if surgery cannot be done	B
SRT titrated to clinical response with additional fractions delivered may be associated with improved cure rates	B
SRT is associated with lower recurrence rates compared to electron beam RT	B
Planning an RT field with less than a 5-mm border around the tumor may be associated with increased risk of recurrence	B
Radiotherapy-induced carcinoma (radiogenic) are extremely rare when RT is delivered at dermatologic doses	A
SRT is the least expensive form of RT and less expensive than RT delivered by radiation oncologists and electronic brachytherapy	B
SRT is a viable treatment for NMSC in the elderly and infirm	A
Hypofractionated schedules of SRT 5–12 fractions are as effective as multiple protracted daily fractions in the treatment of nonaggressive NMSC	B
SRT is a treatment option for large SCC >2 cm in patients unable to undergo surgery	B

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Self-Assessment Questions

1. Superficial/soft radiation therapy is most appropriate for basal cell carcinoma and squamous cell carcinoma in which of the following locations?
   (a) Extremities
   (b) Trunk
   (c) Neck
   (d) Hands
   (e) Nose

2. SRT is suitable for treatment of squamous cell carcinoma in which of the following situations?
   (a) SCC arising in a burn scar on the forehead of a 70-year-old
   (b) SCC on the hand of an organ transplant recipient
   (c) SCC in situ on the malar cheek of a 45-year-old patient
   (d) SCC on the nasal tip, Breslow depth 1 mm, in a 65-year-old on dabigatran for history of deep vein thrombosis
   (e) SCC arising on the foot of a diabetic patient with chronic osteomyelitis

3. Time-dose-fractionation factor tables are most useful for
   (a) Determining how much time to wait between fractions of radiation
   (b) Determining the maximum dose that should be given with each fraction of radiation
   (c) Deciding on the appropriate radiation treatment schedules to prevent over- and underdosing
   (d) Determining the optimum overall length of the radiation treatment schedule
   (e) Determining the appropriate amount of lead shielding to use on patients

4. The best cure rates in the treatment of basal cell carcinoma using SRT are obtained for which of the following histologic subtypes?
   (a) Nodular basal cell carcinoma
   (b) Morpheaform basal cell carcinoma
   (c) Infiltrative basal cell carcinoma
   (d) Multicentric basal cell carcinoma
   (e) Basosquamous carcinoma

5. All of the following are true except:
   (a) SRT is less expensive than electron beam radiation therapy.
   (b) SRT has better cure rates than cryotherapy and electrodessication and curettage.
   (c) The risk of radiogenic carcinoma is extremely low when used by dermatologists to treat skin cancer.
   (d) The risk of radiogenic carcinoma with the use of Grenz ray therapy for benign conditions is extremely low.
   (e) The appropriate TDF factor to aim for when selecting radiation parameters is between 150 and 170.

Correct Answers

1. e: Nose
2. d: SCC on the nasal tip, Breslow depth 1 mm, in a 65-year-old on dabigatran for history of deep vein thrombosis
3. c: Deciding on the appropriate radiation treatment schedules to prevent over- and underdosing
4. a: Nodular basal cell carcinoma
5. e: The appropriate TDF factor to aim for when selecting radiation parameters is between 150 and 170 (between 90 and 110, although some studies go up to 130).

Fat Transplantation

37

Dana L. Ellis and Lisa M. Donofrio

Abstract

The changes that happen as an intrinsic part of aging occur deeper in the subcutaneous tissues and are atrophic in nature (Donofrio, Dermatol Surg 26:1129–1134, 2000). This volume loss can be corrected through several means, including tissue repositioning, implants, synthetic fillers, or autologous tissue (Modarressi, World J Plast Surg 2(1):6–13, 2013). More recently, autologous fat grafting has come to be considered an ideal filler, as fat grafts are biocompatible, nonallergenic, nontoxic, easy to obtain, and synergistic with natural skin (Sinno et al. Plast Reconstr Surg 137:818–824, 2016). Neuber first reported the technique in 1893, followed by Illouz who then pioneered liposuction in the 1980s. In the modern day, Coleman demonstrated techniques for long-term fat graft stability (Sinno et al. Plast Reconstr Surg 137:818–824, 2016). Its first indications were for aesthetic surgery of the face, and more recently in hands (Modarressi, World J Plast Surg 2(1):6–13, 2013). Fat grafting is also useful for tissue loss due to an accident, operation, congenital disease, or lipodystrophy. In addition to a volumizing effect, the injected fat leads to neoangiogenesis, thereby improving the cutaneous elasticity. This technique is also used for wound healing, scar reduction, treatment of radiodermatitis, correction of acne scars, and breast reconstruction and augmentation in plastic surgery (Modarressi, World J Plast Surg 2(1):6–13, 2013).

Keywords

Fat transplantation · Fat grafting · Techniques
Postoperative care · Alternative procedures

Indications for Fat Transplantation

The changes that happen as an intrinsic part of aging occur deeper in the subcutaneous tissues and are atrophic in nature [1]. This volume loss can be corrected through several means, including tissue repositioning, implants, synthetic fillers, or autologous tissue [2]. More recently, autologous fat grafting has come to be considered an ideal filler, as fat grafts are biocompatible, nonallergenic, nontoxic, easy to obtain, and synergistic with natural skin [3]. Neuber first reported the technique in 1893, followed by Illouz who then pioneered liposuction in the 1980s. In the modern day, Coleman demonstrated techniques for long-term fat graft stability [3]. Its first indications were for aesthetic surgery of the face, and

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more recently in hands [2]. Fat grafting is also useful for tissue loss due to an accident, operation, congenital disease, or lipodystrophy. In addition to a volumizing effect, the injected fat leads to neoangiogenesis, thereby improving the cutaneous elasticity. This technique is also used for wound healing, scar reduction, treatment of radiodermatitis, correction of acne scars, and breast reconstruction and augmentation in plastic surgery [2].

The main advantages of fat grafting include a long-lasting result, especially in comparison to the synthetic resorbable products, avoidance of granulomatous and allergic reactions that are often provoked by the more permanent (synthetic) products, a natural consistency, and improvement of cutaneous and subcutaneous trophicity [2].

Lipoaugmentation has become a staple in aesthetic medicine and surgery, and new technologies are continuously being introduced that support current clinical fat grafting efforts [3].

Effectiveness of Fat Transplantation

Autologous fat transfer offers many qualities of an ideal soft tissue filler. The success of fat grafting is thought to provide an abundant source of regenerative pluripotent cells, specifically adipocyte-derived stem cells (ADCs) [2]. These cells are able to integrate into host tissue and secrete important cytokines and growth factors including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGFβ) [4].

Transplanted fat requires contact with living tissue, and these grafts survive by diffusion until the process of neovascularization occurs. As such, one of the major drawbacks to this technique is a somewhat unpredictable long-term survival rate. Long-term results have been documented by operators practicing atraumatic harvesting and multilayer microdroplet infiltration [1]. However, there is difficulty in assessing longevity. First, there are no good objective measurement criteria available. We rely on photographs, but they are a two-dimensional representation of a three-dimensional result and are purposely chosen for their outcome. Second, patients who start with augmentation often supplement their results with other rejuvenation procedures, confounding the effect. Lastly, patients continue to age over the time they are in follow-up [1]. Lasting augmentation is most likely due to neovascularization of the adipocyte grafts; however, volume enhancement may also be caused by replacement fibrosis [1]. Although fat transplantation by structural principles presents a rationale for increased survival, it can occasionally prove to be unreliable, and patients need to be made aware of the often unpredictable nature of fat transplantation [1].

There is a single prospective study on the topic of fat graft longevity to the midface [5]. In this study, 66 patients were grafted with an average of 10 cc of fat using the modified Coleman technique. Using 3D image technology, the authors noted that 32% of the fat grafted to the midface was present at 16 months and concluded that the volumes required to make a visible change in midfacial rejuvenation are considerably less than originally anticipated (4) [5].

This unpredictable long-term survival rate has led to investigations into methods and techniques to increase fat viability and longevity [3].

Preoperative Evaluation

Assessment of the areas of facial atrophy is best accomplished while examining a young photograph. Since the idea that patients need to be filled and not cut is new, it helps to show them visually how they have aged [1]. The areas of future augmentation should be mutually agreed upon and documented. Patients with coagulopathies, a history of deep vein thrombosis, or warfarin intake are excluded. Connective tissue disease warrants caution since theoretically, transfer of an autologous material may stimulate an inflammatory response; however, this has not yet been described [1]. Patients must also be in overall good health with realistic expectations and

acceptance of the gradual sequential nature of the improvement [1]. The procedure works best in patients 30–50 years of age with enough anchoring recipient tissue. Patients with extreme atrophy or advancing age may have limited results or may require numerous transplant sessions [1]. Overweight patients with jowl and neck adiposity may need additional suctioning [1]. The patients should be educated on sun avoidance and textural and pigmentary alterations secondary to photodamage treated with appropriate modalities [1].

Azithromycin 500 mg is initiated on the day before the initial extraction/transplantation procedure and continued at a dose of 250 mg/day for 4 days. All nonsteroidal anti-inflammatory drugs should be discontinued 1 week prior, as well as vitamin E, St. John's Wort, and gingko biloba supplements. Patients should wear dark, loose clothing and bring a snug undergarment such as biking shorts for postoperative compression [1].

Best Techniques and Performance

The donor site should be picked from an area that can benefit cosmetically from fat removal. The outer thighs, buttocks, and abdominal fat have shown to possess the greatest lipogenic activity, and a concerted effort should be made to harvest from these sites [6]. Despite anecdotal reports of differing fat graft quality based on donor site, there are data to suggest no difference exists, as measured by a 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay, in grafts harvested from four of the most common donor sites: the abdomen, thigh, flank, and knee (4) [7]. Another study reviewed 73 patients who underwent fat grafting for breast reconstruction and showed no difference in longevity between fat harvested from the abdomen or thigh based on three-dimensional imaging (4) [8].

Fat extraction takes place with purely tumescent anesthesia using a modified Klein solution [1]. After prepping and draping the donor area, tumescent anesthesia is infiltrated by hand or pump in a manner previously described [9]. It is best to wait 20–30 min to allow even dispersion of the tumescent fluid and maximum anesthesia. Current practice suggests that the amount of lidocaine used be kept to a minimum, since it is toxic to adipocytes [10]. In actuality, the data regarding the effect of local anesthesia on adipocyte biology is somewhat conflicting. Lidocaine, used for local anesthesia, has been reported to inhibit the growth of adipocytes in culture and slow down glucose transport and lipolysis as evaluated by D-[U-carbon 14]-glucose and spectrophotometric determination of glycerol for lipolysis [11]. Prior studies also suggest that local anesthetic may slow adipocyte metabolism, growth, and viability. These findings only persisted while lidocaine was present. Once the lidocaine was removed, so too were its inhibitory effects [11]. More recent studies show no difference in fat treated with infiltrative anesthetic by counting the number of living fat cells in a 100× field (4) [12].

The cardinal principle of structural augmentation involves the atraumatic and gentle harvesting of intact fat cylinders. This is accomplished with a 3-mm open-tipped cannula attached to a 10-ml syringe. Most dermatologic practices avoid the use of suction machines in this procedure because they generate damaging negative pressures [1]. However, there is evidence to suggest that no difference exists in cell viability between syringe aspiration and liposuction-assisted aspiration. One study using human fat, grafted into severe combined immunodeficient mice, argued that there was no difference between a 10-cc syringe or a Byron liposuction pump when comparing the specimen weights and metabolic assays of 12-week-old graft explants (4) [13].

When using a syringe, the plunger of the syringe is withdrawn slowly 1 ml at a time. The to-and-fro motion of the open-bore cannula is enough to fill the syringe with clean yellow fat tissue. A total of 10–20 syringes are filled in this manner, depending on the projected volume and number of transplants required. The collected 10-ml syringes are then spun down in a centrally sterile centrifuge for 20 s to separate the fat cells from the triglycerides and tumescent fluid. Once done, the watery infranate is released from the syringe, and the fat is transferred to 1-ml syringes

with a 16-gauge female-female adapter, stopping short of the oily supernate [1].

The reported rates of fat cell survival vary greatly in the medical literature (10–90%). Different techniques of harvesting and processing the fat cells are so claimed to be responsible for these differences, without any agreement concerning the best way to process [2]. Various studies have assessed the impact of centrifugation on fat transfer, and most have concluded that, unless conducted at very high speeds, in vernal centrifugation does not adversely affect adipocyte viability (3b) [14, 15] Coleman et al. suggest 3000 rpm for 3 min, but 1 min of centrifugation is as efficient with less harm to fat cells [16].

Although many authors may advocate for one fat preparation protocol over another, there are no objective data to support these claims. There is in fact evidence to suggest no difference in graft outcome between several fat preparation protocols. Of note, a previously cited study found no difference in end graft survival of fat without treatment, with centrifugation, with washes of normal saline, with washes of lactated Ringer solution, and with combinations of centrifugation and washes, where graft survival was estimated using explant weights and with an XTT cell viability assay (3b) [13].

Many properties of fat begin to change after processing. Glycerol-3-phosphate dehydrogenase activity, which is a measure of adipocyte destruction, increases linearly until 4 h [3]. Stem cells can be harvested up to 4 h at room temperature and up to 24 h at 4 °C [17]. Therefore, although fat preparation protocols may vary from one operator to another, there is evidence to support the notion that fat transfer should be undertaken as soon as possible after harvesting [3].

After extraction and preparation of the fat, the patient is placed in an upright position and the areas requiring augmentation sketched onto the skin with a sterile marking pen. The face is then prepped with an antiseptic wash and the table reclined. Facial anesthesia is in the form of blocks and local infiltration to effectively cover all the planned areas of augmentation. Entry sites are most often made with an 18-gauge Nokor needle tip in areas affording access and are best hidden at the hairline and in the base of rhytides. All infiltration is by way of a blunt cannula [1]. The large diameter ensures that the fat may pass in intact tissue parcels, and the blunt end prevents perforation or tearing of underlying structures [1]. There are experimental data supporting the notion that low-shear devices maintain fat structural integrity. Specifically, one study used computed tomographic (CT) volume measurements at 4 weeks to show a significantly increased fat viability and significantly lower lipolysis with a low-shear device [18]. This same study noted significantly higher fat volume retention in addition to healthier appearing fat on histologic evaluation in an animal model after delivery through a low-shear device (5) [18].

Optimal cannula diameter for fat injection is a minor topic of debate. One particular study found viability to be greatest with use of a 2.5-mm (~10–11 gauge) cannula compared with smaller cannulas as evaluated by counting live cells using a hemocytometer under 40× magnification [18]. The authors concluded that by increasing the diameter of aspiration and injection cannulas, trauma is minimized and viability and graft survival are improved (5) [18]. Another study stated the best results were achieved with the no. 14 cannula, as compared with smaller ones [19]. A third study found no difference between 14-, 16-, and 20-gauge cannulas. In this study, viability of the fat grafts was evaluated by fat cell isolation with collagenase digestion and staining and subsequently counted with a hemocytometer (5) [20].

During injection, the fat is deposited in minuscule strands of less than 0.1 ml amounts on the withdrawal phase of the motion [1]. The fat is woven in a three-dimensional design starting at the most stable plane (next to bone when available) and working up through the subcutaneous fat. Every attempt should be made to place the fat in virgin tunnels, avoiding excessive positive pressure on the syringe and globular deposits [1]. If at any time the infiltrator becomes clogged, it should be withdrawn and cleared. The purpose of this is to anchor the fat and allow enough room

between adipocytes for survival through respiratory diffusion [1].

Safety

Patients need to consent to all possible developments before the procedure. Expected sequelae are bruising and edema lasting 2–10 days, depending largely on the aggressiveness of the augmentation. Pre-icing as well as post-icing of the face and intramuscular betamethasone decrease this side effect. Other possible complications include local infection, asymmetry, lumpiness and fat cysts, entry site scars or discoloration, perforation of the orbital septum, marginal mandibular injury, parotitis, and reabsorption of fat. Most if not all of these can be avoided with experience and conservative, meticulous technique [1].

Postoperative Care and Follow-Up

Since the conditions favorable to fat cell survival are poorly understood, repeat staged transplants give an added advantage by providing more chances for the fat to take, and healing from initial treatments may increase vascularity and fibrosis in the recipient tissue [1].

Initial transfer procedures use 15–30 ml of the freshly harvested fat. The extra fat syringes are then labeled with name, date, and social security number and stored in a plasma freezer at 30° C. Patients return for additional augmentation procedures at 4–6-week intervals over the course of a year. At these visits, 8–12 ml of fat is placed in areas requiring further augmentation, adhering to the placement principles described above. There is usually no downtime from these smaller treatments, and the patient can put on makeup right after the session and return to work. Viability of thawed adipocytes has been previously demonstrated, and many believe that frozen fat "takes" better than fresh fat [10]. This may be due to dehydration of the tissue with freezing, leaving a more concentrated adipocyte suspension [1].

Alternative Procedures and Modifications

Animal models have proven that a number of tissue scaffolds can improve the longevity of grafted fat. One group of authors used a recently reported protocol to suspend harvested fat in Growth Factor-Reduced Matrigel (BD Biosciences, San Jose, Calif.) [21]. This biological matrix has been shown to improve early angiogenesis [22]. It has also been hypothesized that suspending the purified cells in the resorbable matrix helps to optimize graft viability by meeting the high metabolic demand of lipocytic tissue. This procedure was tested in a murine model that compared harvested fat alone to harvested fat suspended in Growth Factor–Reduced Matrigel. The matrix-assisted fat showed greater maintenance of volume and adipocyte cellularity at 3 months (5) [21].

Although there are numerous studies that focus on improving the harvest and preparation of fat, the recipient site is often forgotten when attempting to optimize the outcome. Microneedling has been proven beneficial in increasing skin vascularity and skin quality, but there have been few studies specifically investigating whether this technique is beneficial for increasing fat graft survival [3]. However, one study showed significantly more vascularity, higher graft survival, and better graft integrity with less fibrosis (by histomorphometric and immunohistochemical evaluation) after preconditioning with microneedling 1 week before grafting in an animal model (5) [22].

Again, there is no consensus concerning the best way to process the harvested fat before reinjection. Based on the recent literature, adding platelet-rich plasma (PRP) to fat preparation may be a means of improving fat survival and rendering a more predictable result [2]. Platelets work via the degranulation of their α-granules, which contain synthesized and prepacked growth factors [3], the most potent ones being PDGF, TGFβ, IGF, VEFG, and endothelial growth factor (EGF). Released growth factors stimulate angiogenesis, cell differentiation, and proliferation, leading to

the reconstitution of the tridimensional matrix that allows the rearrangement of adipocytes into the correct 3D organization. This approach is completely autologous and immediately employed without any type of in vitro preconditioning or media complement [2].

The benefit and safety of PRP are documented in more than 5000 studies where the authors observed enhancement of bone regeneration [23–25], wound healing [26–28], tendon and cartilage healing [29–31], corneal healing [32], and skin rejuvenation [33]. PRP is so used more and more often in the plastic, reconstructive, and aesthetic surgery fields [34–36].

In a series of in vitro studies, it has been demonstrated that PRP increases fat cells' survival rate and stem cells' differentiation [34, 37]. One study showed that fat graft survival rates were significantly increased in rats treated with PRP (4) [38]. There are also some successful cases of facial reconstruction with fat grafting and PRP [39], and this association has also been described for aesthetic cases [2].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	Grade score: quality of evidence
Evidence does not support that abdominal fat demonstrates superior viability to that of other anatomic areas	C
Evidence does not support that infiltrative anesthesia affects the viability of fat from donor sites	C
There is limited evidence to support that liposuction pump aspiration yields fat as viable as that by syringe aspiration	D
There is no evidence to support that washing or centrifugation of fat improves graft survival	B
Evidence does not support an optimal cannula or needle diameter for fat reinjection	C
There is some evidence to support that injecting fat with a low-shear device preserves fat integrity	D
There is evidence to support that fat should be injected as soon as possible after harvesting	D
There is some evidence to support that the viability of thawed adipocytes is better than that of fresh fat	D
There is evidence to support the long-term efficacy of fat grafting to the midface	C
There is evidence to support tissue engineering techniques for improving fat longevity	D
There is some evidence to support that preconditioning the recipient site improves fat graft survival	D
There is evidence that demonstrates that PRP increases fat cell survival rates	C
There is no gold standard that exists for quantifying fat viability after transplant	N/A

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Self-Assessment Questions

1. Which of the below is false?
   Repeat staged transplants give an added advantage by:
   (a) Providing more chances for the fat to take
   (b) Increasing vascularity in the recipient tissue
   (c) Increasing fibrosis in the recipient tissue
   (d) Increasing elasticity in the recipient tissue
   (e) Decreasing fibrosis in the recipient tissue
2. Which of the below are true?
   The main advantages of fat grafting include:
   (a) A long-lasting result
   (b) Avoidance of granulomatous reactions
   (c) Avoidance of allergic reactions
   (d) A natural consistency
   (e) Improvement of cutaneous and subcutaneous trophicity
   (f) All of the above
3. The success of fat grafting is based largely on the provision of an abundant source of regenerative stem cells, specifically:
   (a) Embryonic stem cells
   (b) Pluripotent stem cells
   (c) Hematopoietic stem cells
   (d) Epidermal stem cells
   (e) Epithelial stem cells
4. Lasting augmentation is most likely due to:
   (a) Fibrosis of the adipocyte grafts
   (b) Neovascularization of the adipocyte grafts
   (c) Stimulation of neoadiposity
   (d) Nature of underlying facial anatomy
   (e) Inosculation of the grafts
5. Which are absolute contraindications to autologous fat transfer? (Can pick more than one)
   (a) History of coagulopathies
   (b) History of deep vein thrombosis
   (c) Current use of warfarin
   (d) Current use of statin drug
   (e) Diabetes

Correct Answers

1. e: Since the conditions favorable to fat cell survival are poorly understood, repeat staged transplants give an added advantage by providing more chances for the fat to take, and healing from initial treatments may increase vascularity and fibrosis in the recipient tissue.
2. f: The main advantages of fat grafting include a long-lasting result, especially in comparison to the synthetic resorbable products, avoidance of granulomatous and allergic reactions that are often provoked by the more permanent (synthetic) products, a natural consistency, and improvement of cutaneous and subcutaneous trophicity.
3. b: The success of fat grafting is based largely on the provision of an abundant source of regenerative pluripotent cells, specifically adipocyte-derived stem cells (ADCs). These cells are able to integrate into host tissue and secrete important cytokines and growth factors including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGFβ).
4. b: Lasting augmentation is most likely due to neovascularization of the adipocyte grafts; however, volume enhancement may also be caused by replacement fibrosis.
5. a, b and c: Patients with coagulopathies, a history of deep vein thrombosis, or warfarin intake are excluded from autologous fat grafting procedures. Connective tissue disease warrants caution since theoretically, transfer of an autologous material may stimulate an inflammatory response; however, this has not yet been described. Patients must also be in overall good health with realistic expectations and acceptance of the gradual sequential nature of the improvement.

38

Soft Tissue Augmentation (Temporary Injectable Fillers) of the Upper Face (Cheeks, Brow, Forehead, Ear)

Sue Ellen Cox and Christie Regula

Abstract

Facial aging is a multifactorial process that is caused by changes in the skin, fat compartments, and underlying bony elements. Temporary injectable fillers are commonly used to improve the appearance of the aging face by restoring lost volume, smoothing rhytides, reducing skin laxity, and improving facial contouring. These fillers include hyaluronic acid, poly-L-lactic acid, and calcium hydroxyapatite. Filler selection is important for a successful treatment outcome, as is the pre-treatment evaluation, procedure technique, and follow-up care. This chapter specifically reviews the use of temporary injectable fillers for treatment of the upper face including the cheeks, brow, forehead, and ear. A thorough understanding of upper facial anatomy and other specific considerations are important to maintain a good safety profile and obtain excellent results in this region.

Keywords

Injectable fillers · Soft tissue augmentation Filler safety · Filler effectiveness · Upper face fillers · Temporary fillers · Soft tissue augmentation

Indications for Soft Tissue Augmentation

Temporary injectable fillers are most commonly used to add volume to the upper face. Here, they can restore lost volume, smooth rhytides, reduce skin laxity, and improve facial contouring. In most cases, the changes we wish to correct are secondary to facial aging. Facial aging is a multifactorial process that is caused by changes in the skin, fat compartments, and underlying bony elements. Understanding these individual changes is important to effectively use injectable fillers for facial rejuvenation.

Skin

A decrease of types I and III collagen is a characteristic feature of aged and photodamaged skin [1]. This loss of fibrillar collagen leads to skin laxity and rhytides. Cross-linked hyaluronic acid, poly-l-lactic acid, and calcium hydroxyapatite, common dermal filler components, have all been shown to stimulate collagen synthesis, partially

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restoring dermal matrix components that are lost in aging and photodamaged skin [2–4].

Adipose

Cadaver dissections have shown that the facial adipose system is divided into discrete anatomic compartments that are separated by fibrous membranes [5]. Volume loss and redistribution of fat within the compartments, and migration of these compartments, contribute to the aged appearance [6]. These differential changes are quite noticeable in the periocular and cheek regions.

The orbital septum holds two upper eyelid fat pads (nasal and central) and three lower eyelid fat pads (nasal, central, and lateral) in place within the orbit. Superiorly, the retro-orbicularis oculi fat pad (ROOF) lies under the brow (Fig. 38.1). Inferiorly, the suborbicularis oculi fat pad (SOOF) lies over the malar eminence and is separated from the lower eyelid fat pads by the orbitomalar ligament (Fig. 38.2). Soft tissue is lost along ligaments as one ages; loss along the orbitomalar ligament at the infraorbital rim creates a depressed tear trough. As the orbital septum weakens, the periocular fat pads can herniate forward, resulting in a puffy lid and accentuation of the tear trough.

The cheek has both superficial and deep fat compartments. The superficial fat compartments include five fat pads: the lateral-temporal, middle cheek, medial cheek, nasolabial, and labiomandibular, which are separated by retaining ligaments. The suborbicularis oculi, malar, maxillary, and buccal comprise the deep fat compartments. These are listed superficial to deep, with the deepest lying on the buccinator muscle. Computed tomographic scans examining the midfacial fat compartments reveal that over time, the deep fat compartments, namely the medial cheek and buccal, lose volume. Additionally, an inferior shift of both the fat within these compartments and the compartment itself leads to contour changes of the face and a "bottom heavy" appearance [6].

Bone

The skeletal morphology of the face changes with age, namely by an overall decrease in

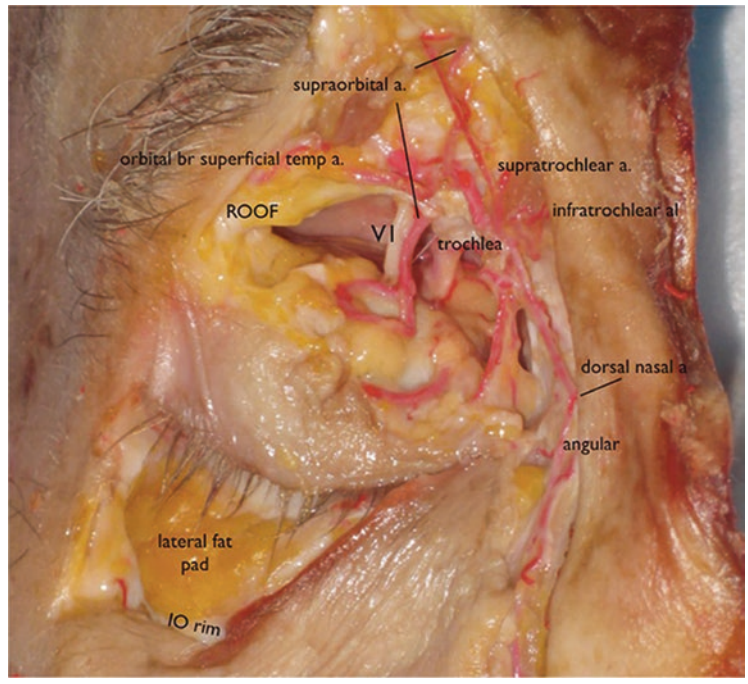

Fig. 38.1 Dissection of the supraorbital region revealing fat pads, vasculature, and innervation. (Anatomical figure courtesy of Julie Woodward, MD)

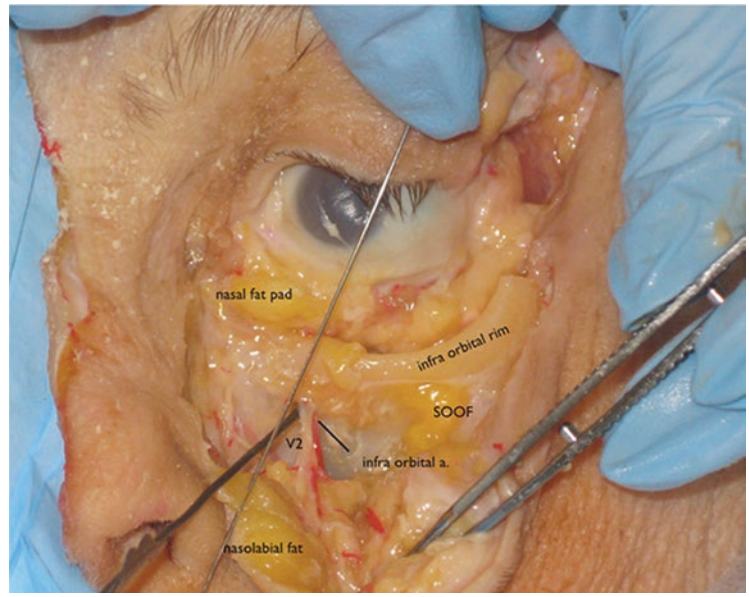

Fig. 38.2 Dissection of the infraorbital region revealing fat pads, vasculature, and innervation. (Anatomical figure courtesy of Julie Woodward, MD)

volume. Computed tomographic scans of 120 subjects objectively characterized these specific changes [7]. The superomedial and inferolateral aspects of the orbital rim resorb over time. This loss of bony volume results in a change of brow position and contributes to the formation of a nasojugal groove. The glabellar angle also decreases, due to bony resorption of the frontal bone and may contribute to brow ptosis and lateral orbital hooding. Results also showed a decreased maxillary angle, which represents a decrease in the height of the maxilla. This volume loss and decreased angle may be responsible for downward and forward movement of the medial and middle cheek fat pads. Overall, the loss of facial skeletal volume results in decreased structural support and projection of the overlying soft tissue.

Effectiveness of Soft-Tissue Augmentations

In 1981, bovine collagen was the first filler to gain FDA approval, and it remained the only FDA-approved filler for over two decades. In several formulations, it was used to treat fine lines, shallow scars, and fill deeper rhytides and folds. It also had several drawbacks including two prerequisite skin tests to minimize allergic reactions and a short duration of less than 3 months. These prompted the development of newer filler materials; most collagen fillers have not been available in the United States since 2010.

In 2003, the first hyaluronic acid (HA) filler was approved for use in the United States. Hyaluronic acid is the most prominent glycosaminoglycan in the skin and, therefore, has a very low allergic potential. It also effectively restores volume loss and is longer lasting than collagen fillers. In fact, since 2003 more than ten hyaluronic acid fillers have been approved by the FDA.

In 2005, poly-L-lactic acid (PLLA) was FDA approved for the treatment of HIV-associated lipoatrophy. This is a synthetic, biodegradable, immunologically inert peptide polymer that serves as a dermal stimulating agent [8].

In 2006, calcium hydroxyapatite (CaHA) was approved for the correction of HIV-associated facial lipoatrophy and in 2009 for correction of facial rhytides and folds in non-HIV patients. This product contains 30% CaHA microspheres and approximately 70% gel carrier. This combination of CaHA provides a filling effect as well as scaffolding for new collagen formation [9].

All of the above mentioned filler materials have been shown to stimulate new collagen formation [4]. This stimulation contributes to the effectiveness of dermal fillers in the upper face, as does the type of filler and injection technique. We will discuss the specific uses, effectiveness, and duration of individual fillers later in this section.

The choice of filler to be used in a particular area influences the effectiveness of the treatment. The three most common fillers, as mentioned previously, are hyaluronic acid, calcium hydroxyapatite, and poly-L-lactic acid. The distinction between these fillers is not only the material that they are made of but also the biophysical properties of the filler. Rheology is the study of flow-related properties and helps us better characterize and understand the differences between fillers.

Several rheologic properties of fillers are important to consider when choosing the appropriate filler for a specific purpose. G prime (G') is the elastic (storage) modulus, which is a measurement of gel stiffness and its ability to resist deformation. The higher the G', the less the filler deforms under pressure which is useful for areas where a "lift" is desired. Viscosity (η) measures the filler's ability to resist shearing forces, those that occur both during and after filling. The lower the viscosity, the less force the filler takes to inject, the easier it flows through the skin, and the easier and more likely it is to spread/mold. For example, lower viscosity filler is useful for filling the nasolabial folds. Cohesivity relates to the cross-linking of the filler molecules and the gel's ability to resist vertical compression to maintain the shape of the gel. Fillers with high cohesivity are especially useful in the midface because they can maintain the outward projection of the cheeks and have a low risk of filler migration. The cohesivity of hyaluronic acid (HA) fillers can also be described as monophasic or biphasic. Monophasic fillers contain homogenous microspheres, while biphasic fillers contain a range of microsphere sizes. Monophasic HA fillers are more cohesive and may not migrate as much following injection. A comprehensive rheologic summary of common fillers is found in Table 38.1.

Table 38.1 Rheologic properties of temporary injectable fillers

Product (Manufacturer)	Cross-linking Technology	G' (Pa)	Viscosity (η or μ)	Concentration (mg/mL)	Cohesivity[a]
Restylane®-L (Galderma Laboratories, LP)	Biphasic, BDDE	565	131,310	20	1.3
Restylane® Lyft (Galderma Laboratories, LP)	Biphasic, BDDE	549	127,090	20	1.7
Restylane® Silk (Galderma Laboratories, LP)	Biphasic, BDDE	344	–	20	–
Restylane® Refyne (Galderma Laboratories, LP)	XpresHAn Technology	–	–	20	–
Restylane® Defyne (Galderma Laboratories, LP)	XpresHAn Technology	–	–	20	–
Juvederm® Ultra XC (Allergan, Inc)	Monophasic, monodensified, Hylacross, BDDE	28	7307	24	4.9
Juvederm® Ultra Plus XC (Allergan, Inc)	Monophasic, monodensified, Hylacross, BDDE	75	17,699	20	–
Juvederm® Voluma (Allergan, Inc)	Monophasic, monodensified, Vycross, BDDE	274	92,902	20	2.4
Juvederm® Volbella (Allergan, Inc)	Monophasic, monodensified, Vycross, BDDE	160	–	15	19
Belotero Balance® (Merz Aesthetics)	Monophasic, polydensified, CPM, BDDE	30	9217	22.5	5
Radiesse® (Merz Aesthetics)	n/a	1407	349,830	n/a	n/a
Radiesse® (+) Lidocaine (Merz Aesthetics)	n/a	1165	310,305	n/a	n/a

Abbreviations: *BDDE* 1,4-butanediol diglycidyl ether, *CPM* cohesive polydensified matrix
[a]Cohesivity on the Gavard-Sundaram Cohesivity Scale

Effectiveness of Individual Fillers

Hyaluronic Acids

Restylane®

Restylane® and Restylane-L® are FDA-approved for correction of nasolabial folds and lips. A split face study comparing the efficacy of Restylane® to collagen in correcting the nasolabial folds included 138 subjects and showed Restylane® provided superior results in the majority of patients [10]. This result persisted the entire duration of the 6-month study. Restylane® can also be effective off-label in treatment of the temples, glabella, and infraorbital folds [11–18].

Restylane® Lyft

Formerly marketed as Perlane®, Restylane® Lyft was originally FDA-approved in 2010 for correction of moderate to severe facial folds and wrinkles, such as the nasolabial folds. It has more recently also been approved for cheek augmentation and the correction of age-related midface contour deficiencies. A split face study including 68 patients comparing the efficacy of Perlane® to collagen in correcting the nasolabial folds showed Perlane® provided superior results in the majority of patients through 6 months [19]. The first study ($n = 40$) looking at the efficacy of Perlane® for treatment of midface volume and contour correction showed a 97.5% initial response rate [20]. An open-label, evaluator-blinded, randomized controlled trial examined the efficacy of Restylane® Lyft for correction of midface volume deficit or contour deficiency in 200 subjects. Periosteal injections of the midface were performed with 89% of treated subjects having initial improvement in the midface and 85% of treated subjects maintaining a global aesthetic improvement at 12 months [21]. Restylane® Lyft has also shown to be effective in off-label treatment of the temples and tear toughs [22, 23].

Restylane® Silk

Restylane® Silk was FDA-approved in 2014 for lip augmentation and correction of perioral rhytides. The original clinical trial of 221 subjects showed improvement in lip fullness and perioral rhytides at 8 weeks with the majority of patients maintaining an improvement at 6 months [24]. Off-label use of this product has been anecdotally reported in the forehead, periorbital rhytides, glabella, and infraorbital hollows [25].

Restylane® Refyne

Restylane® Refyne was FDA-approved in 2016 for the treatment of moderate to severe facial wrinkles and folds. In the pivotal clinical trial of 170 patients, Restylane® Refyne was used to correct moderate to severe nasolabial folds. At 6 months, improvement in nasolabial folds with Restylane® Refyne was observed in 78.8% of subjects. At 1 year, 62.3% of treated folds maintained improvement [26]. An 18-month follow-up, randomized comparison between Restylane® Refyne and Restylane® in treatment of the nasolabial folds showed no difference in the effectiveness, safety, or patient preference between the two fillers [27].

Restylane® Defyne

Restylane® Defyne was FDA-approved in 2016 for the treatment of moderate to severe, deep facial wrinkles and folds. In the pivotal clinical trial of 162 patients, Restylane® Defyne was used to correct moderate to severe nasolabial folds. At 6 months, improvement in nasolabial folds with Restylane® Defyne was observed in 77.1% of subjects. At 1 year, 69.7% of treated folds maintained improvement [28].

Juvederm®

The Juvederm® family of fillers was first approved in 2006 for the correction of nasolabial folds; this included Juvederm® Ultra and Juvederm® Ultra Plus. A multicenter, double-masked, randomized trial of 439 comparing both fillers to Zyplast collagen for correction of nasolabial folds showed both Juvederm® products to be effective in correcting the nasolabial folds, and 81–90% of those treated with Juvederm® Ultra and Juvederm® Ultra Plus maintained their results for 6 months or more [29, 30].

Juvederm® Voluma

Juvederm® Voluma XC was FDA-approved in 2013 for deep injection for cheek augmentation. In a multicenter, single-blinded, controlled study

of 235 subjects treated with Juvederm® Voluma for midface augmentation, 85.6% of the treatment group had significant improvement at 6 months, and nearly half of the subjects maintained correction for 24 months [31, 32]. This filler has also been described for off-label use in forehead reflation [33].

Juvederm® Volbella

Juvederm® Volbella was FDA-approved in 2016 for lip augmentation and correction of perioral rhytides and was shown to last up to 12 months in a prospective, multicenter, open-labeled study ($n = 60$) [34].

Belotero Balance®

Belotero Balance® was approved by the FDA in 2011 for the correction of moderate to severe facial wrinkles and folds. Two original studies showed the superiority of Belotero Balance® to collagen in correction of nasolabial folds. The first study showed correction to be maintained at 6 months ($n = 118$). The second long-term, open-label study ($n = 95$) showed that the effects of Belotero Balance® persisted in the majority of subjects without repeat treatment for at least 48 weeks [35, 36]. Belotero Balance® has also been shown to be effective off-label in treating the infraorbital folds, fine lines of the perioral region, and glabella [37].

Poly-L-lactic acid (PLLA)

Poly-L-lactic acid (PLLA), Sculptra®, was FDA-approved in 2005 for the treatment of HIV-associated lipoatrophy and in 2009 for the correction of nasolabial folds and facial rhytides. Its effectiveness in panfacial re-volumizing and correction of the nasolabial folds can last up to at least 2 years [38–41]. It has also been effective off-label in correction of hill and valley acne scarring, cheeks, and temples [42, 43].

Calcium Hydroxyapatite

Calcium hydroxyapatite (CaHA), Radiesse®, was approved by the FDA in 2006 for the correction of HIV-associated facial atrophy based on an open-label 18-month trial of 100 subjects that showed 100% of the patients had improvement at 3 months and 91% had improvement at 18 months [44]. In 2009, it was also approved for correction of moderate to deep lines and folds, such as nasolabial folds, based on a pivotal trial that compared Radiesse® to collagen ($n = 117$). At 6 months, 82% of CaHA patients showed improvement compared to 27% of collagen patients [45].

Preoperative Evaluation

Patient selection and evaluation is the first step in obtaining a successful outcome. Patients with variable amounts of bone and fat loss who maintain good skin elasticity are better candidates than those with severely sun-damaged skin or extreme skin laxity. The latter may be better suited for skin resurfacing or surgery. The patient interview and clinical examination are used to identify appropriate candidates for treatment. The assessment should begin with a review of the patient's medical history including history of previous fillers (temporary or permanent), prior cosmetic procedures, bleeding disorders or immunosuppression, current medications (particularly anticoagulants), allergies, and history of anaphylaxis. Contraindications should be reviewed; these include active infection near the treatment site, allergy to product components and pregnancy. With the longer-lasting fillers such as those with Vycross technology (Voluma, Vobella, Volift, Allergan Santa Barbara, Ca), a history of recent or near future dental work, chronic infections, or any procedure that potentially sheds bacteria into the bloodstream should be ascertained as this has been implicated as a potential risk factor for soft tissue fillers [46, 47].

During the consultation, the medical history regarding both prescription and over-the-counter medications and herbal and vitamin supplements should be reviewed. Substances that are known blood thinners such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be discontinued 7–10 days in advance to help diminish the risk of bruising. Supplements to be avoided for 1 week prior to injections include garlic, ginger, ginseng, gingko biloba, kava, celery root, fish oils, St John's Wort, vitamin E

(1,000–2000 IU /day), and glucosamine/chondroitin [48]. The patient should avoid these medications for 4–5 days post procedure if bruising is visible within 48 hours post procedure. Moderate doses of alcohol have been associated with inhibition of platelet activation and vasodilatation, so it should also be avoided pre- and post procedure [49]. In regard to therapeutic use of known anticoagulants, such as patients with a history of heart attack, stroke, or blood clot, it is recommended that these patients stay on their medications as the risk of going off outweighs the potential for a bruise [50]. Medications that may reduce bruising including Arnica, Arnica Montana, bromelain, and vitamin K topically should be at the discretion of the treating physician. Evidence is anecdotal and studies have been inconclusive [51–53].

The author (SEC) recommends that the patient curtails exercise for 48 hours after injections to help diminish bruising and swelling. Additionally, patients should be encouraged not to schedule treatments when they have important social functions within 7–10 days in case of bruising. Patients are asked to present to the clinic with a clean makeup-free face on the day of the procedure, so that the photographs are consistent and show the patient's natural appearance. This is also important for appropriate skin prep to minimize the potential for implantation of foreign material into the skin, which could increase the risk of infection or biofilm [54].

Photography and skin prep are important preprocedural considerations. Pre- and postprocedural photographs should be taken to document the clinical improvement for the physician's chart records and to demonstrate the improvement to the patient. The physician only has one opportunity to obtain an excellent pretreatment photo, so this is of critical importance. This photograph will be used as the standard to which all future treatments are compared. It will also document any pre-existing asymmetries. These photos need to be standardized and should be taken with the same camera, at the same angles, at the same distance with the same lighting to reduce any variables. Physicians may choose to implement three-dimensional photography as it allows the patient and physician the ability to visualize the shadows and contours that are corrected with fillers.

Skin prep is important with the advent of longer lasting fillers. To date, there have been no data with specific, universal guidelines on the appropriate method of prepping the skin for injections of soft tissue fillers. Benzalkonium chloride has been recommended [55]. Without data specific to soft tissue fillers, it is useful to consider prior publications regarding clinical experience with surgical procedures [56]. A prospective study of 849 patients undergoing nonfacial, "clean-contaminated" surgery (GI, urologic, and gyn) showed that chlorhexidine-alcohol was more effective than povidone-iodine [57]. General guidelines for reduction of healthcare-associated infections include skin antisepsis using 2% chlorhexidine gluconate in 70% isopropyl alcohol [58]. Chlorhexidine should not be used in the periorbital area due to the risk of keratitis and ocular injury. Avoidance of facial skin exposure to tap water in the periprocedural time frame is also prudent. Rodriguez et al. reported cases of *Mycobacterium chelonae* infection after cosmetic dermal injections of hyaluronic acid. The root of infection was traced to ice cubes used at the injection site. The organisms grown from the patient's culture matched the isolates from the faucet and tap water at the clinical site [59]. Patients can be instructed to wash their face with cleansing wipes, not in the sink, and to avoid reapplication of makeup for several hours posttreatment [60].

Anesthesia can be adequately achieved either with topical or regional nerve blocks. Topical products are used in our office with application 10–15 min prior to injections. SEC prefers Pliaglis (Galderma, Fort Worth TX) as it is the one of the few prescription-strength topical anesthetic creams that is currently FDA-approved. It contains a eutectic mixture of 7% lidocaine and 7% tetracaine and forms a pliable peel on the skin when exposed to air. Many physicians use the compounded higher concentration products, such as BLT (benzocaine, lidocaine, tetracaine); however, there have been reports of lidocaine toxicity when using high concentrations of compounded

products when applied to larger areas. Compounding may decrease product consistency depending on the compounding pharmacy. Less commonly, regional nerve blocks can also be used to achieve adequate anesthesia. A full discussion of the relevant anatomy and injection technique is found in another chapter in this text.

Informed consent is an important aspect to the pre-procedure process. Realistic expectations for treatment outcomes must be thoroughly discussed with patients. Optimal patient satisfaction is dependent on fulfilling the patient's expectations and the technical skill of the injector. This is particularly relevant with soft tissue fillers since the amount of product used can substantially affect the results. Informed consent should detail the risks, benefits, alternatives, and potential complications associated with treatment. The relative infrequency of specific complications should be communicated, but the consequences of complications should not be minimized.

Immediately after the procedure, the most common side effects include slight redness and swelling at the injection sites. Patients should also be reminded that bruising may occur, and we instruct them to avoid exercise for 1–2 days to help minimize this bruising and swelling. We also offer pulse dye laser to help expedite the resolution of the bruise. Follow-up visits are done at 2–4 weeks post procedure for photographs and potential "top off" filler to attain complete correction. Additional future visits will be scheduled depending on the longevity of the filler.

Best Techniques and Performance

The only upper face area that is FDA-approved for injection is the midface, including the anterior cheek, the lateral zygoma, and the submalar hollows. Aging of the midface is characterized by volume loss of the lower eyelid and cheek complex. The lower eyelid region is often referred to as the tear trough or nasojugal fold. This area is contiguous with the upper cheek; therefore correction of both cosmetic units is necessary for harmony of the upper face. Injection practices vary depending on the injector, the filler, and the area to be corrected. It is helpful to have a 3D mental picture of what you are trying to accomplish with reinflation. Experienced injectors will choose high G' fillers using a vertical supra-periosteal depot technique (VSDT) (Fig. 38.3) or the tower technique (TT) (Fig. 38.4) along the lateral zygoma to achieve maximum projection. Treatment of the anterior cheek is best accomplished with a cannula to help prevent intravascular injection. Below the infraorbital rim, the infraorbital artery and nerve exit 8–9 mm beneath the infraorbital rim between the pupil and the medial aspect of the iris. The same high G' product is used to give lift to the anterior cheek. A

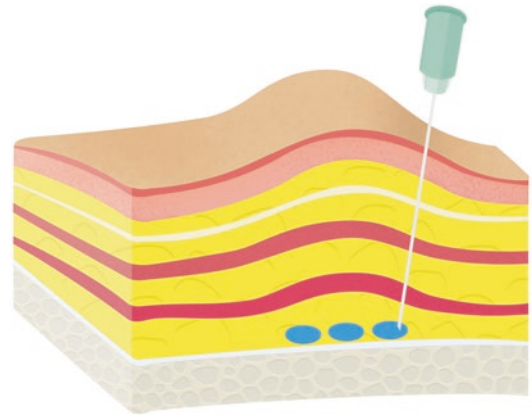

Fig. 38.3 Vertical supra-periosteal depot technique

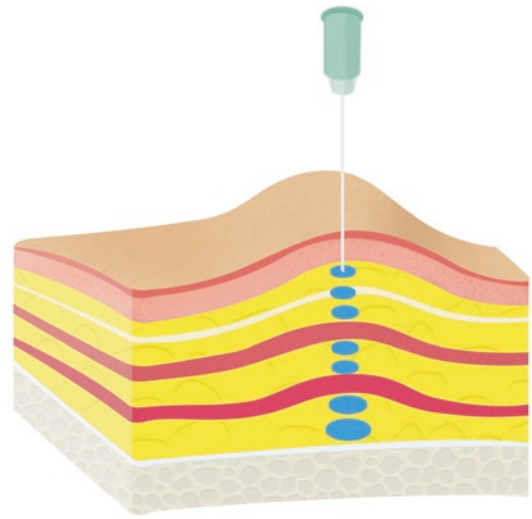

Fig. 38.4 Tower technique

pre-periosteal approach is the preferred depth, and resistance may be felt as the cannula pops through the zygomatic-cutaneous ligament. After the ligament is partially released, a layer of filler is injected beneath the muscle on the periosteum. The final cheek unit to be injected is the submalar hollow. This area is best injected with a lower G' product or reconstitution of the same product with saline to achieve enhanced spread. A longer needle or cannula using a fanning technique subcutaneously can help avoid contouring irregularities. According to the global aesthetic consensus group, no single injection technique, needle vs cannula, ensures complete safety. However, panelists recommended blunt cannulas in areas at higher risk for vascular complication [58]. (CR,PS) Injection of volumizers in the midface has changed the paradigm of facial injections. Replacing lost volume in the cheek area has led to improvement in the lower eyelid region and the nasolabial folds.

Tear trough depression or nasojugal folds are often improved with cheek injection; however, additional augmentation with soft tissue fillers may be necessary to eradicate the unwanted shadows. With the aging process, expansion of the anterior orbital aperture occurs along with atrophy of the orbitomalar ligament and periorbital fat atrophy, hypertrophy, and herniation [61]. Injections are usually done in the pre-periosteal plane along the orbitomalar ligament. A low G' filler that is not hydrophilic is the recommended product of choice. Hylacross technology (Allergan, Santa Barbara, CA) is to be avoided as it has a tendency to produce edema [58]. Injections are done with the patient in a neutral gaze. Upward gaze will produce prolapse of the fat pads and distort the area to be injected. Needles or cannulas can be used when injecting; the lower lid skin can be retracted to reveal 3–5 vertically running veins that should be avoided. Placement horizontally on the pre-periosteal plane can be done either antegrade or retrograde. Others prefer to inject from a point beneath the infraorbital rim fanning the product in a vertical fashion [62].

The brow or ROOF, retro-orbicularis oculi fat, can be re-inflated if it is atrophic. This will result in a beautiful full brow contour and anterior projection in appropriate patients. Care must be taken to inject conservatively to prevent the appearance of a heavy brow. The orbital branch of the superficial temporal artery courses through or above the brow to anastomose with the supraorbital artery. Cannulas may be preferred in this area to avoid the artery [62].

The superior sulcus becomes hollow as fat atrophies in the superior orbit in some patients. "A-frame deformity" refers to atrophy that occurs under the superior-orbital (SO) notch. Aliquots of 0.1–0.2 cc of hyaluronic acid filler placed with a cannula directly under the SO notch is considered an advanced technique [63].

Temples are often injected to produce a youthful facial frame. Temporal volume loss creates a skeletonized shadowing. Poly-L-lactic acid (PLLA) Sculptra® (Galderma Laboratories) and longer lasting HA fillers such as Juvederm® Voluma (Allergan, Irvine, CA) and Restylane® Lyft (Galderma Laboratories, Fort Worth, TX) are often used off-label to treat this area. There are a number of techniques described for filling this area; however, the most important point for safe injection is to inject in a supra-periosteal plane deep to the temporalis muscle. The frontal branch of the superficial temporal artery anastomoses with the supraorbital artery in a subdermal plane. The middle temporal vein (MTV) runs above the temporalis muscle therefore injections must be deep to the temporalis muscle to minimize a potential intravascular injection which could result in blindness [64]. Jung et al. investigated the course and diameter of the middle temporal vein by dissecting 18 cadaver hemifaces [65]. Based on this study, they concluded that the safest area for filler injection in the temporal fossa is one finger width above the zygomatic arch. Additionally the MTV was located superficially in the subcutaneous space; this provides additional rational for supra-periosteal injection [65]. Swift's technique of "1 up 1 over" refers to identifying the temporal fusion line and the lateral supraorbital rim and treating at the intersection 1 cm lateral to the temporal fusion line and 1 cm superior to the supraorbital rim [68]. Palpate to make sure the injection is not

occurring over the arterial pulse. The needle is then inserted perpendicular to the skin penetrating to the periosteum. Aspiration is recommended [58] although the lack of visible blood in the syringe does not rule out an intravascular placement because thin vessels can collapse upon retraction [66]. Typical volume of filler needed will depend on the muscle and fat wasting. Blunt cannulas can be used if a subcutaneous approach is performed; however, irregularities of the skin surface may be more likely with this approach [67]. An additional benefit of re-volumizing the temple is lateral eyebrow elevation.

The forehead is an often under-recognized area for filler injections. Volume loss in the glabella and forehead combined with brow and eyelid ptosis produce a fatigued appearance. Often these patients chronically elevate their frontalis muscle to enhance their visual field, and this produces deep horizontal forehead lines. A youthful female forehead is slightly convex, 12 degrees off vertical [68]. This may be achieved by re-volumizing the supra-brow concavity with a highly cohesive low G' filler that spreads along the periosteum in the subgaleal plane below the level of the frontalis muscle [69]. Volumizing the glide plane in the glabella and medial forehead can lift the medial brow. This "support" along the periosteum allows the frontalis to relax, leading to softening of the horizontal forehead lines. Pertinent anatomy in this area includes the supratrochlear and supraorbital arteries. To identify the location of these vessels, have the patient look straight ahead and mark the medial aspect of the iris. The supraorbital vessel comes out of the skull as a notch in 80% and a hole in 20% and is within 1 mm of the medial aspect of the iris and is deep. The supratrochlear vessel is 8–12 mm medial to the supraorbital vessel. It is easily identified by asking the patient to frown as it is found directly under the glabellar creases. If filler is necessary to efface deep glabellar lines, then it is important to inject in the dermis and not in the subdermal space to avoid intravascular injection. The supratrochlear and supraorbital arteries become subcutaneous 15–20 mm above the superior orbital rim. Filling in this location should be performed deep on the bone and can be done either with a needle or a cannula.

Earlobe rejuvenation with filler is another under recognized anatomic region. As women age, they often find it difficult to wear earrings due to earlobe atrophy. The earlobe typically comprises 20% of the length of the ear and the average length of the lobe is 18 mm [67]. The "deflated" lobe can be significantly improved with injectables. This is one of the easier areas to inject as it often only requires 0.2–0.5 cc of HA injected in the subdermal plane while stretching the skin.

Injection technique will vary according to the filler preparation used, area to be injected, and the experience of the injector. The six most commonly used techniques include vertical supraperiosteal depot, the tower technique, serial puncture, linear threading, fanning, and cross-hatching (Figs. 38.3, 38.4, 38.5, 38.6, 38.7, and 38.8). The glabella, fine lines, and nasolabial folds lend themselves to the serial puncture or linear threading technique. Serial puncture is performed by making multiple injections sequentially along the wrinkle or crease. Linear threading involves inserting the full length of the needle into the skin, and the filler is injected in a linear fashion as the needle is withdrawn (retrograde) or while the needle is being advanced (antegrade), forming a channel of products. The vermillion

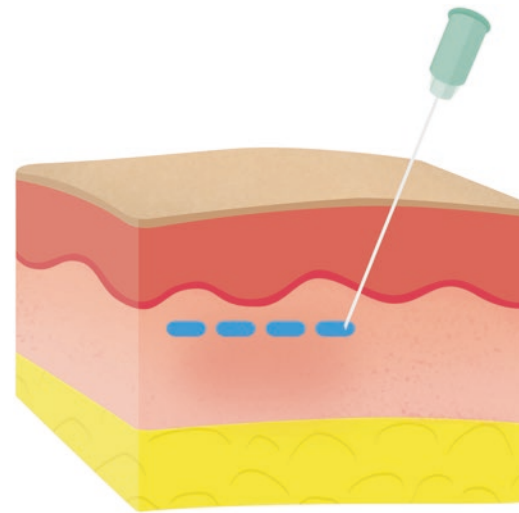

Fig. 38.5 Serial puncture

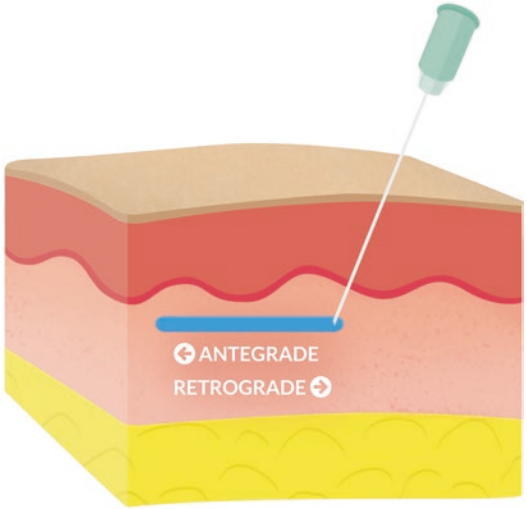

Fig. 38.6 Linear threading

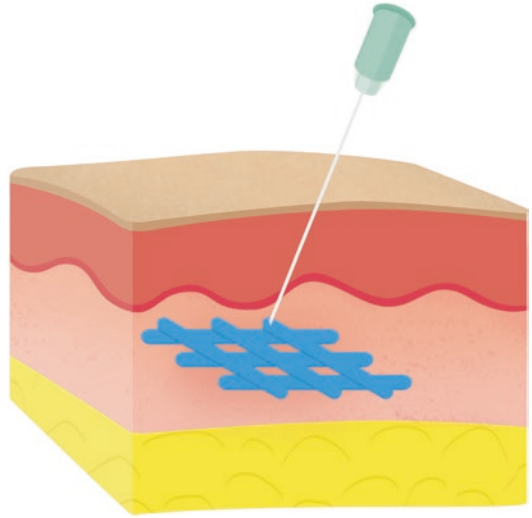

Fig. 38.8 Cross-hatching

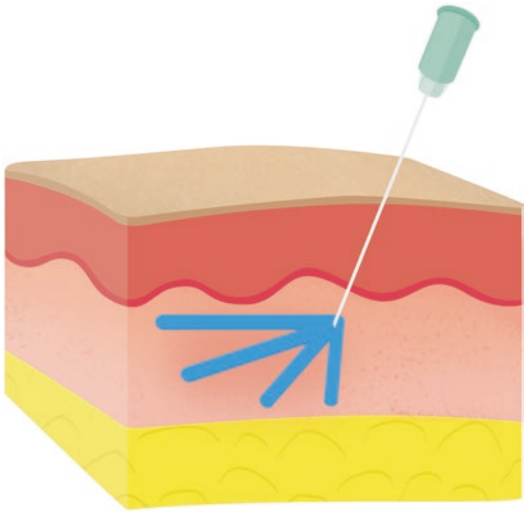

Fig. 38.7 Fanning

border of the lip responds excellently to antegrade injection. For larger areas like the cheek, cross-hatching or fanning can be very effective. Cross-hatching entails making a series of linear threads evenly spaced in a progressive grid and then smoothed together. Fanning is performed by inserting the needle in a similar fashion to linear threading but before it is withdrawn it is advanced in a different direction (clockwise or counterclockwise). This allows the injector to fill a peripheral area from the same injection site.

Vertical supra-periosteal depot (VSDT) involves a perpendicular injection down to the periosteum and placement of the filler on the bone to provide lift and support to the area. Because of the presence of the underlying bony support, very little filler is required for significant correction. The malar eminence is an excellent choice for this form of injection. The tower technique described by Gerhard Sattler is typically used in similar locations but involves the release of the product as the needle is being withdrawn in multiple columns to support the overlying skin [70]. Glogau and Kane found in a randomized, prospective, blinded, controlled study of 283 patients that injection techniques can contribute to the occurrence of adverse events [71]. Techniques that increased adverse events included dissection of the subepidermal plane (i.e., fanlike pattern), increased speed of injection, and high-volume injections [71].

Safety

Soft tissue filler demand continues to increase due to its high safety profile and high rate of physician and patient satisfaction. However, adverse events (AEs) do occur, and as the number of procedures and injectors increases, there

is likely to be an increased incidence of filler complications. Injectors must know how to recognize and manage impending complications. The vast majority of AEs are fairly commonplace and not severe. These tend to be related to the injection itself or the injector's technique and include swelling, erythema, bruising, and lumps or bumps due to too much filler or too superficial placement. Suboptimal product choice or product placement can also result in suboptimal results. Rohrich et al. propose that complications should be categorized as early (less than 14 days), late (14 days–1 year), and delayed (greater than 1 year), and these time points correlate with the underlying etiology [72]. Early complications would include acute inflammation, infection, or ischemic events. Late and delayed may overlap and refer to granuloma formation and biofilm [73].

The true incidence of complications is difficult to ascertain since most available data is based on small case series (Evidence level 4) [54]. Current statistics on fillers and associated complications can be obtained from the FDA (US Food and Drug Administration), manufacturer database, national societies, and from the Physicians Coalition for Injectable Safety. A few other studies deserve mention. A retrospective medical record review from 2007 to 2011, including 1,047 HA patients, 811 PLLA patients, and 231 CaHA patients, revealed 14 complications (Evidence level 2b) [74]. Another retrospective data review over 68 months, with 4,702 treatments with 11,460 ml of Juvederm® Voluma (Allergan, Pringy, France) showed a 0.5% incidence of delayed nodules. The median time from injection was 4 months; the median time to resolution from onset was 6 weeks [75]. One other retrospective review of vascular occlusion cited an incidence of 3 in 1000 to 3 in 10,000 depending on what product was used [76]. Finally, there is a multicenter prospective cohort study of procedures performed using lasers, energy devices, and injectables, among eight geographically different institutional and private practices with 23 dermatologists and a sample size of 20,399 cosmetic procedures. The aggregate AE rate for injectable fillers was 0.52% and mainly attributable to nodules and purpura.(Evidence level 1a) [77].

An excellent comprehensive recent review of soft tissue filler complications can be found in Facial Plastic Surgery journal [73]. The following information will synthesize some of the most important features of both common and uncommon but potentially serious complications. Bruising is a common side effect of soft tissue fillers. It can be minimized by discontinuing anticoagulant medications and vitamin and herbal supplements 7–10 days in advance of injections. Bruising can be minimized by using blunt-tipped cannulas, small gauge needles, slow injection, small aliquots of product, limited number of puncture sites, and injecting using the depot technique at the pre-periosteal level when appropriate. Swelling in the immediate post-procedural period is common and will vary with the agent used and the location of filler placement. The lips and periorbital area are the most common sites of swelling. Pronounced transient swelling of the lips may occur within hours after lip augmentation (Fig. 38.9). This swelling is generally a type 1 hypersensitivity reaction (IgE-mediated immune response that subsides fairly rapidly with antihistamine and oral steroids). Overcorrection and too superficial placement of fillers (Tyndall effect) (Fig. 38.10) are injector-related AEs. Nodules are categorized as non-inflammatory and can be treated with

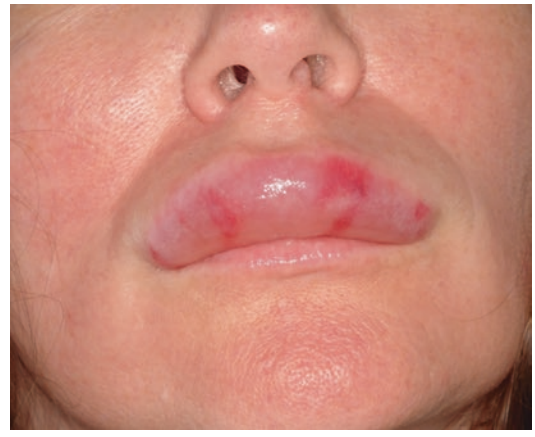

Fig. 38.9 Immediate hypersensitivity reaction to hyaluronic acid lip filler

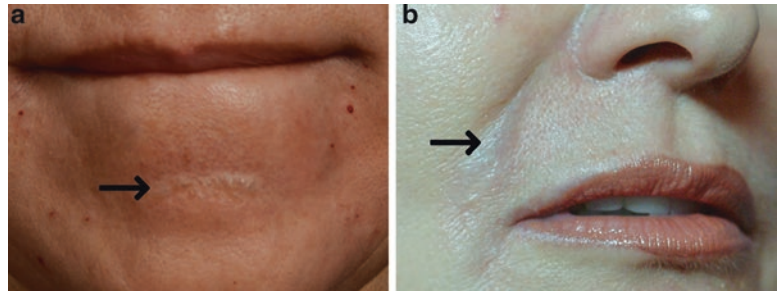

Fig. 38.10 **a** and **b** Tyndall effect

hyaluronidase. Rarely, inflammatory nodules can occur with acute infection, which is due to skin contamination and inadequate preparation of skin. These infections are often secondary to *Staphylococcus aureus* and respond to first-generation cephalosporins. Late onset (>2 weeks) may be due to less common bacteria such as atypical mycobacteria. A third type of inflammatory nodule is a biofilm. These are complex collections of bacteria that secrete a protective adhesive matrix that adheres to the surface of the filler and give rise to a low-grade chronic infection and is often resistant to antibiotics. Distinguishing inflammation due to a bacterial biofilm from a low-grade hypersensitivity reaction is difficult. The incidence of biofilms as a result of filler is not known. The treatment is removal of the material, and in the case of HA, hyaluronidase is used to dissolve the product. In addition, a recent global consensus on prevention and management of AEs with HA recommended empiric therapy with clarithromycin 500 mg daily plus moxifloxacin 400 mg bid for 10 days, ciprofloxacin 500–750 mg bid for 2–4 weeks, or minocycline 100 mg daily for 6 months [58]. The terminology of delayed hypersensitivity reactions to injectable fillers is confusing. The clinical appearance of a hypersensitivity reaction (Fig. 38.11) can mimic a biofilm and appear as firm, tender, red papules, nodules, or plaques that are culture negative. They appear after a latent period often several months after the injection. The mechanism is unknown, and one can speculate idiosyncratic reaction that may be triggered by an unrelated event. Lack of uniform morphology, low case numbers, difference in temporal onset, and deficiency of confirmatory scientific evidence such as skin test or circulating antibodies make it difficult to diagnose [78]. Treatment of HA filler hypersensitivity includes hyaluronidase, IL, or PO corticosteroids and IL 5-fluorouracil and low-dose triamcinolone.

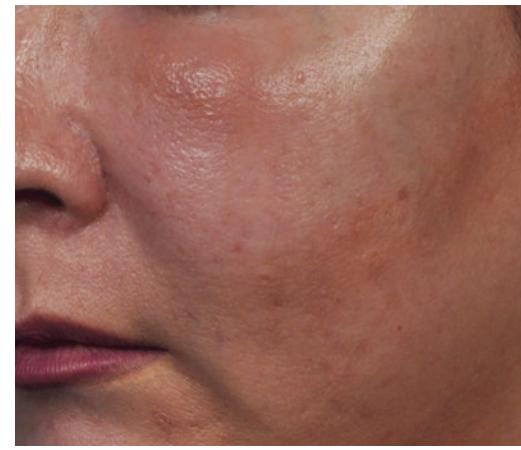

Fig. 38.11 Delayed hypersensitivity reaction to high-concentration hyaluronic acid midface filler

Ischemia/Necrosis

Intravascular injection of fillers can lead to devastating side effects, such as tissue necrosis and rarely vision loss. One recent retrospective review cited an incidence of 3 in 1000 for calcium hydroxyapatite to 3 in 10,000 for hyaluronic acid products [54, 76]. Vascular occlusion occurs in areas which are supplied by only a single artery such as the glabella. In the facial area, injections in the nasolabial fold area can cannulate the angular artery, producing ischemia

and possible necrosis to the skin that it supplies. Vascular infarction can resemble a herpetic outbreak, and these should not be confused. Precautions include aspiration before injection, slow injections, minimal pressure on the plunger, small quantities of filler, and in-depth knowledge of underlying anatomy. Cannulas are advocated by some; however, a recent article by Yeh L, Fabi S and Welsh K et al. describes intra-arterial injection with a blunt-tip cannula [79]. An algorithm from the consensus guidelines for the treatment of intravascular injections includes immediate cessation of the injection, hyaluronidase, warm compresses, and massage. Liberal doses of hyaluronidase (200–300 U) should be injected immediately if signs and symptoms are present. Those signs would include livedo reticularis-like appearance (Fig. 38.12), well demarcated erythema, pain, and blanching. Patients should be reassessed every 24 hours and hyaluronidase should be repeated for a minimum of 2 days. Other strategies (without proven efficacy) include topical nitroglycerin (1%) paste, systemic steroids, aspirin, low molecular weight heparin, and hyperbaric oxygen. Measures to improve retinal perfusion include immediate ophthalmologic consultation, ocular massage, timolol eye drops, hyperbaric oxygen, diuretics, corticosteroids, anticoagulation, and needle decompression of the anterior chamber [80].

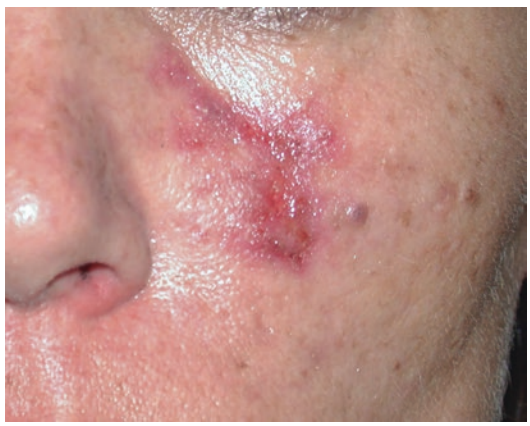

Fig. 38.12 Intravascular injection of an acne scar with subsequent erosion plus reticulation

Alternative Procedures and Modifications

Successful rejuvenation of the upper face requires a combination of minimally invasive modalities to fill hollows, resurface rhytides, improve dyschromia, and smooth mimetic muscles. Unfortunately, there are few studies discussing combination therapy for rejuvenation of the upper face. Most of the studies are case reports; small pilot studies; retrospective, single center studies; and literature reviews combined with clinical experience [81–84]. Commonly performed complementary procedures with upper and mid face fillers include botulinum toxin, laser, intense pulsed light (IPL), microfocused ultrasound (MFUS), and microneedle fractional radiofrequency. There is little data discussing treatment order when doing combination therapy. Clinical studies have shown that hyaluronic acid filler in the nasolabial folds is unaffected by non-ablative laser, monopolar radiofrequency, and IPL treatments [82]. A porcine model revealed that HA-based fillers are unaffected by non-ablative and superficial ablative treatments, but more aggressive deeper laser treatments can produce some filler interactions [85]. Based on the above information, it is possible to administer facial filler before non-ablative laser, light, and MFUS treatments. The author's (SEC) main concern when performing complementary treatments is to avoid injectables on the same day as a device that may produce swelling. Botulinum toxin (BoNT) should be done at a separate session as a procedure that typically produces swelling such as non-ablative fractionated laser because of the concern that the BoNT could migrate down the supraorbital and supratrochlear nerve sheath and into the orbital tissues to cause ptosis or diplopia [86].

Conclusion

Facial aging is a multifactorial process proven to result from changes in the skin, adipose tissue, and bone. Injectable fillers are effective in correcting these changes of the upper face and stimulating new collagen formation. Evidence exists

for treatment of the forehead, temples, infraorbital hollows, periorbital rhytides, glabella, earlobes, and cheeks. Results have been shown to last from 6 to 24 months depending on the specific filler and amount used. Understanding a patient's goals, preoperative examination, discussion of expectations, and clinical photographs are important for patient satisfaction. There are numerous injection techniques that vary among injectors and areas being injected. High-level evidence is not present for any specific injection technique; choice of technique may be based on individual comfort and safety. Temporary fillers used in the upper face have a very good safety profile. The vast majority of adverse events are mild and include swelling, bruising, and lumps or bumps. The incidence of severe complications is more difficult to determine. These complications include type 1 hypersensitivity reaction, Tyndall effect, biofilm, and intravascular injection (leading to tissue necrosis and/or blindness). Injection technique and location can be altered to minimize the risk of these complications. The growing use of injectable fillers to correct facial aging has led to an increased development of new fillers, FDA-approved indications, and reports of non-FDA-approved indications. The evidence for these new fillers and areas for use must be critically examined to best implement them in clinical practice.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Temporary injectable fillers: evidence for FDA-approved and non-FDA-approved indications

Product (Manufacturer)	FDA-approved indications	Evidence level (FDA-approved indications)	Non-FDA-approved indications	Evidence level (Non- FDA-approved indications)	Duration
Restylane-L® (Galderma Laboratories, LP)	Mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	1b/A	Temples Glabella Infraorbital hollows	4/B 1b/B 4/B	6 months
	Submucosal implantation for lip augmentation	1b/B			
Restylane® Lyft (Galderma Laboratories, LP)	Implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds	1b/A	Temples Mandible Chin	4/B	6 months
	Subcutaneous to supra-periosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies	1b/A		4/B	
Restylane® Silk (Galderma Laboratories, LP)	Submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytides	1b/A	Forehead Periorbital rhytides Glabella Infraorbital hollow	4/B 4/B 4/B 4/B	6 months
Restylane® Refyne (Galderma Laboratories, LP)	Injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	1b/B	Lips Periorbital hollows	5/D 5/D	6–12 months

(continued)

Product (Manufacturer)	FDA-approved indications	Evidence level (FDA-approved indications)	Non-FDA-approved indications	Evidence level (Non- FDA-approved indications)	Duration
Restylane® Defyne (Galderma Laboratories, LP)	Injection into the mid-to-deep dermis for correction of moderate to severe, deep facial wrinkles and folds, such as nasolabial folds	1b/B	Cheeks	5/D	6–12 month
Juvederm® Ultra XC (Allergan, Inc)	Injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	1b/A	Hands Submalar	5/D 5/D	6–12 months
	Injection into the lips and perioral area for lip augmentation	1b/B			
Juvederm® Ultra Plus XC (Allergan, Inc)	Injection into the mid-to-deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	1b/A	Temples Cheeks	5/D 5/D	6–12 months
Juvederm® Voluma (Allergan, Inc)	Deep (subcutaneous and/or supra-periosteal) injection for cheek augmentation to correct age-related volume deficit in the midface	1b/A	Forehead Temple Mandible Chin	5/D 5/D 5/D 5/D	24 months
Juvederm® Volbella (Allergan, Inc)	Injection into the lips for lip augmentation and for correction of perioral rhytides	1b/B	Periocular rhytides Infraorbital hollows	5/D 5/D	12 months
Belotero Balance® (Merz Aesthetics)	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds	1b/B	Infraorbital hollows Perioral rhytides Glabella Forehead Periocular rhytides Neck-horizontal rhytides	4/C 4/C 4/C	6 month
Sculptra® (Merz Aesthetics)	Indicated for use in people with healthy immune systems as a single regimen for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (crosshatch) injection technique is appropriate	1b/A	Acne scarring Cheeks Temples Marionette lines Chest Arms Buttocks Knees	4/C 4/C 4/C 4/C	12–24 months
Radiesse® and Radiesse® (+) (Merz Aesthetics)	Subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds	1b/A	Cheeks Mandible Chin Nose	3/B	12 months
	Hand augmentation to correct volume loss in the dorsum of the hands	1b/A			

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Self-Assessment Questions

1. All of the following contribute to aging of the upper face EXCEPT:
   (a) Migration of facial fat pads
   (b) A decrease in types I and III collagen
   (c) Fat redistribution
   (d) Thickening of the frontal bone
   (e) Soft tissue loss along the orbitomalar ligament
2. What rheologic property of fillers is a measurement of gel stiffness and its ability to resist deformation?
   (a) Cohesivity
   (b) Viscosity (η)
   (c) Elastic (storage) modulus (G')
   (d) Concentration
   (e) Cross-linking
3. Which supplement(s) should patients avoid 1 week prior to filler injection to help diminish the risk of bruising?
   (a) Garlic
   (b) Vitamin B3 (nicotinamide)
   (c) Ginseng
   (d) a and b
   (e) a and c
4. Where is the safest injection point for filling of the temple?
   (a) Two finger widths above the zygomatic arch in a supra-periosteal plane deep to the temporalis muscle.
   (b) One finger width above the zygomatic arch in a supra-periosteal plane deep to the temporalis muscle.
   (c) One finger width above the zygomatic arch in the superficial fat.
   (d) Two finger widths above the zygomatic arch in the superficial fat.
   (e) Two finger widths above the zygomatic arch in a periosteal plane above the temporalis muscle.
5. What is an example of a late to delayed complication from filler injection?
   (a) Bruising
   (b) Biofilm
   (c) Inflammation
   (d) Infection
   (e) Ischemia

Correct Answers

1. d: Bony resorption, not thickening, of the frontal bone contributes to brow ptosis and lateral orbital hooding. Facial aging is a multi-factorial process and includes changes in the skin, adipose tissue, and facial bones. These include a decrease in types I and III collagen, volume loss and redistribution of fat in facial fat pads, downward migration of individual fat compartments, weakening of fibrous membranes, and resorption of the frontal bone, orbital rim, and maxilla.
2. c: G prime (G') is the elastic (storage) modulus, which is a measurement of gel stiffness and its ability to resist deformation. The higher the G', the less the filler deforms under pressure which is useful for areas where a "lift" is desired. Cohesivity relates to the cross-linking of the filler molecules and the gel's ability to resist vertical compression to maintain the shape of the gel. Viscosity (η) measures the filler's ability to resist shearing forces, those that occur both during and after filling. Concentration represents the concentration of hyaluronic acid in hyaluronic acid fillers. This does not directly influence gel stiffness. Cross-linking is the process by which individual chains of hyaluronic acid are bound together in the filler and can influence the duration of the filler.
3. e: a and c. Supplements that patients should avoid 1 week prior to filler injection include garlic, ginger, ginseng, gingko biloba, kava, celery root, fish oils, St John's Wort, vitamin E (1000–2000 IU /day), and glucosamine/chondroitin. These can all increase the risk of bruising, and patients should also avoid these medications for 4–5 days post procedure if bruising is visible within 48 hours post procedure.
4. b: The frontal branch of the superficial temporal artery anastomoses with the supraorbital artery in the temporal region in a subdermal plane. In this area, the middle temporal vein (MTV) also runs above the temporalis muscle. To avoid intravascular injection into these vessels, filler injections must be in a supra-periosteal plane deep to the temporalis muscle and one finger width above the zygomatic arch.
5. b: Biofilms are a late to delayed complication of filler injection (>2 weeks). They are complex collections of bacteria that secrete a protective adhesive matrix that adheres to the surface of the filler and give rise to a low-grade chronic infection and are often resistant to antibiotics. The treatment is removal of the material and in the case of HA, hyaluronidase is used to dissolve the product. In addition, empiric therapy with clarithromycin 500 mg daily plus moxifloxacin 400 mg bid for 10 days, ciprofloxacin 500–750 mg bid for 2–4 weeks, or minocycline 100 mg daily for 6 months has been recommended.

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Soft Tissue Augmentation (Temporary Injectable Fillers) of the Lower Face and Neck (Lips, Perioral, Nose, Neck)

Amelia K. Hausauer and Derek H. Jones

Abstract

Soft tissue augmentation with injectable fillers is one of the most popular aesthetic procedures performed in the USA (US; V/B) (Ahn CS, Davis SA, Dabade TS, Williford PM, Feldman SR. Dermatol Surg 39(9):1351–9, 2013; Tierney EP, Hanke CW. Dermatol Surg 35(9):1324–33, 2009). The goal of these treatments is to either restore age- or disease-related volume loss or enhance and contour existing features, and the lower face is frequently an area of concern. In the aging face, bony remodeling, weakened retaining ligaments, and descent of atrophic fat pads contribute to the development of wrinkles and folds around the mouth, at the jawline, and at the chin. The nasolabial folds deepen; the lips thin; and the oral commissures turn down, delving into marionette lines. Bony resorption also makes the jawline less defined with a receding chin (Richard MJ, Morris C, Deen BF, Gray L, Woodward JA. Ophthal Plast Reconstr Surg 25(5):382–6, 2009; Rohrich RJ, Pessa JE. Plast Reconstr Surg 119(7):2219–27, 2007; Rohrich RJ, Pessa JE, Ristow B. Plast Reconstr Surg 121(6):2107–12, 2008; Shaw RB Jr, Katzel EB, Koltz PF, et al. Plast Reconstr Surg 127(1):374–83, 2011; Mendelson BC, Jacobson SR. Clin Plast Surg 35(3):395–404; 2008). Soft tissue augmentation seeks to soften these changes, particularly as part of a multimodal management plan with neuromodulators, resurfacing devices, and topical therapies (Carruthers J, Carruthers A. Dermatol Surg 42(Suppl 2):S89–93, 2016). On the flip side, younger patients also seek lower face enhancement, usually to correct genetically determined deficits such as nasal contour irregularities, to alter their face shapes, or to augment their features such as lips. This chapter evaluates the most commonly used injectable fillers in the USA to better understand the evidence-based literature supporting their safety and efficacy at the lower face, including the nasolabial folds, lips and perioral region, jawline and chin, nose, and neck and décolletage.

Keywords

Calcium hydroxylapatite · Dermal fillers Facial rejuvenation · Hyaluronic acid Liquid injectable silicone · Marionette lines Nasolabial folds · Nonsurgical rhinoplasty Poly-L-lactic Acid · Polymethylmethacrylate Soft tissue augmentation

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Introduction

Soft tissue augmentation with injectable fillers is one of the most popular aesthetic procedures performed in the USA (US; V/B) [1, 2]. The goal of these treatments is to either restore age- or disease-related volume loss or enhance and contour existing features, and the lower face is frequently an area of concern. In the aging face, bony remodeling, weakened retaining ligaments, and descent of atrophic fat pads contribute to the development of wrinkles and folds around the mouth, at the jawline, and at the chin. The nasolabial folds deepen; the lips thin; and the oral commissures turn down, delving into marionette lines. Bony resorption also makes the jawline less defined with a receding chin [3–7]. Soft tissue augmentation seeks to soften these changes, particularly as part of a multimodal management plan with neuromodulators, resurfacing devices, and topical therapies [8]. On the flip side, younger patients also seek lower face enhancement, usually to correct genetically determined deficits such as nasal contour irregularities, to alter their face shapes, or to augment their features such as lips. This chapter evaluates the most commonly used injectable fillers in the USA to better understand the evidence-based literature supporting their safety and efficacy at the lower face, including the nasolabial folds, lips and perioral region, jawline and chin, nose, and neck and décolletage.

Nasolabial Folds

Nearly all currently Food and Drug Administration (FDA)-approved soft tissue fillers first sought an indication for the correction of nasolabial folds, so there is a robust body of literature supporting their use in this anatomic area.

Photonumerical Scales

Photonumeric scales are metrics designed to ensure standardized, reliable, and reproducible grading of severity and response to treatment. Each is unique and proprietary. Some of these scales were developed and validated in the context of clinical trials, as required by the FDA, while others were devised independently or preemptively and have yet to be attached to a specific study. The Wrinkle Severity Rating Scale (WSRS) was the first novel tool presented to the FDA for assessment of primary efficacy in the Restylane® pivotal trial in 2003 (see below). Its validation involved five clinicians evaluating 30 photographs of the lower face over two separate sessions. They ranked the right and left nasolabial folds independently according to a five-point scale. Inter- and intrarater agreement was excellent (weighted kappa, 0.77 and 0.75 for the left and 0.81 and 0.78 for the right, respectively), results suggesting the WSRS is a reliable tool for analyzing nasolabial wrinkles (1a) [9].

Since that time, other photonumeric scales have been published or used in conjunction with other dermal fillers such as the Lemperle Rating Scale with Radiesse® or the six-point Wrinkle Assessment Scores (WAS) scale with Sculptra Aesthetic® (1a) [10–14].

Hyaluronic Acid

Hyaluronic acid (HA) is an endogenous glycosaminoglycan, naturally comprising a large portion of the dermis in all mammals and tissue types. Its anionic structure avidly binds water to produce a gel that hydrates, lubricates, and volumizes [15, 16]. Differences in HA concentration and manufacturing techniques contribute to each product's unique qualities, but on the whole, this class of fillers has become the most popular, completely supplanting collagen injectables, because of HA's increased longevity, good safety profile without the need for prior skin testing to rule out hypersensitivity, as well as reversibility with the enzyme hyaluronidase that degrades bonds within the HA chains to allow for quick metabolism. Treatment of the nasolabial folds was the first on-label indication for nearly all HA-based fillers, and each product has been evaluated independently rather than as a single class of agents. The pivotal trials critical in securing

FDA approval for Restylane®, Restylane Lyft®/Perlane®, Juvederm®, and Belotero Balance® were all of similar design—6-month, split-face, blinded, randomized, controlled, multicenter phase III trials comparing the new HA agent in question to Zyplast® bovine collagen, which is no longer available in the USA and, hence, will be discussed only in comparison to the more commonly used products.

Restylane® was the first to gain FDA approval in 2003 based on the results from a randomized, controlled, multicenter trial of 138 participants with moderate or severe nasolabial fold creases treated with Restylane® versus Zyplast®. Efficacy results from this double-blinded, split-face design suggested that HA required smaller volumes to correct deficits and that at 6 months, the investigator-based WSRS and Global Aesthetic Improvement Scale (GAIS) were superior for HA in 56.9% and 62.0% compared to in 9.5% and 8.0% of bovine collagen-treated subjects, respectively. Moreover, only 29% of Restylane®-augmented sites returned to baseline compared to 67% of those receiving Zyplast®. HA also had a better long-term safety profile, with 26.8% of participants experiencing adverse reactions versus 39.1% status post Zyplast®. Interestingly, Restylane® injection did result in more post-procedural swelling (87% for Restylane® vs. 73.9% for Zyplast®)(1b) [11]. Soon thereafter, an extension trial sought to better assess the duration of correction. Seventy-five patients with moderate to severe nasolabial folds received Restylane® at baseline with retreatment at one side after 4.5 months and at the other after 9 months. Both groups showed similar improvement lasting up to 18 months, irrespective of retreatment schedule, results confirming that repeat injection is safe and extends the duration of correction (1b) [17]. Subsequent studies presented to the FDA had a 6-month primary efficacy endpoint; then patients entered a retreatment phase if clinically indicated. Only the initial Restylane® product had two separate trials for this purpose.

Restylane Lyft®, previously named Perlane®, has the same chemical properties as Restylane® except for a larger particle size (20,000 particles/ml compared to 100,000 particles/ml), which makes it more suitable for treating deeper wrinkles and folds. It received FDA approval based on cumulative data from five studies. A split-face, double-blinded, randomized, controlled, multicenter trial among 180 patients comparing Restylane Lyft®/Perlane® to Hylaform®, a lower concentration HA filler no longer marketed in the USA, confirmed that the Restylane® family product also provided a durable correction with 75% of subjects having at least a 1-point improvement on the WSRS compared to 38% of those treated with Hylaform®. Incidence of injection-related complications, such as swelling, erythema, and pain, was also higher (41.3% for Restylane Lyft®/Perlane® vs. 21.3% for Hylaform®). It is thought that the increased viscosity of the product allowed for more durable correction and better lifting capacity but required larger gauge needles for injection, which produced more minor side effects (1b) [18]. A larger randomized, controlled study enrolled 283 subjects who received Restylane® at one nasolabial fold and Perlane® at the contralateral with a primary efficacy endpoint of change in WSRS from baseline at 12 weeks and secondary endpoints at 2, 6, and 24 weeks. At 12 and 24 weeks, both groups showed improvement, and there was no statistically significant difference between improvement seen with Perlane® versus Restylane® (at least 1-point improvement in WSRS, 12 weeks, 87% with Perlane® and 77% with Restylane®; 24 weeks, 63% with Perlane® and 74% with Restylane®)(1a) [19]. Consequently, Perlane® is considered non-inferior to Restylane®. Since this time, Restylane® Refyne and Defyne have also been FDA approved based on clinical data showing non-inferiority to a commercially available HA(1b) [20–23].

In 2006, Juvederm® Ultra and Ultra Plus entered the market. These products contain higher concentrations of more crosslinked HA than Restylane®. To determine safety and efficacy, the pivotal split-face, double-blinded, randomized, controlled, multicenter trial enrolled 439 participants with moderate to severe nasolabial creases who received either Juvederm® 30,

Ultra, or Ultra Plus at one side of the face and Zyplast® bovine collagen at the other. Juvederm® provided greater improvement and patient satisfaction at 6 months (1b) [24]. Additional post-study surveillance provided long-term efficacy data with 78% of subjects after Ultra and Ultra Plus, maintaining correction for over 1 year (1b) [25].

Belotero® Balance gained approval for correction of facial wrinkles such as the nasolabial fold in 2011. It is the only available product using cohesive polydensified matrix technology to yield a nonparticulate gel with different density zones that integrate into the dermis without causing bluish discoloration from the Tyndall effect [26]. Like the other HAs, Belotero® outperformed bovine collagen in a split-face, blinded, randomized, controlled, multicenter trial of 118 subjects. WSRS, GAIS, and visual analog scale were determined at baseline, 2, 4, 8, 12, and 24 weeks, with changes in WSRS at 12 weeks as the primary outcome measure. Overall, there was a significantly greater change in nasolabial fold grade after Belotero® compared to collagen at 6 months, and this result held true using the other metrics at other follow-up time points. Of the 107 participants who completed satisfaction questionnaires, 85 or 79.4% preferred the HA ($p < 0.001$; mean improvement rating 74.7% vs. 66%). Adverse events were common regardless of product (116 out of 118), but the majority were mild or moderate, resulting from injection technique rather than the actual product (1b) [26]. After 6 months, 95 of the subjects opted to participate in an open-label extension study. They received repeat injection and were assessed similarly at 32, 48, 72, and 98 weeks. As with the original trial, touch-ups were allowed to achieve optimal effect. Both sides of the face showed improvement at all time points, but it was greater after Belotero® than collagen fold. Mean GAIS ranged from improved (grade 2) to much improved (grade 3), and 80% of participants held their correction without repeat treatment for at least one interval of 48 weeks. Despite the high rate of injection-related side effects in the primary phase III trial, only one was reported in the extension. Moreover, a subset analysis of pre- and posttreatment serum antibodies confirmed Belotero's® low immunogenicity, which eliminates the need for skin hypersensitivity testing, routine before bovine collagen augmentation but not necessary for *any* of the HA products, since they are derived from tissue and species nonspecific matrix substance (1b) [27].

In March 2017, the FDA approved Juvederm® Vollure XC for the treatment of moderate to severe facial wrinkles and folds. It is the first product manufactured using Vycross™ intended for this indication and in clinical trials and had a duration of up to 18 months compared to the 12 seen with other available HA products (1b) [28].

With the exception of Belotero®, all HA fillers are now premixed with lidocaine. A prospective, split-faced European study of 60 patients injected with Juvederm® Ultra Plus 0.3% lidocaine versus Juvederm® Ultra only and a second of 126 patients injected with Juvederm® Ultra Plus 0.3% lidocaine versus Restylane® documented significantly less pain experienced by those receiving the HA plus anesthetic without change in filler efficacy (1b) [29]. Subsequently, in 2010, the FDA approved Juvederm® Ultra and Ultra Plus XC and Restylane-L and Restylane Lyft®-L, all of which contain premixed lidocaine.

Calcium Hydroxylapatite

Calcium hydroxylapatite (CaHA), Radiesse®, gained FDA approval for treatment of moderate to severe facial folds and wrinkles such as the nasolabial folds in 2006. Prospective randomized controlled trials have compared Radiesse® to collagen and hyaluronic acid fillers. In the pivotal, split-face, blinded, randomized, controlled study, 117 patients received Radiesse® to one randomly assigned nasolabial fold and human collagen to the other. Up to three injection sessions occurred every 2 weeks until achieving optimal correction. Blinded evaluators rated the aesthetic outcomes seen with Radiesse® on photographic imaging as superior to those seen with collagen at 6 months, and correction required

half the volume (mean 1.2 ml for Radiesse® vs. 3.4 ml for collagen) [14].

When compared to nonanimal stabilized HA (Restylane®), CaHA appeared to provide a more durable response; 79% of Radiesse® and 43% of HA-injected sites maintained acceptable nasolabial fold fill among 60 patients using the WSRS and GAIS at 12 months (1b) [30, 31]. However, these results differ from those seen in the follow-up phase III trial designed to assess longevity of effectiveness after Restylane® where 97% of subjects maintained at least a 1-point improvement in WSRS compared to baseline and 57% improved by 2 points or more at 18 months (1b) [17]. Each study included touch-up injections, so this practice cannot explain the divergent findings. Currently, manufactures of both Radiesse® and Restylane® claim that their products may persist for a year or more depending on anatomic location and patient characteristics.

In addition to randomized controlled trials, there are several notable cohort studies and case series that provide insight into the safety, efficacy, and longevity of CaHA. This filler contains 25–45 micron spheres of calcium hydroxylapatite, the major constituent found in the bone, suspended in an aqueous gel carrier. A pilot study of three patients injected with 0.1 ml CaHA at the postauricular area and bilateral nasolabial folds sought to better understand how the body reacts and processes these microspheres. At 1 and 3 months, 3 mm punch biopsies were obtained for histopathology and electron microscopy. The investigators saw no evidence of inflammatory cell reaction, fibrosis, ossification, and/or granuloma formation. Furthermore, a collagen matrix formed early around the implant and persisted for at least 6 months postinjection, results suggesting that CaHA appears to remain in the body for long periods of time without significant adverse events (4) [32].

The persistence and safety of CaHA were analyzed further over 4 years in a large study of 1000 subjects. Patients received filler most commonly at the nasolabial creases but also at marionette lines and other facial areas. More than 80% reported persistent correction at 12 months, and the rate of complications was low. The most frequent adverse events included: redness, swelling, itching, and bruising. A total of 1.7% of patients developed nodules after CaHA injection into cutaneous facial folds (4) [33].

Because of its similarity to bone and teeth matrix, there was initial concern that injection of CaHA would obscure the interpretation of radiographic images. A year-long prospective study of 58 subjects treated at the nasolabial folds or for human immunodeficiency virus (HIV)-associated lipoatrophy helped better characterize these effects. The CaHA implant was visible on both x-ray imaging and CT scans but did not appear to interfere with interpretation. CT scanning was more sensitive and specific with better filler characterization (4) [34].

Poly-L-lactic Acid

Originally approved for the treatment of HIV-related lipoatrophy, poly-L-lactic acid (PLLA) filler, marketed under the name Sculptra Aesthetic®, gained expanded FDA clearance in 2009 to treat nasolabial fold contour deficiencies in immunocompetent patients. In the phase III trial, Narins et al. described improvement in Wrinkles Assessment Scores (WAS) at 13 months from baseline for 116 participants treated with PLLA and 117 treated with collagen at the nasolabial folds during up to four sessions over 9 weeks. There was also an extended follow-up period of 25 months for the PLLA group only to assess longer-term duration of efficacy. Patients corrected with PLLA showed significantly better outcomes at months 3 through 13 compared to collagen, and these effects persisted for up to 25 months without additional treatments. Moreover, despite similar efficacy at 3 weeks post-injection, the difference was striking by 13–25 months with overall improvement above 85% for PLLA but only 6% for collagen. The percentage of subjects who developed nonvisible and visible papules and/or nodules was higher for Sculptra® than for control, and they were often delayed in onset and persistent, resolving either spontaneously over time or with intralesional

TAC injection (1b) [13]. Secondary reports from this same trial found that over 80% of patients continued to rate their PLLA treatment highly after 25 months; however, satisfaction declined 84% between week 3 and month 3 among collagen-treated subjects (1b) [35, 36].

Lips and Perioral Lines

Photonumeric Grading Scales

There are several unique, patented schemas intended to grade different qualities of the lips and perioral region. Some but not all were devised for pivotal trials presented to the FDA. In 2012, Medicis Aesthetics published their 5-point Medicis Lip Fullness Scales (MLFS) for upper and lower lips, which were used when obtaining approval of Restylane® for lip augmentation. During the two-part validation process, five dermatologists and plastic surgeons assessed 85 images at two separate sittings (photograph-to-photograph comparison), then three of these evaluators graded 39 live subjects followed by a repeat photographic rating of the same subjects 14 days later (live-to-photograph comparison). This two-phase approach made the scale suitable for photographic as well as live evaluation (1a) [37].

The Allergan Lip Fullness Scale is a more recent photonumeric tool used in the pivotal trial of Juvederm® Ultra XC for lip augmentation. It was initially a 4-point scale but was revised at the request of the FDA to a 5-point scale, encompassing a wider spectrum of facial features including grades for *marked* and *very marked* lip fullness as seen among African-Americans. Eight clinicians rating 55 live subjects validated the first iteration; then 21 aesthetic dermatologists and plastic surgeons graded three-dimensional images from 144 subjects at 2 different time points more than 2 weeks apart. Some of these images included participants before and after lip augmentation to determine clinically meaningful differences (1a) [38].

Melomental grooves, also known as marionette lines, and perioral rhytides are other deficits for which there are multiple photonumeric scales, some of which have yet to be attached to the phase III study. Other validated, proprietary scales include: the Marionette Lines Grading Scale; the Merz Lower Face Scales; and three Allergan scales—the Perioral Lines at Rest (POL), Oral Commissures (OCS), and Perioral Lines at Maximum contraction (POLM) Severity Scales (1a) [39–41].

Hyaluronic Acid

Currently, HA-derived fillers are the most common products used for lip augmentation, with Restylane® being the first to gain FDA approval in 2011. One hundred eighty patients participated in a blinded, randomized, controlled, multicenter trial comparing injection of up to 1.5 ml per lip of Restylane® or no treatment, since there were no previously licensed injectable for this anatomic location at that time. The upper and lower lips were rated independently at 8 weeks according to the MLFS. Overall, Restylane® augmentation resulted in more lip fullness than did the control (93% and 29%, respectively, for combined upper and lower lips, $p < 0.001$) with 97% of subjects at 8 weeks and 74% at 24 weeks, four reporting improved global aesthetic appearance (vs. 0% in the no-treatment group throughout; $p < 0.001$). Mild to moderate swelling (58%), bruising (44%), and pain (22%) were common side effects of the treatment (1b) [42]. Following a near-identical protocol, small-particle HA with 0.3% lidocaine, sold as Restylane-L®, was also found to be superior to no treatment for lip augmentation and perioral rhytides at 8 weeks among 199 subjects (1b) [43]. A small open-label study out of Sweden recently tested the efficacy and safety of a new HA filler, Restylane Lip Volume®, over 9 months. Eighty-six percent of the subjects and 97% of independent evaluators reported improvement according to the MLFS and GAIS (1b) [44]. Notably, this product is not currently available in the USA.

Juvederm® Ultra XC is indicated for lip augmentation as of 2015. Dayan et al. published results from the single-blinded, randomized,

controlled, multicenter phase III trial of 213 subjects who received lip injections with Juvederm® Ultra XC versus no treatment. 79.1% of those treated and 26.1% of controls had at least a 1-point increase in lip fullness, measured by the Allergan 5-point Lip Fullness Scale. These effects persisted for 12 months in more than half (56.4%). Improvement in marionette lines/oral commissures and perioral rhytides—secondary outcome variables—hovered between 40% and 50% at 3 and 12 months. The authors hypothesized that these percentages may have underestimated the actual degree of correction due to the more restrictive 4-point scales used when rating the perioral areas (validated Allergan Perioral Lines and Oral Commissure Severity Scales) (1b) [45]. Juvederm® Ultra XC outperformed Belotero Balance® in the randomized controlled treatment of perioral lines. At 6 months, a significantly higher proportion of participants had at least a 1-point improvement in the Allergan Perioral Lines Severity Scale after Juvederm® (87%) over Belotero® (72%). The Juvederm® group also experienced less treatment-related pain, likely because that product contains lidocaine, which is not premixed into Belotero Balance® (1b) [46].

Instead, Belotero® may be better suited to filling true fine lines rather than volume deficits, as it can be injected intradermally without producing blue discoloration. A new blinded, randomized, controlled trial of Belotero® for etched-in, fine lines at the forehead, cutaneous lip, melolabial folds, nasolabial folds, and/or radial cheeks found that all areas maintained statistically significant improvements at 26-week follow-up according to the Merz Aesthetic Assessment Scales and Lemperle Facial Wrinkle Scales (>1-point improvement for each site; $p < 0.001$). For the perioral regions only, over two-thirds of subjects reported greater than 50% correction, and all (100%) would repeat the treatment if necessary [47].

Juvederm® Volbella with lidocaine is a more recent dermal filler to gain FDA approval in September 2016 for lip augmentation and correction of perioral fine lines based on data from European and American, prospective, double-blinded, randomized, controlled, multicenter studies. Among 280 participants, Volbella® was non-inferior to Restylane-L® at 3 months according to the Allergan Lip Fullness, Perioral Lines, and Oral Commissures Severity Scales. The blinded investigators preferred Volbella® for correction of perioral and oral commissure rhytides (77.3% vs. 61.3%, $p = 0.0292$; 69.9% vs. 58.7%, $p = 0.0126$, respectively), although subjects did not appreciate significant differences. They were, however, more satisfied with the Volbella®, mainly due to less short-term, acute swelling (severe swelling, 22.1% for Volbella® versus 49.1% for Restylane-L®) (1b) [48, 49]. The US pivotal trial enrolled another 224 patients who were randomized to receive Volbella® ($n = 168$) or Restylane-L® ($n = 56$) into the lips and perioral region in a 3:1 ratio. Volbella® again was non-inferior at 3 months, and the majority of subjects maintained a clinically significant improvement in lip fullness (≥ 1-point change from baseline) at 1 year. Of note, seven participants developed lumps, bumps, or swelling weeks to months after treatment (1b) [50]. Similar delayed inflammatory reactions have been reported with all HA fillers produced by Vycross™ technology, Juvederm Voluma®, and Volbella®, which contain both high- and low-molecular weight particles [51, 52]. The short polysaccharide chains in these smaller molecules form more crosslinks and provide a greater lifting capacity and longevity [53] but may also act as a better immune stimulus in a subset of patients[52].

Calcium Hydroxylapatite

In contrast to the relatively low rate of nodules and papules in the skin, there is a significantly higher incidence when CaHA is used in the lips. One large-scale cohort reported papules after 5.9% of lip injections compared to 1.7% of cutaneous injections. Incidence declined over time, perhaps as the clinicians' experience increased. Based on this data, many experts consider Radiesse® contraindicated at the lips (1b) [33].

Jawline and Chin

None of the currently available soft tissue fillers has FDA approval for augmentation of the jawline and chin. However, there are ongoing studies for these indications.

Photonumeric Scales

Merz and Allergan have both sponsored the development of validated grading systems for the regions of the mandible that could severe in future phase III trials. Developed by a multidisciplinary team of experts, the Merz Aesthetic Scale for Jawline is the first quantitative metric to evaluate changes in facial shape, such as loss of oval (1a) [40]. The Allergan 5-point Chin Retrusion Scale is a photonumeric grading system designed to facilitate objective comparisons of chin projection before and after augmentation. Based on the responses from expert raters evaluating 298 patients during two sessions 3 weeks apart, a 1-point difference in rating reflected clinically significant differences in chin retrusion. The scale does not account for 3-dimensional projection, shape, contour, volume, or texture of the chin (1a) [54].

Hyaluronic Acid

Single and multicenter clinical trials for the safety and efficacy of Juvederm Voluma® at the chin and jaw are underway (1b) [55, 56]; however, existing evidence primarily comes from case series or in the context of full facial volume restoration. A consensus statement published by Matarrosso et al. found that 4% of experts reported chin and jawline as their second most common site of HA injection, whereas another 6% rated this region their least comfortable site for treatment (5) [57].

To ensure better outcomes and higher patient satisfaction, it is important to determine first who is a candidate for surgical versus less invasive chin augmentation. The authors of a retrospective review of 345 cases of microgenia with sagittal deformities proposed a decision-making protocol for optimal management. In their cohort, 135 patients underwent sliding genioplasty with piezoelectric scalpel via intraoral approach, 60 patients silicone implant via external approach, and 150 patients cross-linked HA filler (Juvederm® Voluma) injection. The subjects were followed with the GAIS for up to 3 years post-procedure and patient satisfaction questionnaires at 6 and 12 months. Among the patients in the group who received HA, average postoperative soft tissue pogonium projection was 2.6 mm from the true vertical line—a line through the subnasal point perpendicular to the Frankfurt horizontal plane—compared to 5.6 mm status postsurgery. Two more injection sessions every 8 months helped maintain results over the 3-year study period. Thirteen of the 150 subjects developed less than 2 mm nodules that resolved with massage and/or 0.2-ml hyaluronidase. Based on these outcomes, the investigators concluded that patients should be stratified to either surgical or soft tissue filler augmentation according to age, size of defect (less than or greater than 4 mm), soft tissue thickness, and degree of alveolar bone atrophy. Injectable HA substances may be especially beneficial for those with less than 4 mm deficiency from the true vertical line, mild reduction in soft tissue chin thickness, and little to mild alveolar bone loss. Participants in this Italian study were all Caucasian and majority female, so the results may not be generalizable across ethnicities and gender where ideals of beauty and proportion differ (4) [58].

Other publications focus on the use of HA fillers for chin augmentation in the context of full facial reshaping. A European postmarketing study reported the perceptions of Juvederm Voluma® for restoration of facial volume at the malar cheeks and chin in patients who had previously received Restylane® injections. Twenty-seven of the 84 cases received Juvederm® Voluma to the chin, at an average volume of 0.66 ml per treatment. Nearly all patients (98%) and providers (98%) noticed improvement with 69.1% of injectors and 61% of patients preferring the results seen with Juvederm® Voluma to those with Restylane® ($p < 0.001$) [59]. Hoffmann and

the Juvederm® Voluma Study Investigators Group conducted another prospective, pan-European, postmarketing evaluation including treatment to the chin in 9% of patients. Injections were effective as measured by the Global Aesthetic Improvement Scale and Facial Volume Loss Scale, well tolerated, and simple, with over 90% of patients likely to recommend the treatment or seek it again. Additionally, physicians found the product easy to inject (95.6%) and mold (96%) and would recommend it to colleagues (98%) (4) [60].

Facial remodeling, including chin augmentation, is also popular among those of Asian descent. Bae et al. authored a retrospective review of 320 young, Asian women treated with Juvederm® Voluma, according to what they term the "diamond volumizing technique." Injections at the four points of an imaginary diamond (glabella, malar eminences, chin) help achieve a more anteriorly projected and narrow facial contour. According to this protocol, patients were anesthetized using sensory nerve blocks and received a total of 4–6 ml of Juvederm® Voluma with 0.5–1 ml at the chin from periosteal to subcutaneous layer via a 21 gauge cannula. Nearly 95% of physicians and patients notes very much or much improvement on the GAIS at 4 weeks. Adverse effects were minimal (4) [61].

Calcium Hydroxylapatite

Reconstitution of the prejowl sulcus and jawline with calcium hydroxylapatite is considered off-label in the USA but has received the Conformité Européenne (CE) certification mark in Europe. A consensus document by French experts published in the Journal of Cosmetic Dermatology provides a discussion of guidelines for jaw augmentation according to stages of the Merz Aesthetics Scale. CaHA should be injected in the deep dermis or along the dermal-hypodermal junction in a combination of linear retrograde, fanning, and/or depot techniques originating from six points to address the [1] lower jawline at the mandibular angle and prejowl sulcus; [2] upper jawline at the posterior cheek and cheek bone, as well as [3] the mid-cheek groove. More specifically, for the lower jawline, they recommend linear retrograde or fanning injections originating at the mandibular angle and prejowl sulcus at the level of the dermal-hypodermal junction or deep dermis. Periosteal injections extending from an insertion point at the inferolateral mandible and threading either submandibularly or laterally builds the jaw angle. A depression called the prejowl sulcus appears along the medial jawline anterior to the jowl as the face ages and can be filled in a similar fashion. The degree of sagging dictates the number of insertion points and requisite injection volumes. For patients who are a Merz Stage 1, inject along the lower jawline points totaling 1–2 ml; for Stage 2, inject at the lower and upper jawline totaling 3–6 ml. Those with stage 3 or 4 changes are typically better surgical candidates, but injection of over 4.5 ml CaHA can be helpful as an adjunct or if they cannot or do not want to undergo surgery. The authors noted that pretreating with botulinum neurotoxin 1 week prior minimizes muscle contractions and enhances neocollagenesis and fibroblast ingrowth. Injection at the chin to increase anterior projection can further bolster the jawline and counteract age-related bone absorption (5) [62].

Jansen and Graivier described long-term efficacy and safety data from 609 subjects treated with CaHA at multiple facial areas. Four percent of the procedures involved the chin and jawline (i.e., central dimple, prejowl sulcus defect). For these sites, patients were marked in the upright position and then injected in a retrograde technique in the subdermal-subcutaneous plane using a 27 gauge, 1.25 inch needle. The product was molded around the inferior border of the mandible and chin immediately post-procedure and during follow-up appointments over the subsequent 10–14 days. Importantly, only aggregate results for all facial injections were reported, and they were not stratified by anatomic location. At 6 months, 155 patients completed satisfaction questionnaires with a mean satisfaction score of 3.94 out of 5. Eighty-nine percent would repeat the treatment if necessary. By 12–24 months, ongoing satisfaction had declined to 69% (112 patients completed surveys), with 74%

responding they would repeat injections in the future (4) [63].

The ACELIFT is another proposed algorithm for minimally invasive cervicofacial rejuvenation that utilizes CaHA or HA along the jawline as one component in a multimodal treatment plan. In the case series, ten healthy women aged 50–62 years underwent laser lipolysis of the neck with a 1440 nm nd-YAG laser and helium-neon aiming beam (PrecisionTx™ laser system; Cynosure Inc., Westford MA) followed by fractional carbon dioxide laser resurfacing of the face and neck as well as 6–8 syringes of calcium hydroxylapatite at the midface, jawline, and chin; 40–80 units of botulinum toxin A; and topical regimen. Additional CaHA or HA was laced along the geniomandibular creases, marionette lines, and prejowl sulcus as necessary. All patients improved at least 1-point on the GAIS and Cervicomental Angle Scales at 9 months. Considering these findings, the investigators posited that although facelift is still the treatment of choice for patients with severe cervicofacial aging, the ACELIFT protocol may be an effective and safe alternative among appropriate candidates (4) [64].

Poly-L-lactic Acid

Lorenc published a review of the existing literature and clinical experience using PLLA for facial and extrafacial rejuvenation and volumization. He recommended treating areas overlying bony prominences, including the mandible and prejowl sulcus, with a 5–10 ml sterile water dilution deposited as 0.2–0.3-ml aliquots using a 28 gauge, 5/8 inch needle or cannula. As with other locations, massage should occur for 5 min, five times per day for 5 days, although there are no studies specifically investigating the benefit of this practice in lower facial regions (5) [65]. Vleggaar authored another paper on the European experience using PLLA for addressing mid- and lower-face volume deficits, and one of the three representative cases presented emphasized jawline injections with techniques similar to that outlined by Lorenc (4) [66].

Nose

None of the currently available soft tissue fillers is FDA approved for correction of nasal contour deformities. However, since the 1980s, multiple reports have documented successful nonsurgical rhinoplasty with bovine or human collagen, medical grade silicone, autologous fat or fibroblasts, HA products such as Restylane® and Juvederm® Ultra, and CaHA, with the latter two being the most common and safest (4) [67–79]. While a comprehensive review of all case studies and reports is beyond the scope of this chapter, we appraise some of the largest or most impactful below. There are also two ongoing trials that may be influential: one multicenter, single arm study of Voluma® to enhance the Asian nose [80] and one randomized, controlled study of Perlane® in the nasal dorsum and root [81].

Hyaluronic Acid

HA has been injected on the nose for multiple indications. In 2006, Han et al. described injectable HA at the nasal dorsum among 11 patients. The clinicians combine Restylane® with autologous human fibroblasts in the hopes that this cellular scaffold would stimulate collagen production even after Restylane® resorption. Results persisted at 1 year for over half, but six patients saw a 10–40% resorption in the first 6 months and then stabilized thereafter. Of note, the substantial preparatory time needed to harvest and culture in vitro fibroblasts limits the use of this technique (4) [69].

Subsequent studies have focused on the use of HA only [76]. A retrospective review of 280 cases of nonoperative rhinoplasty with EME HA, which is not available in the USA, evaluated the improvement in nasal tip ptosis among Chinese women, 15 of whom had undergone surgery in the past. Filler was layered in multiple planes (supraperiosteal, suprachondrial, intramuscular, and subcutaneous) at the nasolabial angle, nasal columella, nasal tip, nasal dorsum, nasal root/medial brow junction, and lateral sidewall via a combination of sharp needles and blunt cannulas.

At 1 month, 94.1% of third-party evaluators, 93.2% of treated patients, and 90.5% of plastic surgeons rated the results as excellent or satisfactory on a 4-point scale (excellent, satisfactory, moderate, dissatisfactory). There were no complications over 9 months (4) [82].

Another approach to correcting a dropped nasal tip involves combining HA with botulinum toxin. In a Master Class article, Redaelli reported his experience with 95 patients. Forty-five percent of subjects received preliminary botulinum toxin A to the depressor septi nasi muscles (1.5 units per side at the columella) for muscle hyperactivity, then 100% received 0.6–1.5 ml of Juvederm® Ultra at the procerus to increase the nasofrontal angle; at the tip to increase projection; and as needed, at the nasal spine to widen the nasolabial angle. Photographs taken at baseline, immediately post-injection, and every 3 months showed improvement for at least 6 months (8.8 out of 10 on a composite scale of patient and physician rating) and possibly out to 1–2 years, although the number of patients who followed up was small (eight patients at 2 years with mean 6.6 out of 10 improvement). Six patients required reinjection at 2 months. Complications were mild to moderate with one patient experiencing prolonged erythema that spontaneously resolved by month 1 (4) [83].

Vascular compromise with tissue necrosis and retinopathy are the most feared complications of injectable rhinoplasty. Direct occlusion, arterial compression, dermal and epidermal congestion, or embolization are all proposed mechanisms. A national survey by the Korean Retina Society identified 44 cases of ophthalmic artery occlusion status post filler injections at the glabella, nasolabial folds, and nasal dorsum, in descending order of incidence. Compared to those receiving HA (n = 13), patients injected with autologous fat had a significantly higher rate of severe, diffuse occlusions (86% versus 39%, respectively; p = 0.007); cerebrovascular lesions on MRI (46% versus 8%, p = 0.03); and visual deficits (p = 0.01) with more persistent vision loss at 6 months (100% versus 43%, p = 0.02)(IIIb/B) [84]. Hence, autologous fat is now infrequently used in these regions, and nasal injections are often deep on the perichondrium below the vasculature, although the tissue in this region is often thin such that vessels can lie directly over bone or cartilage.

Calcium Hydroxylapatite

The first prospective study of postsurgical or posttrauma CaHA among 13 patients to correct minor nasal sidewall depressions, deeper supratip breaks, alar asymmetries, and/or dorsal irregularities was published in 2007. Three blinded observers evaluated pre- and post-injection photographs and rated 88% of participants (15 of the 17 treated regions) as improved. Eight of 13 (62%) graded their outcomes as excellent and 2 as good. There was one case of transient dorsal erythema. The authors argued that these findings were similar to those seen with HA filler or autologous fat (4) [85].

A larger, 4-year retrospective analysis of 385 racially/ethnically diverse subjects treated in a single private practice also chronicled efficacy and safety data of CaHA. The procedures included 235 injections onto the radix area, 229 into the tip, 229 into the dorsum, 92 into the sidewall, and 17 into alar creases. Twenty-five percent received treatment to a combination of sites with an average filler volume of 0.3–0.5 ml, depending on the defect(s) size and number. Of the 295 patients for whom there were good follow-up data, the majority had some degree of resorption and required touch-ups within the first year: 44% (136) within 2 months, mainly due to undercorrection; 28% (82) between 2 and 6 months; and 18% (54) between 6 and 12 months. Adverse events were stratified by history of prior operative rhinoplasty. Approximately 80% had never had surgery, and their incidence of complications was substantially lower. Prolonged erythema and swelling for more than 2 weeks were the most common in both groups. Others included telangiectasias, sensitive tips, bruises/hematoma, cellulitis, and skin irregularities. One case of skin necrosis occurred in each group, but only the patient with a history of rhinoplasty had visible scarring (4) [75].

In contrast, some experts argue against the use of CaHA for nasal recontouring, since it is irreversible and the thin nasal skin may be susceptible to more nodularity (V/C) [86]. A head-to-head comparison of 46 patients injected with either CAHA (26 cases) or HA (20 cases) at 88 anatomic sites on the nose over a 3-year period found no significant difference in patient satisfaction between the two products. Nonetheless, all five mild to moderate complications occurred after CaHA: one case of filler migration, two of hematoma, one of nodules persisting for 2 months, and one of nasal tip erythema. There were also two severe reactions status post CaHA, including fascial cellulitis and dislocation of a polyethylene rhinoplasty Medpor implant with consequent nasal tip abscess and skin necrosis. The investigators concluded that HA should be the exclusive agent injected in the nose, given these results (4) [87].

Other Filler Agents

There are reports of other products used for minimally invasive rhinoplasty, but these are injected infrequently or have largely been abandoned altogether. In 1986, Webster et al. published the first series of 347 subjects who had received liquid silicone touch-up after rhinoplasty using small volumes of 0.03–0.08 ml per session in an attempt to limit the risk of inflammatory reactions (4) [68]. There is also a retrospective chart review of 153 patients treated with Artecoll (4) [88], and in 2014, another study compared the results of 378 patients treated with either Restylane®, Artecoll®, or silicone. All achieved substantial improvement post-procedurally, yet these effects dissipated at 1 year in the Restylane® group compared to the others. Those injected with silicone had a higher rate and more severe adverse events (4) [89].

Neck and Chest

Soft tissue fillers can be injected off-label at the neck and décolletage, but none have FDA approval for these indications.

Photonumeric Scales

The Allergan Transverse Neck Lines Scale is another validated, patented rubric based on the presence and depth of the single most severe horizontal wrinkle at the anterior third of the neck. It requires assessing visually effaceable and non-effaceable lines, but does not take into account vertical banding, which can be addressed often with neuromodulators. An expert panel used the scale to rate images from 297 participants over 2 sessions and found that 1-point differences reflect meaningful clinical differences in transverse lines. It is posited that these changes may be more related to decreasing collagen and elastin rather than platysmal muscle contraction so are more amenable to correction with fillers (1a) [90].

Hyaluronic Acid

Belotero® is effective for the treatment of facial fine lines [47] and has been used clinically at the neck, but there is little literature to support this practice.

Calcium Hydroxylapatite

A case study of a 55-year-old Taiwanese woman exemplifies the use of dilute CaHA for horizontal neck lines. She received 1.3 ml Radiesse® mixed with 1.4 ml of 2% lidocaine (1:1 dilution), deposited at the dermal-subdermal junction via serial puncture technique along each transverse wrinkle. Post-procedural bruising and edema resolved in the first week, and the patient had been observed for 16 weeks at the time of publication with sustained improvement and no complications. Chao and colleagues argued that in their experience over 20 cases, this technique was highly effective perhaps due to the neocollagenesis and decreased skin laxity that comes from CaHA, though there was no accompanying histopathologic examination. Importantly, 2 of their 20 cases developed beading along the injection sites from too superficial

placement, which resolved with saline irrigation and massage (4) [91].

Poly-L-lactic Acid

Some experts consider the neck and chest unsuitable for treatment with PLLA, as there is a paucity of adnexa and subcutaneous fat relative to the face so the risk of adverse effects (i.e., nodules) increases [66, 92]. Nevertheless, several case reports demonstrate efficacy using increased reconstitution dilutions ranging from 7 to 24 ml (4) [65].

A retrospective series of 36 patients investigated injection of PLLA at the neck (33 patients) or neck plus chest (3 patients) for flaccidity, atrophy, and wrinkling. The product was diluted with 10 ml sterile water 48–72 h in advance and then 0.1 ml of 2% lidocaine added to each 0.9 ml of suspension. 0.5 ml depots were injected every 1 cm along horizontal rhytides and massaged for 2 min. Subjects were instructed to massage for 5 min, three times daily for 7 days. This protocol required a mean 1.8 treatment sessions per patient with only one necessary among those with mild changes (n = 15) and one to four among those with more severe, visible deficits (mean 2.38 sessions). Injected volumes ranged from 4 to 7 ml per session. At baseline, 15 subjects had palpable but not visible neck deficits reported on questionnaire; another 21 had visible skin changes. Overall, 91.6% (33 out of 36) were pleased with the results, which persisted at 18 months, and would undergo treatment again. 8.3% would not—two because of unsatisfactory results and one because of ecchymoses. Three independent dermatologists also evaluated photographs taken at baseline and 60 days to determine changes over time. In the subset of patients with visible deficits, 81–100% demonstrated improvement ($p < 0.001$). Nearly 100% had some degree of ecchymoses or hematomas that resolved within 2 weeks. One patient developed nodules at the anterior cervical region but admitted to not massaging as instructed, so the bumps were injected with sterile water and vigorously massaged three times daily for 10 days. By the 60th day of the final evaluation, 80% had resolved, a case that highlights the possible importance of massage in thin décolletage skin (4) [93].

Combination Therapy

A consensus report drafted by 15 expert aesthetic dermatologists for a special issue of Dermatologic Surgery outlined combination therapies for the neck to address fat accumulation, skin laxity, structural ptosis, platysmal banding, and necklace lines. They recommended a multitier approach depending on the severity of changes with botulinum toxin A as first-line followed by microfocused ultrasound with visualization (MFU-V) and then microaliquots of low-viscosity HA or CaHA fillers at a 1:1 or 1:2 dilution with saline or lidocaine. The additions of fractionated carbon dioxide lasers or radiofrequency were other considerations. Skin tightening procedures should be performed prior to injectable filler therapy, but botulinum and fillers or MFU-V could be performed at the same appointment (5) [94]. To support these recommendations, a retrospective chart review of 101 patients treated with MFU-V plus incobotulinum toxin A (18%) and Belotero® or Radiesse® (81%) suggested that the combining procedure was as safe as each individually (4) [95].

Conclusion

The growing popularity of soft tissue augmentation has led to many novel applications. And while well-designed clinical trials exist for FDA-approved indications such as the injection of HA, CaHA, or PLLA at the nasolabial folds and of HA at the lips, there is a paucity of rigorously designed studies to support their use in other regions. Medical practitioners must carefully review existing and future literature as it becomes available, as this field is rapidly changing with the introduction of newly approved filler agents and new treatment indications almost annually since the early 2000s.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Multiple, unique proprietary validated grading scales exist for the nasolabial folds, lips, perioral regions, jawline, chin, and transverse neck rhytides. Some were developed in the context of an FDA pivotal trial, and others have yet to be attached to clinical studies	B
Hyaluronic acid fillers can be used to treat moderate to severe facial wrinkles and folds lasting up to 1 year. Juvederm® Vollure XC is unique because correction may persist for up to 18 months	A
Hyaluronic acid fillers (Restylane®, Juvederm®, Belotero®) provide longer lasting correction of facials wrinkles, such as the nasolabial folds, than bovine collagen (Zyplast®)	A
Hyaluronic acid fillers have a similar or lower risk of adverse events compared to bovine collagen (Zyplast®). There is little risk of hypersensitivity reaction	A
Hyaluronic acid fillers (Juvederm®) with lidocaine are better tolerated than those without local anesthetic	A
Calcium hydroxylapatite filler (Radiesse®) can be used to treat moderate to severe facial wrinkles	A
Calcium hydroxylapatite filler (Radiesse®) provides longer lasting correction at the nasolabial folds than nonanimal stabilized hyaluronic acid filler (Restylane®) and human collagen filler	A
Calcium hydroxylapatite filler (Radiesse®) appears to be safe and does not interfere with interpretation of radiographic studies but does have an increased incidence of nodule formation when injected in the lips	B
Poly-L-lactic acid filler (Sculptra® Aesthetic) can be used to treat moderate to severe facial wrinkles	A
Subcutaneous papules and nodules are the most common adverse events post cosmetic injection of poly-L-lactic acid (Sculptra® Aesthetic)	A
Two hyaluronic acid fillers (Restylane®, Juvederm® Volbella) are FDA approved for augmentation of the lips and perioral region	A
Other hyaluronic acid fillers (Juvederm® Ultra) can also be used off-label in the perioral region	A
Correction of deeper, perioral rhytides with cohesive polydensified matrix filler (Belotero®) is less durable and more painful than with other hyaluronic acid filler (Juvederm®)	A
Nonsurgical, filler chin augmentation may be appropriate for patients with mild deficits. Severe micrognathia, soft tissue atrophy, or alveolar bony loss may be better corrected surgically	B
Postmarketing data suggest that patients and providers prefer Juvederm® Voluma over Restylane® for nonsurgical chin augmentation	B
Experts frequently recommend calcium hydroxylapatite (Radiesse®) for jaw augmentation and mandibular restoration	C
Bovine and human collagen, medical grade silicone, autologous fat or fibroblasts, polymethylmethacrylate (Artecoll®), hyaluronic acid (Restylane® and Juvederm® Ultra), and calcium hydroxylapatite (Radiesse®) fillers have all been used for nonsurgical rhinoplasty, with the latter two being the safest and most common. There are no currently FDA-approved agents available	B
Risk of vascular compromise, tissue necrosis, and retinopathy is more common after injection of autologous fat, compared to hyaluronic acid, at the glabella, nasolabial folds, and nasal dorsum (in descending order of incidence)	B
Calcium hydroxylapatite (Radiesse®) and poly-L-lactic acid (Scupltra® Aesthetic) are the most commonly reported fillers used for rejuvenation of the neck and décolletage	B
Multimodal therapies may be helpful for neck rejuvenation, and botulinum toxin A may be first line followed by hyaluronic acid or calcium hydroxylapatite (Radiesse®) fillers plus other procedures	C

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Self-Assessment Questions

1. Hyaluronic acid fillers are FDA approved for treatment of which of the following indications?
   (a) Moderate to severe facial wrinkles such as the nasolabial folds
   (b) Lip augmentation
   (c) Correction of perioral rhytides
   (d) Chin and jawline augmentation
   (e) Nonsurgical rhinoplasty
   (f) Transverse neck lines
   (g) a, b, and c
2. Calcium hydroxylapatite fillers are FDA approved for treatment of which of the following indications?
   (a) Moderate to severe facial wrinkles such as the nasolabial folds
   (b) Lip augmentation
   (c) HIV-associated lipoatrophy
   (d) Chin and jawline augmentation
   (e) Nonsurgical rhinoplasty
   (f) Transverse neck lines
   (g) a and c
3. Data from clinical trials suggests hyaluronic acid fillers at the nasolabial folds last for how long?
   (a) 3 months
   (b) 6 months
   (c) 12 months
   (d) 18 months
   (e) 24 months
   (f) c and d
4. (True or false) Autologous fat is the filler of choice for injection at the glabella and nasal dorsum.
5. (True or false) Multimodal therapy with neuromodulators, hyaluronic acid or calcium hydroxylapatite fillers, microfocused ultrasound with visualization, ablative lasers, and radiofrequency is the best approach to neck rejuvenation.

Correct Answers

1. g: a, b, and c. There are dermal fillers FDA approved and currently available in the USA for the treatment of moderate to severe wrinkles (i.e., nasolabial folds) as well as lip augmentation and perioral rhytides. The other uses listed above are considered off-label. Products approved for the correction of moderate to severe wrinkles: Restylane® and Restylane® Lyft, Refyne, Defyne; Juvederm® Ultra and Ultra Plus; Juvederm® Vollure XC; Belotero® Balance; Sculptra Aesthetic®; Radiesse®; and Bellafill® (formerly Artecoll®/Artefill®). Products for lip augmentation: Restylane®, Restylane® Silk, and Juvederm® Volbella XC. Silk and Volbella are also approved for correction of perioral rhytides
2. g: a and c. Calcium hydroxylapatite is FDA approved, under the brand name Radiesse®, for treatment of moderate to severe facial wrinkles as well as HIV-related lipoatrophy. In 2015, it also received approval to correct dorsal hand volume loss.
3. f: Most HA fillers have been shown to last up to 1 year at the nasolabial folds. However, Juvederm® Vollure XC is unique with data suggesting up to 18 months duration.
4. False. These are high-risk areas, and complication rates (i.e., vascular occlusion and necrosis) are higher with injection of autologous fat compared to hyaluronic acid fillers.
5. True

40

Soft Tissue Augmentation (Temporary Injectable Fillers) on the Trunk and Extremities (Hands, Feet, Trunk)

Alyx Rosen, Shino Bay Aguilera, Drew Taylor, and Eduardo Weiss

Abstract

In 2015, over 2.4 million patients had treatments with soft tissue fillers, with the largest population between 40 and 54 years of age and ranging in age from teenagers to nonagenarians (ASPS, Plastic Surgery Statistics Report 2015, 2015) (4). This data is also representative of the patient population seeking treatment with temporary fillers of the trunk and extremities where the average age is around 60 years, with females significantly outweighing males. All skin types are represented in this demographic, but skin types II–IV are far more common than V–VI.

Keywords

Dorsal hands · Temporary fillers · Volume loss Extremities · Trunk · Soft tissue

Indications

In 2015, over 2.4 million patients had treatments with soft tissue fillers, with the largest population between 40 and 54 years of age and ranging in age from teenagers to nonagenarians [1] (4). This data is also representative of the patient population seeking treatment with temporary fillers of the trunk and extremities where the average age

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is around 60 years, with females significantly outweighing males. All skin types are represented in this demographic, but skin types II–IV are far more common than V–VI.

Soft tissue augmentation is utilized to help counteract the visible signs of aging that result from both intrinsic and extrinsic factors. Intrinsic factors refer to natural thinning of the dermis, bone resorption and osteoporosis, fat atrophy, and loss of elasticity, while extrinsic factors include photodamage, chronic friction, extreme temperatures, and repeated exposure to harsh chemicals especially on the hands. In photoexposed areas, long-term ultraviolet damage amplifies the natural intrinsic factors of aging.

The indications for temporary fillers inherently vary depending on the treatment location. As aesthetic procedures on the face continue to rise in popularity, there is a growing need for appropriate aesthetic interventions of non-facial areas. The application of dermal fillers solely to the face limits the possibilities that dermal fillers offer. On the hands, temporary fillers improve the appearance of pronounced muscles and tendons, prominent bones, large intermetacarpal spaces, and visible reticular veins. They can also improve the overall skin texture and turgor. Similarly, subdermal injection of temporary fillers on the dorsal feet can conceivably treat many of the same features of aging that affect the dorsal hands and improve the overall aesthetics. Chest and décolletage procedures have become increasingly popular as patients with rejuvenated and youthful facial appearances appreciate a drastic inconsistency between the treated facial and untreated non-facial skin. Temporary fillers on the chest are becoming popular treatments to address factors such as skin laxity and atrophy, fine lines, and deeper rhytides. While more traditional surgical approaches and novel, minimally invasive, heat- or ultrasound-based technologies are in much higher demand for treatment of upper arm ptosis, temporary fillers in this area have infrequently been used to reduce skin laxity and rhytides. Aesthetic complaints of the buttocks and thighs are often complex and multiple; however, those best managed with temporary fillers are lipoatrophy or volume loss and platypygia (sad buttock). There can also be a secondary minimal reduction in striae and cellulite appearance. Fillers are now utilized for augmentation while simultaneously improving the skin laxity of the buttocks. Finally, isolated cases have been reported for the use of temporary fillers to revolumize the medial ankles, improve postoperative soft tissue loss after surgery, ameliorate acne scars, or relieve metatarsalgia from high heels. Results from these procedures are based solely on anecdotal cases, and therefore significantly more data is needed to determine their overall benefit.

Calcium hydroxyapatite (CaHA; Radiesse®) was Food and Drug Administration (FDA) approved in 2015 for soft tissue augmentation of the dorsal hands [2] (1b). It was approved previously in 2010 in Canada for the same indication. While no other temporary fillers, including hyaluronic acid (HA) fillers or poly-L-lactic acid (PLLA, New-Fill®/Sculptra®, Dermik Laboratories, Berwyn, PA, USA), are FDA approved for use on the trunk or extremities, they clearly demonstrate benefit in these treatment zones and can improve the signs of aging. Most published literature supports the use of temporary fillers on the dorsal hands and chest with only a few studies, case reports, and expert opinions discussing the success of temporary fillers on the upper arms, buttocks, thighs, dorsal feet, abdomen, and other scar-like deformities. The bulk of this chapter will focus on the former.

Effectiveness

The longevity of temporary fillers on the trunk and extremities is similar to their well-established duration on the face. HA fillers last for approximately 4–6 months with few patients having sustained improvement beyond 8 months. PLLA and CaHA both have the benefit of long-term collagen stimulation. PLLA promotes neocollagenesis by fibroblasts and correction can last up to 2 years [3, 4] (2c; 5). One study demonstrated that PLLA increased dermal thickness by 4–6 mm on the cheeks and nasolabial regions, which may be extrapolated to injections off the face [5] (1b). CaHA microspheres provide aesthetic improvement by both volume enhancement and collagen biostimulation leading to improvement in skin elasticity and firmness. Evidence suggests that

CaHA can have effect from 12 or even up to 24 months [6] (1b). The longevity of PLLA and CaHA along with the collagen-stimulating effects are often advantageous over HA fillers.

Hands: Radiesse® (Merz; CaHA) received FDA approval for correction of hand volume loss in 2015 based on the results of three separate clinical studies funded by Merz [2]. The first clinical trial of Radiesse® for hand augmentation was conducted in Germany in 2008 [7] (1b). Busso et al. evaluated 101 patients with hand volume loss in a multicenter randomized trial. Patients were randomized to treatment with CaHA or delayed treatment (control group) with CaHA to the dorsal hands. After anesthetization with a lidocaine bleb, each hand was injected with CaHA in a bolus in the areolar plane. Total mean volume of CaHA injected was 3.1 ml for both hands. Only one Radiesse® treatment was performed through 12 months. Efficacy was assessed using the Busso Hand Volume Severity Scale and the Global Aesthetic Improvement Scale (GAIS) (Fig. 40.1), which was modified to include additional categories of "Much Worse" and "Very Much Worse." Blinded evaluators using study photographs reported that 66% and 56% of hands showed at least a 1-point improvement on the Busso Hand Volume Severity Scale at 3 and 6 months, respectively. Additionally, 89% and 75% of hands at 3 and 6 months, respectively, were rated as being at least improved on the revised GAIS. Of all patients treated with CaHA, 51% were still improved at 12 months after a single treatment.

In 2012, a study in Canada demonstrated the clinical utility of the Merz Hand Grading Scale (MHGS) (Fig. 40.2). The MHGS is a photonumeric scale that was initially validated for making photographic and later (in 2015) in-person assessments [8, 9] (5; 1b). Thirty patients were enrolled with 20 patients randomized to the CaHA treatment group and 10 patients randomized to an untreated control group. CaHA (1.5 ml; *note modified syringe volume) was mixed with 0.26 ml of 2% lidocaine and injected using small boluses (0.2–0.5 ml) into the dorsal hands bound laterally between the first and fifth metacarpals, proximally by the dorsal wrist crease, and distally by the metacarpophalangeal joints using a 27-gauge needle. The total number of injection points varied, and a maximum of 3.0 ml of CaHA could be injected per hand per treatment session. After injection, the hands were massaged until the desired cosmetic effect was achieved. At 1-month follow-up, all 40 hands in the treatment group had ≥1-point improvement on the MHGS compared to none in the control group, which highly correlated with a rating of "improved" or better on the GAIS. The authors concluded that a ≥1-point improvement on the MHGS was both clinically meaningful and aesthetically pleasing.

The final study performed in the US provided the primary effectiveness and safety experience that ultimately led to FDA approval [2]. In this prospective, randomized, controlled study of 114 patients, 85 were randomized to immediate treatment with CaHA and 29 were randomized to delayed treatment at 3 months. Injections were performed in the same way as the Canadian study described above except that patients were eligible for retreatment at 6 months after initial injection at

Fig. 40.1 5-Point graded global aesthetic improvement scale

Rating	*Description*
Very much improved	Optimal cosmetic result for the implant in this patient
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition

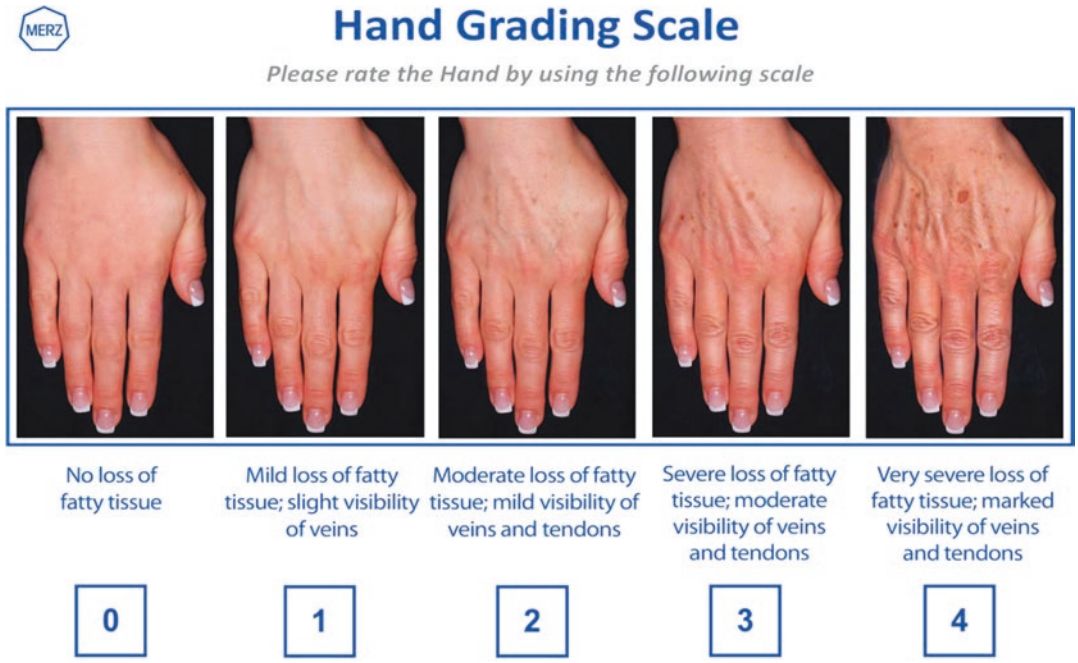

Fig. 40.2 Merz Hand grading scale [9]

the discretion of the investigator with 69% of patients receiving retreatment. Live assessments were performed by blinded nonphysicians using the validated MHGS with 75.3% of treated patients demonstrating a ≥1-point improvement from baseline in both hands compared to 3.4% in the control group. At 12 months, 71.7% of patients who received a single injection of CaHA had a ≥1-point improvement on the MHGS. The findings of these three clinical studies supported the effectiveness of CaHA in rejuvenation of the dorsal hands.

Subsequently, several other authors reported similar outcomes of patient satisfaction and duration of effect. CaHA remains the only FDA-approved soft tissue filler for rejuvenation of the dorsal hands. Although differences in dilutions, total volume injected, and total treatment sessions have been reported, no comparative studies have been performed [10, 11] (4; 5).

In addition to CaHA, both PLLA and HA fillers have been utilized for soft tissue augmentation of the dorsal hands. In 2006, Redaelli injected the dorsal hands of 27 patients with PLLA. On average, patients received 4 sessions (range 3–6 sessions) with 1 month between the first 3 injections and up to 3 months between the third and subsequent treatments. PLLA was reconstituted 12 h prior to injection. The author developed a standardized protocol for treatment with 2 ml of a 5-ml dilution (0.5 ml of 3% Carbocain and the rest distilled water) per hand at initial treatment and a 1.5–2 ml of a 6–8-ml dilution (0.5 ml of 3% Carbocain and the rest distilled water) on subsequent treatment sessions. Patients were injected using a 25–27-gauge needle into the subcutaneous tissue overlying tendons in a linear bolus technique. Volumes of 0.05–0.1 ml of PLLA were delivered per injection [12] (4). Patients were evaluated using a Definitive Graduated Score (DGS) from 1 to 10 using photographic results combined with physician and patient satisfaction scores. The time point of evaluation postinjection was typically 3 months post the last treatment, and results ranged from 4 to 9 with an average of 6.55. When they evaluated the scores of all case histories of patients treated, it was a 7.8. The authors did report improvement in the appearance of tortuous veins that were sustained at 15 months postinjection. Redaelli and Forte in 2009 went on to report

the cosmetic results of 568 patients treated with PLLA in their experience. One hundred and one patients received treatment to the dorsal hands using the same 6–8-ml dilution as above. Overall, the DGS for the hands was 6.3, the lowest of all areas treated. The authors attributed the low scores to possibly using too dilute solutions and the number of sessions needed to treat the dorsal hands [13] (4). Other experts have similarly reported on the successful use of PLLA for rejuvenation of the dorsal hands [11, 14] (4).

Several HA fillers have been evaluated for use in rejuvenation of the dorsal hands. HA fillers can be either non-stabilized (native) or stabilized, meaning the native polysaccharide is made more resistant against degradation by dermal hyaluronidases through chemical cross-linking. Williams et al. looked at changes in skin physiology and clinical appearance after injection with non-stabilized versus stabilized HA fillers. Fifteen volunteers were randomly assigned to injections with either stabilized HA (Restylane Vital®, Q-Med) or non-stabilized HA (Teosyal Meso®, Teoxane) to the left and right hands. They received 0.5 ml of filler injected per hand using microdroplet placement in the mid-to-deep dermis at weeks 0, 4, and 8. Efficacy was based on a clinical hand aging score performed by a blinded dermatologist as well as biophysical parameters, including skin surface morphology, elasticity, stratum corneum hydration, and transepidermal water loss. Overall, improvement in the clinical appearance was seen with both HA fillers; however, the difference in clinical improvement at week 12 was significantly greater for the stabilized HA-treated hands. Only the stabilized HA-treated hands showed significant improvement in skin elasticity and surface roughness at week 12 compared to baseline, and there was a significantly higher hydration level and lower transepidermal water loss at week 12 for the stabilized HA-treated hands compared to the non-stabilized treated hands. Overall, efficacy trended towards baseline by week 24 [15] (1b).

Man et al. performed a blinded comparative study of the HA filler, Restylane (Medicis, Scottsdale, AZ) to collagen (Cosmoplast, Allergan Inc., Irvine, CA). Ten female patients were randomized to receive two vials of HA (1.4 cm^2) and two vials of collagen (2.0 cm^2) to different hands. Material was injected into the subcutaneous plane. Evaluation was performed based on pretreatment and 3-month posttreatment photographs assessing for vein clearance on a visual analog scale from 1 (worse than before treatment) to 5 (complete clearance of veins). Mean scores in difference for clearance were 0.95 for HA versus collagen, indicating a better clearance with the HA filler. Patient satisfaction was also evaluated and was rated higher for HA than collagen, although it did not reach statistical significance [16] (1b). Alternatively, Gubanova et al. compared HA with saline for rejuvenation of the hands. In this study, patients received 1.0 ml of HA (Restylane Vital®, Q-Med) in one hand and 1.0 ml of saline (0.9% NaCl) in the other hand. Injections were done using a multipuncture, microinjection technique into the dermal layer. Three treatments were performed 1 month apart. Efficacy was determined using the GAIS and by calculating multiple biochemical properties. When compared against saline, patient's GAIS scores from month 1 to 3 were significantly higher for HA versus saline-treated hand. Statistically significant improvements in hydration and elasticity for the HA versus the saline hand were also seen at month 3. Sixty-one percent of patients injected with HA felt the treatment effect was maintained at 12 months [17] (1b).

Chest: There are few studies looking at the benefits of temporary fillers on the chest and décolletage, and most data exists for the utilization of PLLA in this area. Mazzuco and colleagues performed a prospective study of PLLA for neck and chest rejuvenation [18] (4). Thirty-three patients had PLLA injections to the neck area, and another three patients received injections to the neck and chest. Patients with mild signs of photoaging received an average of one treatment, whereas patients with moderate to severe signs received an average of 2.38 treatments. Variations occurred in the total amount of product injected. Overall, there was improvement in flaccidity, atrophy, and rhytides with 91.6% of patients pleased with their results at evaluation 60 days after the last treatment. Independent data for patients who had both the neck and chest regions injected were not reported.

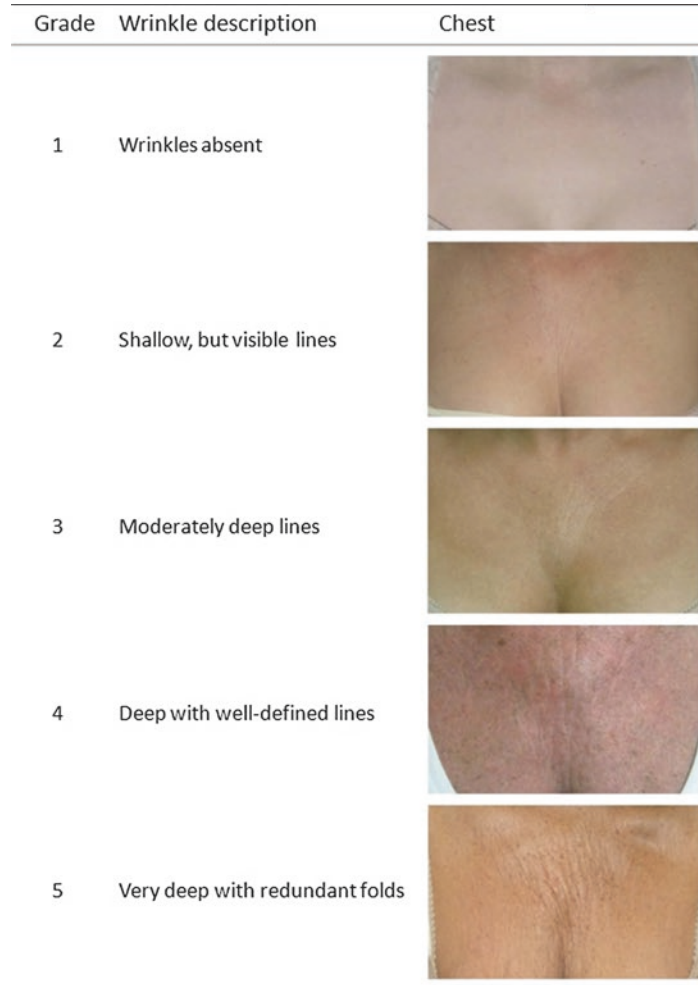

Fig. 40.3 Fabi–Bolton 5-point chest wrinkle scale (F–B scale) [20]

Bolton et al. performed a retrospective study of 28 patients using PLLA for chest rejuvenation [19] (2b). The authors simultaneously created and validated a 5-Point Chest Wrinkle Scale to address photodamage and rhytides on the chest (Fig. 40.3) [20] (1b). Patients with baseline scores of 3 or higher were candidates for the study. The authors primarily used a 16-ml dilution (PLLA; 150 mg: 14-ml saline + 2-ml lidocaine). The average number of treatments was 2.3 (range, 1–7 treatments) with a cumulative average 28.5 ml of PLLA injected (range, 3.75–104 ml). Best improvements were seen in patients who received at least three PLLA treatments with 16 ml per treatment. Eleven of the 28 patients had follow-up photography and were noted to have a 1- to 2-point improvement on the 5-Point Chest Wrinkle Scale. No difference in effectiveness was noted based on the severity of pre-treatment score.

The benefit of the HA filler, Restylane Vital® (Galderma, USA), for aesthetic improvement of the chest was evaluated by Streker et al. in an open, randomized, intra-individually controlled, split-side, single center study [21] (1b). Thirty patients were enrolled and one side of the chest was injected with the HA, using an auto-injector device. Patients received up to 4 ml per treatment session across the face, dorsal hands, and chest at weeks 0, 4, and 8. Total amount injected into the chest area was not specified. Subjects and independent blinded dermatologists used the 5-point graded GAIS [22] (1b). Significant improvement was noted for the chest at 12, 20, and 28, but not at 36 weeks, with greatest

improvement seen between 8 and 20 weeks after initial injection.

Aside from these studies, there are several reports of expert opinion or consensus recommendations regarding the treatment of the chest and décolletage with temporary fillers. In 2016, Fabi et al. published consensus recommendations for combined aesthetic interventions in the neck, décolletage, hands, and other body sites and discussed the roles of HA and CaHA in soft tissue augmentation [23] (5). For early intervention of fine lines and rhytides on the chest, Fabi et al. recommend low-viscosity HA or CaHA to stimulate neocollagenesis and improve skin hydration and elasticity. For patients requiring more aesthetic restoration for significant rhytides, low-viscosity HA or diluted CaHA is recommended in combination with microfocused ultrasound. Combined therapy will be discussed in greater detail in a later section. Chest rejuvenation with HA and PLLA has also been described in several expert opinion reports [13, 24, 25] (5; 5). PLLA injected over 2–4 treatment sessions 4 weeks apart can improve flaccidity, atrophy, and rhytides for up to 2 years. Alternatively, low-viscosity HAs Belotero® (Merz) or Restylane Silk® (Galderma) can be used successfully on the chest and last up to 8 months. Vanaman et al. are also currently investigating the safety, efficacy, and patient satisfaction of CaHA for treatment of chest rhytides. There is no consensus on which patients would benefit from treatment with an HA versus CaHA versus PLLA.

Arms: Historically, treatment of upper arm laxity and fat accumulation required a surgical approach with brachioplasty. However, there are several trials supporting the use of temporary fillers for appropriate patients desiring less invasive treatments. In a small study of 16 women with moderate brachial ptosis (corresponding to stages 1, 2a, and 2b on the Brachial Ptosis Scale) and loose upper arm skin (Fig. 40.4) [26] (4), 1 ml of

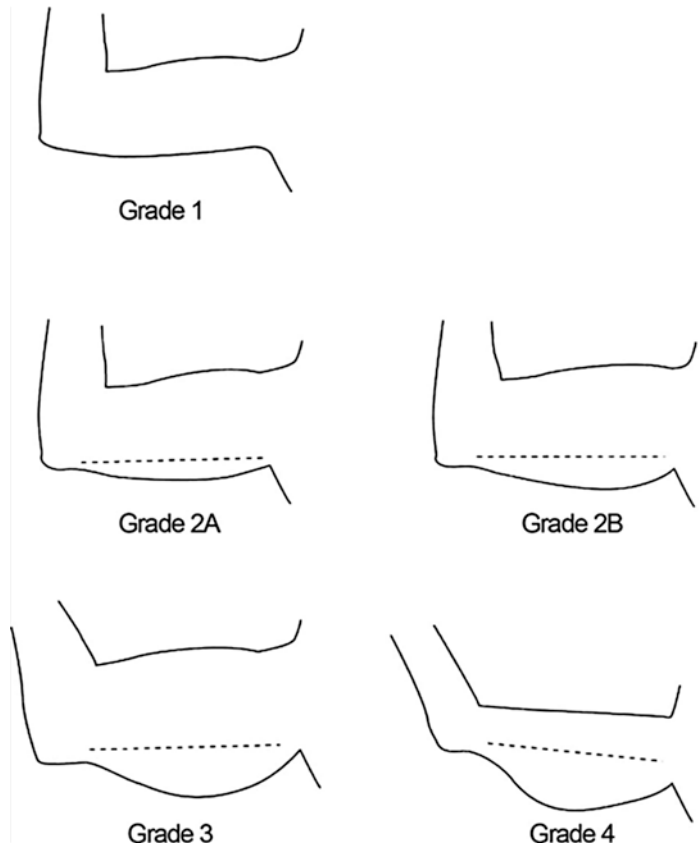

Fig. 40.4 Schematic drawing of the classification of brachial ptosis. The dotted lines denote the brachial sulcus [26]

HA (Restylane Vital®, Q-Med) was injected into the upper arm at 3 intervals 1 month apart. The authors used a capacitance device, an ultrasound Dermascan, and a suction device, Cutometer, to objectively measure stratum corneum hydration, skin thickness, and skin elasticity, respectively. Statistically significant improvement was seen in all parameters [27] (4). Two separate studies evaluated CaHA with lidocaine for rejuvenation of the upper arms. In a prospective study, 30 subjects received 1.5 ml per arm at 2 treatment sessions 1 month apart. Five months after initial injection, statistically significant improvements in skin flaccidity were observed with persistent incremental improvements with time after injection. Overall, 100% of patients were at least satisfied with the results. In this study, the authors also developed an Arm Visual Analog Score (Arm VAS) and noted no distinction of benefit based on severity. Cogorno Wasylkowsi instituted a novel body vectoring technique with CaHA for tightening of the abdomen, thighs, and brachial zone. Overall, 12 brachial zones were injected with 1.5 ml of diluted (0.6-ml 2% lidocaine without epinephrine) CaHA. Cutometer and ultrasound measurements were obtained at baseline and 5 weeks after treatment. Approximately 70% of patients had improvement in flaccidity with a mean reduction of 0.0924 mm, and 60% of patients had improved skin thickness and density of the brachial zone at 5 weeks posttreatment [28, 29] (4; 4).

Buttocks: In the buttock region, temporary fillers may be used alone or in combination with microfocused ultrasound or radiofrequency for augmentation and to improve irregularities in the surface of the skin [23]. They are best utilized in patients desiring mild to moderate correction in buttock projection and volumization who do not want silicone implants or surgical correction. Lorenc uses PLLA in this region in patients with low body mass index and insufficient fat for autologous fat transfer [30] (5). A single published report of two patients demonstrated aesthetic improvement with PLLA for the gluteal region. Although different treatment volumes and number of sessions varied for the two patients, the authors observed decreased flaccidity and improved projection in both patients [18]. Alternatively, Coleman and Pozner highlight combination therapies and sequences of treatments for correction of aesthetic concerns of the outer thigh and buttocks. Temporary fillers, including PLLA or HA fillers, can be used as second- or third-line treatments mainly for volume loss, laxity, and cellulite, in combination with other modalities (Fig. 40.5) [31] (5).

Thighs/knees/ankles/abdomen/others: Similar to the body vectoring technique used on the brachial zone, Cogorno Wasylkowsi injected 17 thigh regions and 7 hemi-abdomens with 3.0 ml and 1.5 ml of diluted (0.6-ml 2% lidocaine without epinephrine) CaHA, respectively. Cutometer and ultrasound measurements 5 weeks after treatment demonstrated a 0.0117 mm and 0.0814 mm reduction in flaccidity from baseline for the thighs and abdomen, respectively. Skin thickness of the thighs improved for 88% of patients, and a similar improvement in skin density was seen on the abdomen. Overall, 100% of subjects reported improved skin thickness in this study [29]. Redaelli and Forte demonstrated promising results for 17 patients injected with PLLA to the upper arm and medial thighs although no specifics of the treatments to these areas were provided [13]. Consensus recommendations for aesthetic improvement of the abdomen include combined treatment of CaHA to reduce skin flaccidity and increase skin density and thickness with microfocused ultrasound to tighten residual loose skin [23]. Individual reports of PLLA injected into the medial ankles, lateral abdominal depression, postoperative scar, axillary folds, pectus excavatum, and inferior breast have all been reported with improvement [13, 30, 32–34] (5; 4; 5).

Preoperative Evaluation

Although patients seeking soft tissue augmentation of the trunk and extremities encompass a wide age range, they are typically healthy and do not require any specific preoperative evaluations prior to treatment (unless considering a semipermanent filler like Bellafill® that would require a prick test prior to injection). Since

	Option 1	Option 2	Option 3
Striae	1. 595 nm/532 nm laser	1. 595 nm/532 nm laser	1. Nonablative fractional laser
	2. Nonablative fractionated laser	2. Microneedling	2. Ablative fractional laser
Laxity/volume loss	1. Microfocused ultrasound/ radiofrequency	1. Microfocused ultrasound/ radiofrequency	
	2. Fat transfer	2. PLLA or HA filler	
Volume loss/adiposity (separate locations)	1. Liposuction	1. Nonthermal focused ultrasound/Hi-frequency focused ultrasound/Focused Field radiofrequency	1. Cryolipolysis
	2. Fat transfer	2. PLLA or HA filler	2. PLLA or HA filler
Cellulite/volume loss	1. Subdermal release/ subdermal laser/subdermal ultrasound	1. Radiofrequency	1. Subcision
	2. Fat transfer	2. PLLA or HA filler	2. PLLA or HA filler
Cellulite/adiposity	Liposuction performed sequentially with subdermal release, subdermal laser, or pulsed ultrasonic ultrasound	1. Radiofrequency tightening	1. Radiofrequency
		2. Nonthermal focused ultrasound/Hi-frequency focused ultrasound/Focused Field radiofrequency	2. Liposuction
Cellulite/laxity	Subdermal release + radiofrequency/microfocused ultrasound	1. Radiofrequency/ microfocused ultrasound	
		2. Subdermal laser/ultrasound	

Fig. 40.5 Potential combination therapies and sequences of treatment for common conditions of the outer thigh and buttock [31]

Radiesse® for rejuvenation of the dorsal hands is the only FDA-approved temporary filler for use on the trunk and extremities, patients should be made aware that all other fillers in these areas are being used off-label. A patient's comprehensive medical history, including prior cosmetic treatments and a full list of medications, should also be obtained.

There are no specific criteria regarding temporary cessation of blood thinners for injections on the trunk and extremities. The ASDS Guidelines of Care for Injectable Fillers does recommend that patients without a medical indication for anticoagulants discontinue therapy for about 1 week before the procedure [35] (5). Patients with a medical indication for anticoagulants, however, should not discontinue their therapy prior to treatment with fillers. Additionally, patients may benefit from discontinuation of any foodstuffs, herbal supplements, and over-the-counter medications that may increase their risk of bleeding. Older patients with evidence of actinic purpura, who may or may not be on blood thinners, should be informed of the increased risk of ecchymosis, especially in areas prone to skin thinning, such as the dorsal hands or chest.

There are few absolute contraindications to injectable fillers. A major contraindication is a known allergy or hypersensitivity to the filler material or the lidocaine mixed in the syringe of the filler. Acute or delayed allergic reactions can occur with the HA products and to a lesser extent with PLLA or CaHA. CaHA is contraindicated in patients with severe allergies manifested by a history of anaphylaxis. Patients with ongoing skin infections in the area to be treated or adjacent skin should not be treated in an effort to avoid inoculation with the infecting organism. On the trunk or extremities, certain infections to consider include verruca vulgaris, herpes simplex virus, bacterial infections such as impetigo, and folliculitis. Patients with diabetes, compromised lower

extremity circulation, or any conditions that may predispose to the formation of ulcers should also be advised against temporary fillers to the feet [36] (5). Specifically, patients with bleeding disorders should avoid injections with CaHA.

Questionable contraindications or skin conditions that can be aggravated by the use of temporary fillers include connective tissue diseases, immunosuppression, and immunobullous disorders. The available data, however, is limited. Similarly, injectable fillers should be avoided in patients with active granulomatous disease as the materials can elicit an unwanted granulomatous foreign body response [4, 30].

The chest and décolletage areas demonstrate variable distribution of subcutaneous fat and decreased pilosebaceous structures in comparison with facial skin. This results in slower healing and a higher risk of scarring (secondary to a lack of stem cells in the bulge area of the hair follicle.) Also, it is important to inquire about a personal or family history of keloidal or hypertrophic scarring and educate patients on the theoretical risk with any procedure. While keloid scarring after injury occurs 18 times as often in African American patients as in Caucasian patients, the safety data from post-market studies of soft tissue fillers on the face has not shown an increased risk of keloid development [37] (5). It is unclear if this data can be extrapolated to treatment on the trunk or extremities given the proclivity of patients developing keloids on the trunk and extremities.

Best Techniques and Procedures

Prior to injection with soft tissue fillers, the areas to be treated should be cleansed with alcohol or an appropriate antiseptic. The use of topical anesthetic cream to decrease pain from needle insertion is at the discretion of the provider. When utilized, the cream is applied under occlusion on areas to be treated for 30–45 min. Nerve blocks are typically not necessary when injecting the trunk or extremities. Additionally, temporary fillers are typically diluted with lidocaine to help decrease the discomfort with injections. Lidocaine with or without epinephrine can safely be used when mixing. Although the manufacturer of PLLA recommends using sterile water for reconstitution, some practitioners safely use bacteriostatic saline, which is associated with decreased patient discomfort during injection secondary to the benzyl alcohol component. It is important to keep in mind that HA fillers vary in the degree of crosslinking, gel hardness, gel consistency, viscosity, extrusion force, HA concentration, extent of hydration, and whether they are pre-mixed with lidocaine. Global availability varies among different countries. Similarly, PLLA is supplied as a 367.5 mg or a 150 mg vial of freeze-dried powder of synthetic L-polymer of polylactic acid in the United States and Europe, respectively. The effect of injection of PLLA is dose- and not volume-dependent. CaHA can also be combined with lidocaine to mitigate the pain associated with injection. Mixing the CaHA and the lidocaine lowers the viscosity and the extrusion force found in the original Radiesse® formulation but does not compromise the properties of the CaHA [36]. CaHA with powder lidocaine (Radiesse® (+)) is now commercially available.

Hands: The area to be injected of the dorsal hand includes the space bound laterally by the fifth metacarpal, medially by the second metacarpal (although some use the first metacarpal), proximally by the dorsal wrist crease, and distally by the metacarpophalangeal joints. Regarding CaHA injections of the hand, this section will focus on the techniques used in the studies that led to FDA approval as well as alternative injection techniques that have been described in the literature.

As described above, Merz conducted three clinical studies to investigate the effectiveness and safety of CaHA (Radisse®) in treating volume loss of the hands [2]. In the US study, the 1.5-ml syringe of Radiesse® was mixed with 0.26 ml of 2% lidocaine and injected using small boluses (0.2–0.5 ml) into the dorsal hands. Following injection, the hand was massaged to evenly distribute the material. A maximum of 3 ml of CaHA could be injected per hand per treatment session. No detrimental effect on hand function was found after treatment with

Radiesse®, and there were no new safety issues identified during this 12-month study. In the German study, Busso et al. injected one vial (1.3 ml) of CaHA mixed with 0.1 ml of 2% lidocaine per hand [7]. Material was injected into the subcutaneous areolar plane as 0.5–1.4-ml boluses. The hands were massaged with the patient making a fist to evenly distribute the product.

Since the initial studies, alternative dilutions and injection techniques have been described in the literature. Most authors mix the vials of CaHA with some volume of lidocaine (ranging from 0.015 to 0.5 ml) to decrease pain with injection as well as the viscosity and extrusion force of the filler. Some experts will mix one vial of CaHA (1.5 ml) with 0.3–0.5 ml of 1% lidocaine and 1.0–1.2 ml of bacteriostatic 0.9% saline in a 1:1 dilution. Injections can be performed as small boluses of 0.2–0.5 ml of material over the entire dorsal hand or as larger boluses up to 1.5 ml. A tunneling or fanning technique with a blunt cannula can also be implemented. The thickness of the dorsal hand tissue, including epidermis, dermis, and subcutaneous tissue is 1–2 mm. Skin tenting is therefore often performed to help magnify the areolar fatty plane of injection just deep to the dermis and provide more separation between the needle or cannula and the important vascular or tendinous structures below. Regardless of injection technique, the material should be evenly spread using gentle massage after injection is complete. This is most easily performed using an emollient for ease of massage and with the patient's hand in a first position to allow for more even distribution. Injection technique for CaHA to the dorsal feet is identical to that of the hands [10, 38–40] (5, 5, 5).

Injection techniques for PLLA on the dorsal hands are based mainly on expert experience. Redaelli, in the first published case series of PLLA for rejuvenation of the dorsal hands, used an average dilution of 6 ml (range 5–8 ml) (PLLA; 150 mg). More concentrated dilutions (5 ml dilution) injected in the subcutaneous intermetacarpal tissue with a max volume of 2 ml per hand were given at the first session. Subsequently, less concentrated dilutions (max 2 ml of 6–8 ml dilutions) were used at monthly follow-up visits [12]. Lorenc recommends using a 14-ml reconstitution volume (PLLA; 367.5 mg: 5 ml of sterile water and 9 ml of 1% lidocaine) with 7 ml used per dorsal hand. Injections are performed using a 1-inch, 25-gauge needle or cannula into the loose areolar space. He recommends this high volume of reconstitution because of the close proximity of the dermis to the tendon sheaths, especially with volume loss, and also because of the reduced risk of nodule formation. Only one patient who had five sessions was noted to develop a palpable, nonvisible nodule at 15 months [30]. Sadick summarized treatment techniques from three clinical practices that used dilution volumes of 8 (6-ml sterile water + 2 ml of lidocaine) to10 ml (5-ml sterile water + 5 ml of lidocaine) [11]. Patients received an average of 1.28 vials per treatment and 2.38 treatments between 4 and 8 weeks apart. Injections were performed with a 1.5-inch, 25-gauge needle. Palm et al. described treating 130 patients with PLLA, of which 8 patients received injections in the dorsal hands [14]. Average dilution volume and number of treatments for the hands were 10.25 ml and 2.5, respectively. Only one patient developed a nodule after a single treatment with a 12-ml dilution. The 12-ml dilution will be described in detail since a single PLLA vial can only hold up to 10 ml of solution. The day prior to injection, a single vial of PLLA is reconstituted with 1 ml of 1% lidocaine and 5 ml of bacteriostatic saline or sterile water. The reconstituted product is agitated immediately prior to injection and then 1.5 ml is withdrawn into a 3-ml syringe. Next, another 1.5 ml of bacteriostatic saline is withdrawn into the syringe for a combined total volume of 3 ml. These steps are repeated until a final total of 12 ml is mixed and drawn in the 3-ml syringes [39].

Injection techniques also vary among physicians. Redaelli performed injections with patients in the Trendelenburg position to reduce vein pressure and risk of bleeding [12]. Injections can be performed using a linear threading technique or a retrograde fanning technique, usually depositing up to 0.1 ml per injection. Some experts vary the injection plane and technique depending

on the exact location on the hand. Sadick used a subdermal threading technique more proximally and a depot technique in the mid-hand. The interosseous areas were injected using a fist maneuver and into the muscle belly. Most experts perform a postinjection massage for 5–15 min, and then patients are advised to follow the rule of 5 s; massage for 5 min, five times a day for 5 days [11].

Man et al. injected 1.4 ml of HA (Restylane®, Q-Med) into a single dorsal hand. Injections were performed with the patients also in the Trendelenburg position and with their hand at rest. HA was placed subcutaneously using a threading technique adjacent to the dorsal veins. Gentle massage was performed after injection, and patients kept their hands in a neutral rest position for 2 h. Neither anesthesia nor posttreatment cooling was used [16]. In their expert review, Fabi et al. describe a similar injection technique, although they recommend mixing one vial of HA with 0.2 ml of 1% lidocaine with epinephrine [39]. Williams and Gubanova both used a microdroplet technique with a 30-gauge needle for injection of HA (Restylane Vitale®, Q-Med) on the dorsal hands. Patients received three treatment sessions 1 month apart. Williams injected a total of 0.5 ml of product per hand per session versus Gubanova who injected 1 ml per hand per treatment session. Topical anesthetic applied for 20–45 min in both studies [15, 17]. When injecting the dorsal hands, Rivkin first determines the amount of volume loss using the MHGS prior to treatment. For patients with a score of 2–3, he uses the HA filler Juvederm Voluma® XC (Allergan) and dilutes it 1:1 with 0.8 ml saline and 0.2 ml of 1% lidocaine. He injects using a 30-gauge 0.5–1-inch needle or a 27-gauge cannula. When treating patients with more severe volume loss, or MHGS score of 4, he uses undiluted Juvederm Volume® XC (Allergan) [41] (5).

Finally, one group determined a purely anatomical approach to injectable fillers of the dorsal hands. They dissected 19 fresh cadaveric hands and conducted duplex ultrasounds of 28 healthy hands to generate an anatomically designed injection technique. The technique was then validated on another eight fresh cadavers followed by magnetic resonance imaging (MRI) and dissection and compared with other common injection techniques like the ones described above. Their technique named Scrape Skin Threading Technique used a cannula to scrape the deep side of the dermis for placement of product in the fascial plane using a fanning technique with retrograde injections at two entry points. The authors of this study refrained from skin tenting as they found it lifted the desired fascial plane of injection and the dorsal veins with the skin and therefore increased the risk of vascular trauma with injection. They also performed only gentle massage to smooth out small local defects and avoided broad massaging to redistribute the product. This technique is unique and demonstrates how a thorough understanding of anatomy and incorporation of imaging techniques may help improve the approach to soft tissue augmentation of the dorsal hands or other body sites. The Scrape Skin Threading Technique can be used with any temporary filler for the dorsal hands [40].

Chest: PLLA for chest rejuvenation was most clearly delineated in a retrospective study of 28 cases [19]. The authors primarily used a 16-ml dilution (PLLA; 367.5 mg) with 14 ml of bacteriostatic water and 2 ml of 1% lidocaine with epinephrine 1:100,000, and reconstitution typically occurred overnight. Injections were performed using a 26-gauge 1.5-inch needle or cannula using a retrograde linear threading technique in the reticular dermis and subcutaneous fat layers. The central chest rhytides between the breasts were treated first, and injections followed a centrifugal pattern until all visible rhytides were treated. The boundaries of injection when treating the chest are the suprasternal notch superiorly, mid-clavicular line laterally, and the fourth rib inferiolaterally (Fig. 40.6) [25]. Most patients were treated with 16 ml of PLLA, although the authors did say that treatment volume did vary per patient depending on the severity of rhytides and volume loss. During and immediately after treatment, the chest area was vigorously massaged using a liquid soap to ensure equal dispersion of the microparticles and patients were then directed to follow the rule of 5 s. On average, patients received 2.3 treatments with a total of 28.5 ml of PLLA solution. The best

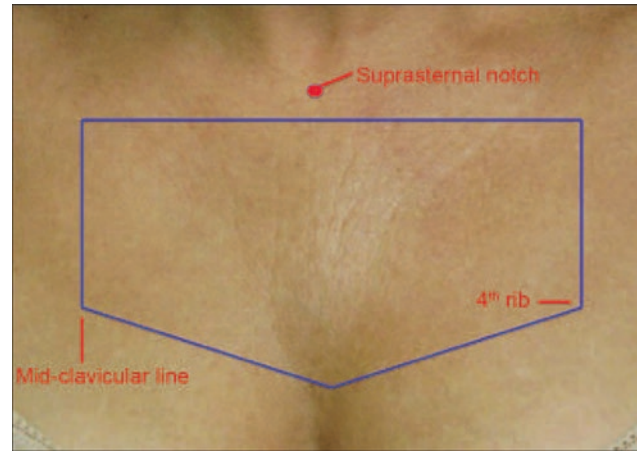

Fig. 40.6 Map of area on the chest most commonly injected with dermal fillers, with landmarks used to create boundaries [25]

improvement was noted in patients who received at least three PLLA treatments with a 16-ml dilution with 16 ml injected per treatment. Using this technique, no nodule formation was noted over the study period.

Most reviews discussing PLLA for chest rhytides also use ~16-ml dilutions with similar injection techniques. Subsequent injections are performed at monthly intervals as needed. Typically, three to four treatments are needed to establish optimal aesthetic improvement [24, 25]. The 16-ml reconstitution technique is similar to the 12-ml dilution technique described above for hand rejuvenation except that 1–2 ml of lidocaine and 6–7 ml of saline are used.

HA fillers have also been successfully used for rejuvenation of the chest. Restylane Vital® (Q-Med) is available in parts of Europe and Asia for enhancement of the neck, chest, and dorsal hands. Alternatively, Belotero Balance (Merz) or Restylane Silk (Galderma) are HA fillers available in the US that have a low viscosity and therefore spread evenly over the chest. In general, low-viscosity HA fillers that spread more easily on the chest are recommended. In a prospective study, Streker et al. used HA filler (Restylane Vital®, Q-Med) and treated half of the chest, one dorsal hand, and one side of the face. The HA material was injected using a pre-filled injector device into the mid-dermal layer using a micropuncture technique. Each injection delivered 10 μL of material. All three areas were simultaneously injected with a cumulative 4 ml at each of the three visits. No specification of volume used for the chest was delineated [21]. Belotero Balance® (Merz) mixed with 0.2–0.5 ml and Restylane Silk® (Galderma) mixed with 0.5 ml of 1% lidocaine without epinephrine can both be injected in the chest using a 30-gauge needle with either a serial micropuncture or retrograde linear threading technique. Belotero Balance® (Merz) is injected into the superficial dermis while Restylane Silk® (Galderma) is placed in the deep dermis. This provides a smoother cosmetic appearance and reduces the risk of Tyndall effect. In total, 2–3 ml of HA product are often required for treatment of chest rhytides [25].

There are no established optimal treatment methods for injection of soft tissue fillers of the upper arms, thighs, abdomen, or buttocks. This section will summarize the methods described in the literature in published studies, case reports, and expert reviews.

Arms: Independently, Amselem and Cogorno Wasylkowski evaluated CaHA to improve the skin flaccidity and aesthetic appearance of the upper arms. The enrolled subjects received treatment with CaHA 1.5 ml mixed with 0.5 ml of lidocaine solution per arm at two sessions 1 month apart. The total volume injected was 4 ml/arm. The areas to be treated were initially marked with the patient standing and arms extended away from the body with subsequent injections performed with the patient lying supine. Each arm was injected over a 150-cm^2 surface area with 50 injection points 1–2 cm

apart using a 27-gauge needle. If patients experienced bruising after the initial treatment, a 25-gauge cannula was used for the second treatment with only one or two injection points. CaHA was injected into the sub-dermis in a retrograde fanning technique. After treatment, the area of the posterior arm was gently massaged to ensure even distribution of the material [28].

Cogorno Wasylkowski similarly treated 12 separate brachial zones with CaHA. Pretreatment assessment was performed using a cutometer and an ultrascan to measure skin density, thickness, and flaccidity. Prior to injection, vector maps were designed with patients in a standing position to determine needle position during administration. For the arm, a fix point was found at the deltoid muscle, then one line was drawn 3 cm into the axillary zone, and a second line was drawn to protrude two-thirds into the arm. Several protruding lines were then drawn to cover the whole internal brachial zone. In this study, 3 ml of CaHA was diluted with 0.6 ml of 2% plain lidocaine and 1.5 ml was injected per arm in a single treatment. Injections were performed with a 27-gauge needle with 0.5 ml of CaHA injected into the deep dermis per each line of the vector map [29].

Distante et al. evaluated the aesthetic appearance of the upper arm after treatment with HA filler (Restylane Vital®, Q-Med). Patients were treated in three sessions 1 month apart. Areas to be injected were also marked with patients standing upright. A total of 1 ml of HA was injected per arm per session in small 0.03 ml aliquots spaced 1.5–2 cm apart over a 160-cm^2 surface area. Material was injected into the mid- to deep dermis using a 30-gauge needle. Follow-up evaluation was performed 3 months after the initial treatment.

Coimbra and Amorim described the use of PLLA for rejuvenation of the medial and anterior region of the arms [42] (5). One vial of PLLA was diluted with 16 ml of distilled water and 4 ml of 2% lidocaine without epinephrine with a total of 5 ml injected per arm via a "parallel stick" technique. Sessions were at intervals of 4 weeks, and the total number of sessions ranged from two to four.

PLLA, CaHA, or HA fillers can be used successfully for treatment of mild to moderate upper arm ptosis. Since each study utilized different methods for pre- and posttreatment assessment, including different arm ptosis scales, it is difficult to determine if one treatment method was superior to the others. Additional studies using consistent arm ptosis grading scales are needed to decide on ideal treatment regimen. Cogorno Waskylkoski's vector maps provide the clearest directions for injection technique and could likely be implemented independent of treatment material.

Buttocks: Mazzuco et al. describe injection of PLLA of two patients desiring nonsurgical correction for flaccidity and volume loss of the gluteal region. One patient received a total of three treatments spaced 1 month apart with two vials of PLLA injected per buttock per session. The second patient received a total of two treatments spaced 1 month apart with three vials of PLLA utilized per session. Each vial of PLLA was reconstituted to a total of 12 ml (PLLA; 367.5 mg) by mixing 10 ml of sterile water 24 h before the treatment procedure with 2 ml of plain lidocaine just before the start of the treatment. PLLA was injected with a 27-gauge 1-inch needle in a retrograde manner at a 60° angle. Aliquots of 0.1 ml were injected 1 cm apart into the superficial layer of the subcutaneous tissue. Patients massaged the area three times daily for 5 min for 1 week and were told to avoid rigorous exercise for 2 weeks [18]. Lorenc also recommends using a 12-ml dilution (PLLA; 367.5 mg) when treating the buttocks with PLLA although he reconstitutes using 5 ml of sterile water and 7 ml of lidocaine. He performs a single treatment with one vial of PLLA per buttock per session injected into the subcutaneous plane with a 25-gauge needle or cannula using a tunneling technique. Patients are re-evaluated at 6 weeks to determine the need for further augmentation [30]. One author (SBA) uses a 16-cc dilution of PLLA for cellulite on the buttocks. The areas of depression (the valleys)

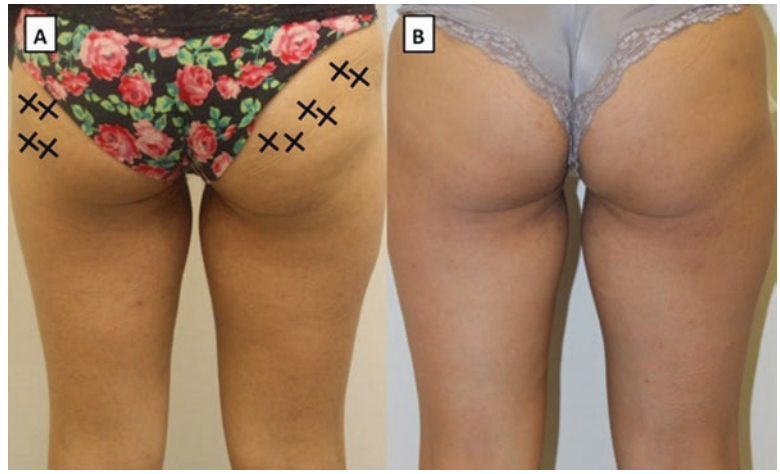

Fig. 40.7 Before (**a**) and after (**b**) one treatment of PLLA injections with 16-cc dilution in the buttocks for cellulite. X indicates point of injection

are marked with the patient standing using indirect light (Fig. 40.7) and then injected with the patient lying prone. Appropriate patient selection for soft tissue augmentation with temporary fillers of the gluteal region is essential, and patients should be educated on realistic expectations. Injections of PLLA in the buttock are typically safe because the subcutaneous tissue is thick and does not contain any main vasculature or nerves and provides an alternative to implants, permanent fillers, or fat transfer.

Abdomen/thighs: CaHA was also injected into the abdomen and thighs using the same body vectoring technique as described above [29]. For the thighs, the point of transition of skin types between the inner and outer thigh was used as an anchor from which two lines were drawn. One line followed the transition of the skin types vertically and the other extended to the middle of the fat on the inner thigh. Protruding lines were drawn from these landmarks. The vector map for the thigh was created with the intention of lifting the fat tissue from the internal side of the leg. The vector map for the abdomen was described for treatment of only one hemi-abdomen with the aim of correcting naval shape. The design can be extrapolated for bilateral injections. The anchor point was located under the ribs. A periumbilical vertical line and a second line at a 45° angle were drawn. Protruding lines were then drawn to cover the entire zone. Three ml and 1.5 ml of CaHA was injected per thigh and per hemi-abdomen in a single treatment. Injections were performed with a 27-gauge needle with 0.5 ml of CaHA injected into the deep dermis per each line of the vector map [29].

For correction of a lateral abdominal depression, one patient had improvement with two treatments 1 month apart with one-half vial of PLLA that was diluted with 8 ml of saline. PLLA was also used successfully with a 6-ml dilution (PLLA; 367.5 mg: 5 ml of sterile saline and 1 ml of 1% lidocaine) to provide volume enhancement to a postoperative scar on the upper arm after wide local excision for melanoma. The area was treated with a total of 6 ml of PLLA into the deep dermis and superficial subcutaneous fat using a 25-gauge needle [33]. One author (SBA) uses a 10-cc dilution of PLLA for skin laxity on the abdomen. The areas of depression (the valleys) are marked using indirect light similar to the markings of cellulite on the buttocks (Fig. 40.8).

Overall, these scant reports have demonstrated successful off-label use of temporary fillers for difficult-to-treat areas including the upper arms, medial thighs, and abdomen. However, additional studies are needed to determine if there is a true consistent cosmetic result. The same is true for the use of collagen-stimulating soft tissue fillers for postsurgical volume loss.

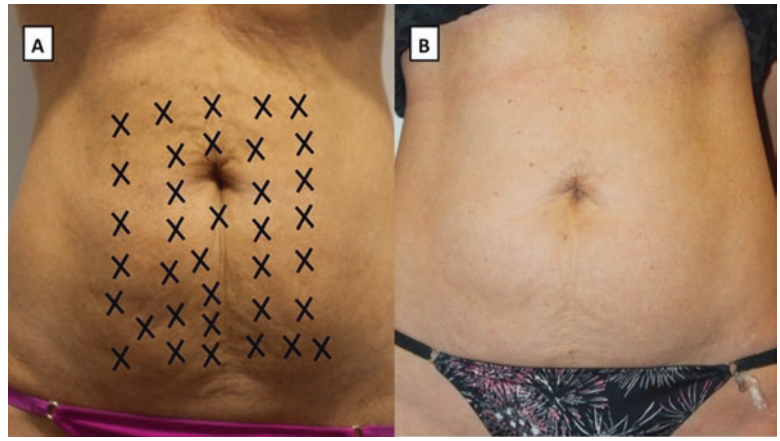

Fig. 40.8 Before (**a**) and after (**b**) one treatment of PLLA injections with 10-cc dilution in the abdomen for skin flaccidity. X indicates point of injection

Safety

Adverse reactions to temporary soft tissue fillers can be attributed to the injection technique, the product injected, and patient comorbidities. Some of these reactions are preventable, whereas others are inevitable. Most adverse events are mild and transient.

Overall, the most common temporary adverse events experienced by patients treated with temporary fillers on the trunk and extremities are bruising, edema, and pain. These occur in >90% of all patients and require no treatment. Common duration of swelling for patients with PLLA is about 3 days postinjection due to the sterile water used to dilute the product, which is resorbed within 48–72 h [43] (5). Some patients may however experience bruising or swelling for up to 14 days posttreatment. One expert reported intolerance reactions in 1.2% of patients injected with PLLA who developed slight edema, pruritus, and erythema in the areas injected. This was not specific for sites on the trunk or extremities, but it did prompt early termination of the procedure [13].

The most notable adverse event of temporary fillers is the formation of subcutaneous nodules. While nodule formation is most commonly seen in patients injected with PLLA, it can also occur in patients treated with other fillers. Early formation of papules and nodules results from overcorrection in the injected area, uneven distribution of the product in suspension, or uneven dispersal in the injected areas [32]. In the literature, the incidence of subcutaneous nodules from PLLA varies from 1% to 6%, and even up to 44% [44] (4). They are typically palpable, asymptomatic, and nonvisible. Nodule formation from PLLA is considered a product-related adverse event that can be reduced with proper injection technique and pre- and postinjection care.

There are several well-established techniques by experts to reduce the incidence of nodule formation from PLLA in all areas of injection, particularly the trunk and extremities. The label recommendations for injectable PLLA indicate reconstitution with 3–5 ml of sterile water. Many experts have found that treatment site-specific dilutions result in decreased nodule formations. For the chest, reconstitution volumes of 16 ml or up to 24 ml are recommended. For the hands, buttocks, and medial ankles, 14 ml, 12 ml, and 12 ml have been reported, respectively. Reconstitution volumes for the abdomen and scars are clearly patient dependent and at the discretion of the physician. The label recommendations for PLLA also state that after reconstitution, the vials should sit for at least 2 h to allow for complete hydration; however, reconstitution for at least 12 and up to 72 h may also reduce nodule formation [19, 23, 24, 30]. Additionally, subcutaneous injection of PLLA, avoidance of overcorrection with excessive quantities of injected material per session, spacing of treatments at least 6–8 weeks

apart, and massaging the area posttreatment are all techniques to decrease the incidence of nodule formation. There is little objective data regarding the benefit of posttreatment massage although it is routine practice for patients injected with PLLA to help disperse the microparticles [19]. Patients are massaged during treatment, for several minutes immediately after treatment, and then with the rule of 5 s [32, 45] (4). The higher rates of nodule formation were seen in the earliest studies of PLLA with lower volumes of reconstitution and improper plane of injection. As discussed earlier, various injection techniques, including threading or multiple punctures, can be used for temporary fillers on the trunk and extremities as long as there is even distribution of the product.

The HA filler, Restylane Vital® (Q-Med), is available in Europe in a pre-filled auto-injector that delivers 10 μL of HA gel per micropuncture injection into the mid-dermal layer of the skin. With the precise amount of product placed per injection, this technology is thought to allow for more uniform results. One study performed in Europe utilized the Restylane Vital® auto-injector with no serious adverse events.

A significant proportion of nodules will resolve spontaneously with time, but treatment options for persistent lesions include excision, intralesional steroids, needle fragmentation of the nodule followed by flooding the area with saline, and massage.

Aguilera et al. recommend management of CaHA nodules with an intralesional injection of 5-fluorouracil (5-FU), dexamethasone, and triamcinolone solution [46] (4). The 1.6-ml solution is constituted using 1.0 ml of 5-FU 50 mg/ml, 0.5 ml of dexamethasone 4 mg/ml, and 0.1 ml of triamcinolone 10 mg/ml. Although this specific publication discussed management of a CaHA nodule, the authors acknowledge the solution can be utilized to treat PLLA nodules.

Granulomas are considered by some to be a separate adverse reaction that occurs with temporary fillers months or even years after injection. They are more ill-defined in comparison to the discrete early papules and nodules and are characterized by erythema and edema. The incidence ranges from 0.2% to 2% though the etiology is largely unknown [32]. Histopathologically, there is a dense granulomatous inflammation with multinucleated cells and a foreign body reaction. Steroids (intralesional, intramuscular, or oral) are the mainstay of treatment. Alternative therapies include intralesional 5-fluorouracil alone or in combination with intralesional steroids as well as oral antibiotics. The authors have found success with the tetracycline family of antibiotics in conjunction with intralesional injections of 5-FU/triamcinolone (0.9 ml 5-FU 50 mg/ml and 0.1 ml of triamcinolone 40 mg/ml) repeated at 6–8 week intervals until resolution. No studies of temporary fillers on the trunk or extremities reported granuloma formation.

Injections of fillers into the tendons of the dorsal hands can weaken tendons and cause tendon rupture. Injection into the veins can cause embolization or thrombosis. In one study, 48% of patients reported difficulty performing activities after injection to the dorsal hands. Other rare side effects reported included loss of sensation of the hand. In the pivotal CaHA study, hand function testing conducted regularly throughout the 12-month study showed no negative effect. Similarly, there was no worsening of touch sensation response at 3 months for any subject. Some authors also feel that increased bruising of the hands is associated with higher volumes of injection and therefore recommend injecting a maximum dose of 3 ml of CaHA per hand per treatment. Although necrosis has been described after CaHA injections on the face, no studies reported necrosis of the hands after injection [2, 7, 41].

Postoperative Care and Follow-Up

Patients should be directed to remove all jewelry, especially rings, prior to treatment of the dorsal hands and until all swelling has resolved to avoid compromise of circulation. Immediately after treatment with temporary fillers on the trunk or extremities, the application of ice or cold com-

presses can help minimize bruising or swelling. This is especially true for the dorsal hands. Some physicians will also prefer to wrap the hands with light compression after treatment to help minimize swelling. Other postinjection recommendations for the dorsal hands include avoiding workouts for 1–2 days and elevation of the hands above the level of the heart for 15–20 min several times the day of treatment. Patients treated with temporary fillers to the dorsal feet should also avoid wearing tight-fitting footwear for 2 weeks postinjection. Topical *Arnica* applied for several days after injection may also help reduce bruising. There is no clear data to support these techniques to reduce swelling [36, 47] (5).

Treatment with PLLA on the chest, arms, dorsal hands, and buttocks requires 2–4 treatment sessions every 6–8 weeks to obtain optimal results. Some patients require additional treatments depending on the desired aesthetic outcome. If nodule formation occurs, patients may benefit from closer follow-up. Subsequently, patients should have yearly visits for maintenance injections. There are no clear recommendations for follow-up after injection of PLLA to the medial ankles, abdomen, postoperative scars, or other off-label sites; however, patients treated in these areas should return at monthly intervals to determine response to treatment and the need for additional injections.

Follow-up visits for patients treated with CaHA or HA fillers may be scheduled from 4 to 8 weeks post initial injection to document any adverse events and provide touch-up injections as necessary. When injected into the dorsal hands, arms, thighs, and abdomen, CaHA can have 12–24 month longevity. In comparison, patients treated with HA fillers on the chest or dorsal hands typically require repeat injections every 6–8 months.

Alternative Procedures and Modifications

With the increased number of available aesthetic procedures and technologies, a multidimensional approach with complimentary treatment modalities often creates the best possible outcome. Limitations of one procedure may be easily addressed by another procedure either concomitantly or with some delay depending on the situation. There is limited data evaluating the objective benefit of complementary procedures on the trunk and extremities, and most information is based on consensus recommendations from expert physicians. Patient desire for minimally invasive procedures has drastically expanded the development of body contouring devices. When multiple modalities will be used in a single treatment site, expert consensus recommends performing skin tightening with heat or energy-based devices first, followed by injectable therapies. For areas particularly susceptible to photodamage, including the hands and chest, daily application of broad-spectrum sunscreen that protects against UVA and UVB is essential. Finally, each patient requires a detailed tailored treatment plan based on a thorough assessment of skeletal and muscular changes, the degree and location of volume loss, and the appearance of fine lines and rhytides [23].

Hands: Volume loss of the dorsal hands leads to the appearance of pronounced muscles and tendons, prominent bones, and large intermetacarpal spaces and is best treated with volume restoration. Aside from temporary fillers, autologous fat grafting has been used for rejuvenation of the dorsal hands. The invasive nature of the technique, time required for harvesting of fat from a donor site, unpredictable results, and reported complications make temporary fillers a more desirable treatment modality [48, 49] (5; 5). Fabi et al. recommend CaHA as first-line treatment followed by low-viscosity HA fillers for aesthetic restoration of the dorsal hands [23]. In addition to volume replacement with fillers, extrinsic signs of aging such as telangiectasias, erythema, solar lentigines, actinic keratosis, and ephelides of the dorsal hands can be successfully treated with the combined use of chemical peels, light-based devices, or lasers [39, 50–52] (4; 4; 5). Finally, sclerotherapy can improve the appearance of tortuous hand veins that are persistent after volume restoration [39].

Chest and décolletage: Microfocused ultrasound with visualization is the only technology FDA cleared for the improvement of rhytides in the décolletage and can significantly lift, tighten, and reduce the appearance of rhytides on the chest [53, 54] (2b; 2b) and can be used in combination with temporary fillers. As discussed earlier, the chest and décolletage have a thinner epidermis and dermis and fewer pilosebaceous units in comparison to the face. This results in slower healing and higher risk of scarring with ablative procedures. Therefore, non-ablative lasers, light-based therapies, and ultrasound technology can be used in combination with fillers. Additionally, chemical peels, sclerotherapy, and photodynamic therapy can also be part of a multi-modality treatment plan for rejuvenation of the chest.

Upper arms: Traditional brachioplasty is indicated in patients with significant adiposity and posterior arm laxity. It unfortunately has the disadvantage of being an invasive surgical approach that leaves patients with a large linear scar. Alternatively, liposuction can be used to reduce excess volume from the posterior arm. Newer energy-based devices and lasers can be used alone or in combination with temporary fillers to improve laxity, skin tightening, and irregular pigmentation of the posterior arm and elbow. Fractionated CO_2 laser for the arm has been used in one study with a 50–70% improvement in wrinkle reduction, skin tightening, and pigmentation [55] (4). Additionally, transcutaneous microfocused ultrasound, which is FDA approved for noninvasive skin tightening of the face and neck, has demonstrated success in tightening and lifting of lax skin at the elbow, arm, thigh, and knee [56] (1b).

Buttocks: As discussed earlier, the approach to aesthetic restoration of the buttocks is often complex. There are several alternative treatments for gluteal lipoatrophy or volume loss, with autologous fat transfer as the preferred procedure for patients with significant volume loss. This procedure requires an adequate supply of fat with which to transfer and is therefore performed in conjunction with liposuction. More than 200 ml of fat per side is often needed to make a substantive change [57] (4). Permanent solid silicone implants can also be used for buttock volume enhancement but require surgical creation of a pocket in the middle of the gluteal muscles for placement [58] (2b). The permanent filler polymethyl methacrylate (PMMA)-microspheres has also anecdotally been used in Brazil for the treatment of HIV-associated buttock lipodystrophy [59] (4). Typically, a single approach to volume enhancement of the buttocks with autologous fat, silicone implants, or temporary fillers is preferred.

Abdomen: Only one study demonstrated reduction in skin flaccidity on the abdomen using CaHA [29]. Therefore, improvement in the aesthetic appearance of the abdomen is best approached with treatments targeting a specific indication: skin-contour irregularities, lipohypertrophy, or dermal elastosis (e.g., after pregnancy or weight loss). Patients with significant abdominal obesity often require a combined approach with diet, exercise, and surgery. Ultrasound technology or Coolsculpting (ZELTIQ Aesthetics) can also help tighten loose abdominal skin and reduce abdominal fat.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Indications	
Injections with soft tissue fillers for the trunk and extremities are most often indicated for patients with visible intrinsic and extrinsic signs of aging	D
Effectiveness	
Consistent use of validated grading scales for specific treatment sites will improve the objectivity of posttreatment evaluation	D
Preoperative evaluation	
Aside from Radiesse® for rejuvenation of the dorsal hands, the use of temporary fillers on the trunk and extremities is considered off-label	D
There are few absolute contraindications to injectable fillers on the trunk or extremities. These include a known allergy or hypersensitivity to the filler material or lidocaine mixed in the syringe and known skin infection in the area to be treated or adjacent skin	D
Best techniques and performance	
Advanced imaging techniques and a thorough understanding of anatomy can improve injection techniques	D
Safety	
Bruising, edema, and pain are the most common adverse events experienced by most patients treated with temporary fillers on the trunk and extremities	D
There are several well-established techniques to reduce the incidence of nodule formation when treating areas on the trunk and extremities	D
Postoperative care and follow-up	
Appropriate follow-up is dependent on the material injected, site of treatment, and occurrence of any adverse events	D
Alternative procedures and modifications	
A multidimensional approach with complimentary treatment modalities often creates the best possible aesthetic outcome for treatment of the trunk and extremities	D

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Self-Assessment Questions

1. Which temporary filler is FDA approved for use on the trunk and extremities?
   (a) Radiesse
   (b) Belotero
   (c) Juvederm
   (d) Sculptra
   (e) Voluma

2. What is an absolute contraindication to filler use on the trunk and extremities?
   (a) Allergy to component in filler
   (b) History of hypertrophic scars
   (c) Connective tissue disease
   (d) Tobacco use
   (e) Anticoagulant use

3. Which PLLA dilution for trunk and extremity rejuvenation is correct?
   (a) Chest: 12 cc dilution
   (b) Arms: 6 cc dilution
   (c) Abdomen: 10 cc dilution
   (d) Buttocks: 4 cc dilution
   (e) Legs: 16 cc dilution

4. Nodule formation secondary to PLLA can be reduced with all of the following options except?
   (a) Site-specific dilution
   (b) Reconstitution for 24–72 h prior to injection
   (c) Subcutaneous injection plane
   (d) Massaging of the treatment area after injection
   (e) Addition of 5-Fluorouracil to PLLA vial prior to injection

5. The most common adverse events associated with temporary filler injection on the trunk and extremities include all of the following except?
   (a) Bruising
   (b) Pain
   (c) Pruritus
   (d) Edema
   (e) Biofilm formation

Correct Answers

1. a: The answer is a. Radiesse is the only currently available temporary filler to be FDA approved for the dorsal hand. The remaining fillers are used off-label for this area.
2. a: Answer choice a is the correct answer. Hypersensitivity to a component within the filler is an absolute contraindication and must be avoided in patients.
3. c: Answer choice c is correct. Chest is recommended to be diluted with 10 cc, arms with 10–12 cc, buttocks with 16 cc, and legs with 10–12 cc.
4. e: Answer choice e has not been shown to reduce the risk of nodule formation. The remaining options have evidence suggesting they reduce the risk of nodule formation with PLLA.
5. e: Answer choice e is incorrect. Biofilm formation can occur but is much less common than the others that occur in >90% of patients undergoing filler injections.

Treatment of Precancers with Topical Agents

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Paola Chamorro and Bahar Firoz

Abstract

Actinic keratosis (AK) is one of the most common skin conditions worldwide. AK represents an intraepidermal dysplastic proliferation of keratinocytes (Berman B, Cockerell CJ. J Am Acad Dermatol 68:S10–9, 2013). It is a potential precursor to squamous cell carcinoma (SCC), with estimates of AK progression to invasive SCC ranging from 0.025% to 20%. With the incidence of non-melanoma skin cancer on the rise, treatment for AKs has been recommended to reduce the development of invasive SCC, lower healthcare expenditure, and improve patient well-being (Vale SM, Hill D, Feldman SR. Pharmacoeconomics 107:674–680, 2016). Several treatment modalities have been employed to treat AKs in an attempt to prevent progression to invasive SCC. The modalities which will be discussed and evaluated in this chapter include topical sunscreen, cryotherapy with liquid nitrogen, topical 5% (Efudex) and 0.5% (Carac) 5-fluorouracil (5-FU), topical 5% imiquimod cream (Aldara), topical diclofenac with sodium hyaluronate gel (Solaraze), ingenol mebutate (Picato), topical retinoids, and chemical peels including trichloroacetic acid and Jessner's solution applied to affected skin.

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Keywords

Actinic keratosis/actinic keratoses (AK)
Solar keratosis · Senile keratosis
Cryotherapy · Chemical peels
5-Fluorouracil · Imiquimod · Diclofenac
Ingenol mebutate · Retinoids
Organ transplantation

Introduction and Definition of Procedures to Be Discussed

Actinic keratosis (AK), also termed solar keratosis and senile keratosis, is one of the most common skin conditions worldwide. It is the most common diagnosis made by dermatologists for patients over 45 years of age, with a US prevalence of 11–26% and as high as 55% in patients 65 to 75 years old [3, 4]. In the United States in 2004, the prevalence of AK was estimated to be almost 40 million [5]. AK represents an intraepidermal dysplastic proliferation of keratinocytes and follows one of three paths: spontaneous remission, stable existence, or malignant transformation [1]. It is a potential precursor to squamous cell carcinoma (SCC), with estimates of AK progression to invasive SCC ranging from 0.025% to 20% [6]. The two largest studies suggest a 1-year transformation risk from less than 0.1% up to 0.6% of lesions [4, 7]. The 10-year risk of malignant transformation of AK to SCC

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has been estimated to range from 6% to 10% [8]. Metastatic risk of an SCC ranges from 0.5% to 3.3% and may account for up to 20% of deaths from skin cancer [9]. With the incidence of non-melanoma skin cancer on the rise, treatment for AKs has been recommended to reduce the development of invasive SCC, lower healthcare expenditure, and improve patient well-being [2, 5].

AKs are usually diagnosed clinically and appear as rough pink to brown macules, papules, or plaques with scale, which may be significantly hyperkeratotic. They may appear in conjunction with other signs of solar damage, specifically telangiectasias, solar lentigines, rhytides, and poikiloderma. Histologically, AKs exhibit varying degrees of intraepidermal keratinocytic atypia. Clinical and histological subtypes of AKs include the classic variant already described, hyperplastic (or hyperkeratotic), pigmented, lichenoid, atrophic, bowenoid, "cutaneous horn," and actinic cheilitis of the lips.

Much like non-melanoma skin cancer, AKs are thought to develop due to ultraviolet (UV) light exposure and resulting DNA mutations. They occur more frequently in fairer-skinned individuals but can be seen in all races. Most AKs occur in sun-exposed areas such as the head, lower lip, neck, dorsal hands, forearms, and upper chest. Increasing age, male gender, a history of AKs, and non-melanoma skin cancer are other risk factors for developing AKs. High-risk AKs are mainly associated with immunosuppression. Organ transplant recipients have a 250-fold higher risk of developing AKs and a 100-fold higher risk of developing invasive SCCs [10]. While approximately 40% of immunosuppressed patients develop invasive SCC, only 6–16% of immunocompetent individuals with AKs show this progression [10].

Several treatment modalities have been employed to treat AKs in an attempt to prevent progression to invasive SCC. The modalities which will be discussed and evaluated in this chapter include topical sunscreen, cryotherapy with liquid nitrogen, topical 5% (Efudex) and 0.5% (Carac) 5-fluorouracil (5-FU), topical imiquimod cream (Aldara), topical diclofenac with sodium hyaluronate gel (Solaraze), ingenol mebutate (Picato), topical retinoids, and chemical peels including trichloroacetic acid and Jessner's solution applied to affected skin.

Consensus Documents Regarding Procedure

Several consensus documents exist regarding AKs and the treatments employed to eliminate them [11]. The American Academy of Dermatology (AAD) published guidelines in 1995 that defined AKs as common premalignant skin tumors, which show varying degrees of epidermal atypia that may progress to SCC. They estimated that 60% of predisposed persons older than 40 years have at least one AK. Without treatment for AKs, they assert that a significant number of patients will develop one or more invasive SCCs. They list several treatment modalities and recommend consideration be given to size, location, duration, change in growth pattern, previous treatment, and certain anatomic locations such as the scalp and ear [11].

The European Dermatology Forum has also published guidelines for the management of AKs in 2006 [10]. They assert that AKs "should be classified as in-situ SCC" [10]. They mention UV exposure with or without iatrogenic exposure to psoralens and human papilloma virus as risk factors for the development of AKs. They quote a 15% prevalence rate of AKs in men and 6% in women based on a UK study. Before discussing treatment modalities, they also recommend evaluating the duration and course of lesions, lesion quantity, patient age, comorbid conditions, the patient's mental condition, anticipated patient compliance, pre-existing skin cancers, and particularly immunosuppression. They discuss that although cryotherapy is widely used, controlled studies are missing. Complete responses differ from 75% to 98%, and recurrence rates are estimated from 1.2% to 12% at 1-year follow-up. Imiquimod and 5-FU are discussed with impressive remission rates and low recurrence rates. Diclofenac in hyaluronic acid gel also shows AK remission in a few randomized controlled trials when applied for 60 or 90 days with minimal side effects.

The British Association of Dermatologists has also published guidelines for the management of AKs in 2006 [12]. In contrast to the European guidelines, they define AKs as "focal areas of abnormal keratinocyte proliferation with low risk of progression to invasive squamous cell carcinoma and higher potential for spontaneous regression." The authors discuss several factors to help determine the choice for therapy, based on efficacy, ease of use, morbidity, and cost–benefit analysis. They conclude that "there is good evidence" that 5% 5-FU cream used twice daily for 3 weeks is effective at reducing AKs on the face and back of hands by about 70% for up to 12 months. Multiple randomized controlled trials (RCTs) of imiquimod produce a similar pattern of side effects and response to 5-FU. Diclofenac gel, a relatively mild agent, reduces AK lesion count, but long-term follow-up data is lacking. Studies show topical tretinoin, when used for 1 year, has some efficacy on the face, with partial clearance of AKs. Sun block, emollient, and 2% salicylic acid ointment may reduce the AK count by a similar amount [12].

Sunscreen

Topical sunscreens are applied to the skin and ideally block both UVA and UVB ultraviolet radiation, theoretically preventing the formation of AKs. The AAD recommends application of a water resistant sunscreen with broad-spectrum coverage, and sun-protection factor (SPF) 30 or higher approximately every 2 h to sun-exposed areas [13].

A blinded, RCT undertaken in Australia during the summer between September 1991 and March 1992 evaluated the effect of sunscreen with SPF of 17 vs. vehicle cream on AKs in 431 subjects aged 40 years or older. AKs were diagnosed clinically, although a subsample had biopsies for verification and there was 81% concordance between clinical and histologic diagnosis. Subjects were asked to keep daily diaries that recorded the frequency of cream application and to avoid sun exposure and other sunscreen products during the study. Approximately, 25% of the AK lesions present at baseline had remitted in the sunscreen group after 7 months compared to 18% in the vehicle cream group. The mean number of AKs increased by 1 per subject in the vehicle cream group, whereas it decreased by 0.6 per subject in the sunscreen group (1b) [14].

In a blinded, controlled trial over 4.5 years, 1621 adults were randomized to 4 groups comparing the application of daily use of sunscreen with SPF 16 vs. application of sunscreen at subjects' usual discretionary rate. They were also randomly assigned to take either one 30 mg beta-carotene or placebo tablet each day. Beta-carotene is an antioxidant that in theory may prevent skin cancer by lowering free-radical-induced DNA damage in UV-exposed skin cells. The prevalence of AKs increased over the course of the trial for all groups; however, the increase in AK counts was 24% lower in the daily sunscreen group than that experienced in the control group, while a beta-carotene supplementation had no influence on the occurrence of AKs (1b) [15]. This RCT was conducted in conjunction with a RCT evaluating the effectiveness of daily sunscreen application and beta-carotene supplementation in preventing basal cell carcinoma (BCC) and SCC over 4.5 years, in which daily sunscreen use significantly reduced the incidence of SCC compared to no sunscreen use. Sunscreen and/or beta-carotene use had no effect on the incidence of BCC (1b) [16].

Cryotherapy

Cryotherapy is a destructive method for treating AKs that utilizes liquid nitrogen (−196 °C) to freeze and thereby destroy both normal and dysplastic cells and eliminate diseased epidermis by creating a separation of the epidermis from the dermis. Cryotherapy is a widely used and long-established treatment option that exhibits very good clinical efficacy for single lesions. In order to achieve efficacy and avoid cosmetic defects, the recommended therapy of AK lesions is a freeze time of approximately 20–30 seconds (s). As with other procedures, the potential for side effects exists, but these are, for the most part, predictable

or minimal [17]. Side effects include pain, blistering, hypopigmentation, hair loss, and scar. There are few contraindications to cryosurgery.

In a prospective, multicentered, non-blinded study, which was a subsidiary of a RCT, 90 patients with 421 clinically diagnosed AKs of 5 mm or greater on the face and scalp were treated with cryotherapy. Freeze-thaw cycles of differing lengths were employed depending on the treatment center. At 3-month follow-up, there was a 57% complete clearance rate in the intention to treat population. Complete response was 39% for freeze times less than 5 s, 69% for freeze times greater than 5 s, and 83% for freeze times greater than 20 s (2b) [18]. Cure rate for AK is technique dependent, with longer freeze times having greater clearance rate.

A RCT evaluated 71 subjects with ≥ 10 AKs on the face and scalp and compared treatment efficacy, safety, and skin quality outcomes of cryotherapy (10s freeze/thaw time, 10 lesions per session, up to 4 sessions every 3 months) and imiquimod (3 times per week for 3–4 weeks, up to 2 courses). Clinical complete response rates were 85% (260/306 lesions) for cryotherapy and 66.9% (234/350) for imiquimod. Because of bias and imprecision, the study was considered low-grade quality, and there was no statistical difference between cryotherapy and imiquimod with respect to complete clearance. The participant cosmetic outcomes and global skin quality was 82% for cryotherapy versus 100% for imiquimod. Blister formation was noted to occur at a higher rate in cryotherapy arm compared to the imiquimod arm (1b) [19].

A RCT trial with 75 patients with at least 5 AKs diagnosed clinically and confirmed histologically compared cryotherapy (20–40 s per lesion), topical 5-FU (twice daily for 4 weeks), and imiquimod (3 times weekly for 4 weeks, 1–2 cycles) with a 12-month follow-up period. Initial clinical complete clearance of lesions 4–8 weeks after therapy completion was 68% (17/25) for cryosurgery, 96% (23/24) for 5-FU, and 85% (22/26) for imiquimod. Histological clearance was only 32% for cryosurgery compared to 67% for 5-FU and 73% in the imiquimod group. The sustained clearance rate for individual lesions at 12 months was 28% for cryosurgery, 54% for 5-FU, and 73% for imiquimod. Evaluating the entire treatment field, sustained clearance at 12 months was 4% for cryosurgery, 33% for 5-FU, and 73% for imiquimod. Imiquimod resulted in superior cosmetic and sustained clearance rates, although the overall number in each group was small (1b) [20].

A strong recommendation is given for the use of cryotherapy in patients with single AK lesions or multiple discrete lesions. Low cost, availability, safety, effectiveness, and compliance make it a widely available and effective treatment modality.

Chemical Peels

Chemical peels are also an ablative modality that destroys the epidermis and variable depths of the dermis depending on the peel type. They are typically applied to the general affected area, as opposed to spot treatment, and thus are recommended for extensive facial AKs. A medium-depth chemical peel with 35–50% trichloroacetic acid (TCA) alone or a 35% TCA in combination with Jessner's solution (salicylic acid, lactic acid, and resorcinol), 70% glycolic acid, or solid CO2 may effectively treat multiple non-hypertrophic AKs [21]. Medium-depth peels cause injury at the level of the papillary dermis, and side effects may include stinging or burning pain, visible peeling (which usually lasts 5–7 days), pigmentary changes, infections, and rarely scarring. Higher rates of complications may occur in patients with a history of herpes simplex virus (HSV) infection, previous radiation exposure, immunosuppression, post-inflammatory hyperpigmentation, keloids, recent facial surgery, or taking photosensitizing medications. Patients likely to be noncompliant with posttreatment sunscreen use or who are unable to avoid sun exposure are unsuitable candidates for a chemical peel. The efficacy depends on the agent used and has been quoted as high as 75% (agent dependent) with a recurrence rate at 1 year between 25% and 35% [10].

In a nonrandomized split-face study of 15 patients, a single application of 35% TCA plus Jessner's solution was compared with 5% 5-FU applied twice daily for 3 weeks. Evaluations were conducted 1, 6, and 12 months after treatment, and both treatments reduced the number of visible AKs by 75% (3b) [22].

In another split-face comparison study, 13 patients were evaluated for response to 70% glycolic acid plus 35% TCA compared to Jessner's plus 35% TCA. AKs, fine wrinkling, and solar lentigines were evaluated prospectively with a 60-day follow-up. Improvement was clinically noted for both peels (3b) [23].

Eight patients with severe facial actinic damage were treated with Jessner's and 35% TCA on the left face and with twice daily application of 5% 5FU for 3 weeks on the right face. Clinical evaluation was performed at 1, 6, 12, and 32 months and included AK counts, random skin biopsies, and sun exposure surveys. A 78% reduction in the mean number of clinical AKs was observed at 12 months for both treatments, but the mean number of AKs increased between 12 and 32 months. They suggest 18-month follow-up in all AK patients (3b) [24]

Sixteen men with actinic damage were treated with 40% TCA peels and evaluated at 6 weeks and 6 months after treatment. Half were pretreated and post-treated with topical tretinoin. Examiners assessed clinical outcome using photographs, and patients used a self-assessment tool. The peel, both with and without tretinoin, produced improvements in actinic damage, although quantitative measures are lacking in this study (4) [25].

5-Fluorouracil

Topical 5-fluorouracil, a chemotherapeutic antimetabolite approved by the US FDA in 1970, is the most established field treatment for AK and is considered by some the traditional gold standard to which all other topical agents are compared [26]. It is a pyrimidine analog, which interferes with DNA synthesis by stopping the conversion of deoxyuradilic acid to thymidylic acid, which prevents cell proliferation preferentially in rapidly dividing cells, especially those of AKs and basal layers of the epithelium [27]. Topical 5-FU is available as a cream in 5, 1, and 0.5% concentrations and as a solution in 5% and 2% concentrations. The typical treatment regimen is either 5% cream twice daily or 0.5–1% cream once daily for 2–4 weeks. The widespread application has the advantage of treating multiple and clinically undetectable AKs. Topical 5-FU causes inflammation, erosion, and ulceration during treatment, which is necessary for therapeutic success, which develops after the first week and subsides approximately 2 weeks after treatment when re-epithelialization has occurred. These transient side effects can result in non-compliance.

A randomized double-blinded, placebo-controlled clinical trial of 932 veterans with 2 or more AKs evaluated 5% 5-FU cream and vehicle control cream applied to the face and ears twice daily for up to 4 weeks. The 5-FU group had statistically significant fewer AKs compared with the control group at 6 months (3.0 vs. 8.1) and for the overall study duration of 3 years. The 5-FU group also had higher complete AK clearance rates (38% vs. 17% at 6 months) and fewer spot treatments at 6-month intervals (1b) [28].

Three randomized controlled studies provided data evaluating 0.5% 5-FU in comparison with vehicle. Across the 3 studies, approximately 400 adult patients with at least 5 AK lesions were pooled, in which 0.5% 5-FU cream or vehicle cream was applied once daily to affected areas of the face or scalp for either 1, 2, or 4 weeks. The rate of complete clearance and mean reduction in lesion count from baseline to 4 weeks and 6 months was statistically significant and higher in the 0.5% 5-FU group than in the vehicle group (1b) [29–31].

In one intraindividual split-patient RCT of 21 patients with $\geq$ 6 AK lesions, the participant's preference of different concentrations of 5-FU cream (0.5% 5-FU applied once daily vs. 5% 5-FU applied twice daily for mean duration of 19 days) was compared. At the end of the 4-week posttreatment period, participants preferred the 0.5% concentration to the 5% concentration. No

statistically significant differences were found between the two formulations regarding minor adverse events: erythema, erosion, and pain. Complete clearance was 43% in both study groups. The mean reduction in lesion counts from baseline to end of study was higher in the 0.5% 5-FU concentration compared to 5% concentration (2b) [32].

A meta-analysis investigating the efficacy of 5-FU for AKs of the face and scalp included six studies, 146 patients with variable follow-up times ranging from 1 to 11 months. Different formulations 5, 1, and 0.5% of 5-FU were included. The meta-analytical average complete clinical response rate for 5-FU across these studies was 52.2% (SD = 18%). In one study, at 11-month follow-up, complete clearance was seen in 86.4% of the 5% 5-FU group compared to 0% in the 1% 5-FU group. Two other studies showed differing results with 5% 5-FU applied twice daily over 2 weeks, with only complete clearance of facial AKs in 6.7% of subjects at 1-month follow-up compared with 100% of subjects in another study. Two separate studies investigating 0.5% 5-FU applied for 4 weeks showed complete clearance rates at 4-week follow-up of 57.8% and 47.5% in patients with facial AKs (1a) [29, 30].

5-FU pulse therapy was evaluated in a RCT of 20 patients with a clinical diagnosis of AK on the scalp and/or face. Thirteen patients applied 5% 5-FU twice daily for 3 weeks and were compared to seven patients who applied the same cream twice daily for 1 day per week for 12 weeks. Follow-up was performed at weeks 3, 12, 24, and 52, and clinical photographs and a lesion count were performed. The groups had the same median lesion count at baseline (17.5), but in the first group, the lesion count fell and remained at 0 after week 12, whereas the second group fell to 6 at week 12, 5.5 at week 24, and 3 at week 52. Applying 5% 5-FU twice daily for 3 weeks had a statistically significant and superior efficacy than pulse therapy (1b) [33].

With regard to combination therapy, one randomized controlled investigator-blinded study of 60 patients with an average of 12 AKs compared the addition of 5-FU to cryotherapy versus cryotherapy alone. Patients underwent cryotherapy followed 3 weeks later by self-application of 0.5% 5-FU cream or placebo moisturizer cream once daily. At week 8, the reduction of AK lesions was 84% (5-FU) vs. a 69% (placebo). At week 26, however, the reduction of AK lesions was 72% (5-FU) vs. 73% (placebo). There was no significant difference between 0.5% 5-FU cream and comparator cream for either 100% or 75% clearance by the end of the study (1b) [34].

In a multicenter, randomized, double-blind, placebo-controlled, parallel group trial, 470 patients with 4–10 AK lesions on the face or bald scalp were treated with topical 0.5% 5-FU + salicylic acid 10.0% [Actikerall®] once daily or diclofenac HA or vehicle twice daily for 12 weeks. The histological clearance rate of one predefined lesion and clinical clearance rate of all treated lesions were evaluated at week 20. Respectively, the week 20 biopsy revealed AK clearance in 72% of the 5-FU/SA group, 59.1% of the diclofenac HA group and 44.8% of the vehicle group. Significantly more lesions were cleared with 5-FU/SA (74.5%) compared to diclofenac HA (54.6%) or vehicle (35.5%). Application site disorders, mainly burning and inflammation were more frequent with low-dose 5-FU/SA but were of mild to moderate intensity. Low-dose 5-FU was determined to be an effective lesion-directed treatment for AKs (1b) [35].

In a RCT, 66 patients with histologically confirmed moderate/severe hyperkeratotic AKs on the face or scalp were treated with either a 6-week course of once daily 0.5% 5-FU/10% SA or 2 cryotherapy treatments 3 weeks apart. Although the study was not powered to explore statistical differences in clinical efficacy, topical treatment with 0.5% 5-FU/SA achieved greater histological clearance (62.1% for 5-FU/SA group vs. 41.9% for cryotherapy group at day 98) and lower recurrence rate (39.4% for 5-FU/SA group vs. 84.8% for cryotherapy group) of grade II/III hyperkeratotic AKs than cryosurgery. Mean change in lesion count from baseline to day 98 was −5.2/patient for 0.5% 5-FU/SA group vs. −5.7/patient in cryotherapy groups. Drug-related severe adverse events were all skin reactions, reported in 24.2% of 5-FU/SA and 6.1% of cryotherapy patients, respectively (2b) [36].

Imiquimod

Imiquimod (IMQ) is a topical immunomodulator approved by the United States FDA in 2004 for actinic keratosis treatment. Imiquimod is a toll-like receptor-7 agonist, activating antigen-presenting cells to produce interferon, other cytokines, and chemokines. These cytokines stimulate the nonspecific innate immune response and help direct the acquired immune response. Available dosages within the United States include 5%, 3.75%, and 2.5% formulations. The manufacturer-recommended dosing regimen is application of 5% cream twice weekly for 16 weeks or 3.75% or 2.5% creams once daily for two 2-week treatment cycles separated by treatment-free intervals, whereby 250 mg of cream is applied to a 25 cm^2 area on the face or scalp. Shorter-course therapy of 5% cream with treatment-free intervals may also be effective.

A meta-analysis of nine randomized controlled trials compared the clinical efficacy of imiquimod 5% cream to placebo vehicle cream for the treatment of multiple AKs. Approximately 2300 pooled patients self-applied imiquimod 5% cream or vehicle cream 2– times weekly for 4–16 weeks. Imiquimod 5% was statistically significantly more effective than vehicle cream with complete clearance rates of 46% (imiquimod group) vs. 5.7% (vehicle) and partial (> 75%) clearance rates of 61.4% (imiquimod) vs. 11.4% (vehicle) [37, 38]. Only one study evaluated the optimal frequency and long-term effectiveness of imiquimod beyond 12–16 weeks. Approximately 82% of the patients who achieved complete clearance after imiquimod treatment were followed 16 months after treatment, in which recurrence was observed in 25% of the patients treated 3 times weekly compared to 43% who were treated twice weekly and 47% who were treated with vehicle cream (1a) [38].

Although treatment adherence to the approved imiquimod dosing regimens was good in clinical studies, the long duration of dosing may be inconvenient for patients and affect compliance. Shorter treatment duration with daily dosing imiquimod 5% cream, however, is not well tolerated. As such, the effect of varying dosing frequency of imiquimod was investigated [39]. In a phase II, multicenter, double-blind, RCT, 149 patients with ≥ 10 and ≤ 50 clinical AKs, one of which histologically confirmed, were randomly assigned to imiquimod or placebo cream applied to the forearms or hands once daily for 2, 3, 5, or 7 times per week for 8 weeks and complete clearance clinically measured. Complete clearance rates were low, however, partial clearance rates increased with increased dosing frequency. Twenty-eight subjects discontinued the study due to adverse effects. Imiquimod 5% applied more frequently than three times per week to AKs was not well tolerated (1b) [39].

To evaluate an imiquimod product that could be applied daily for AK for a short duration and to expand treatment area to face/scalp, lower concentrations were evaluated. In two randomized, placebo-controlled studies, 479 pooled patients with multiple AK lesions were randomized to placebo, imiquimod 2.5% or imiquimod 3.75% once daily for two 2-week treatment cycles separated by a 2-week treatment free interval. Both studies showed that both imiquimod 2.5% and 3.75% creams were more effective than placebo and were well tolerated in the treatment of AK. Complete and partial clearance rates were 6.3% and 22.6% for placebo, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75%, respectively. Median lesion count reduction from baseline was 25% (placebo), 71.8% (imiquimod 2.5%), and 81.8% (imiquimod 3.75%.) Lesion reduction was greater with imiquimod 3.75% compared to imiquimod 2.5%, yet these results were not considered statistically significant (1b) [40].

Thirty-six patients with four or more clinically diagnosed AKs were randomly assigned to receive 5% 5-FU cream twice daily for 2–4 weeks or 5% imiquimod cream twice weekly for 16 weeks in a physician-blinded study. Evaluations were performed at baseline and every 4 weeks until 24 weeks. At week 24, the total AK count was reduced by 94% from baseline with 5-FU compared to 66% with imiquimod. Complete clearance of AKs was 84% in the 5-FU group compared to 24% in the imiquimod group. Erythema levels were initially higher in the 5-FU

group but were comparative to imiquimod by week 16. Limitations of this study include twice weekly application of imiquimod which may be a substandard regimen, small sample size, clinical diagnosis of AK made by one evaluating physician without histologic confirmation, and failure to perform an intent to treat analysis (2b) [41].

Please refer to cryotherapy section for information comparing imiquimod and cryotherapy.

Topical Diclofenac with Sodium Hyaluronate Gel

Topical Diclofenac 3% gel is a potent nonsteroidal anti-inflammatory formulated with 2.5% hyaluronic acid. There is evidence that diclofenac induces regression of AKs. Arachidonic acid (AA) metabolites have been shown to promote epithelial tumor growth by stimulating angiogenesis, mediating the conversion of procarcinogens to carcinogens, and inhibiting apoptosis [42].The production of these prostaglandins from arachidonic acid COX-2 pathway in keratinocytes increases in response to UVB radiation and may play a role in UVB-induced skin cancers (BCC and SCC) as well as AK [43]. As a selective cyclooxygenase-2 (COX-2) inhibitor, diclofenac exerts its anti-tumor effects by inhibiting the arachidonic acid cascade, subsequently decreasing the synthesis of prostaglandins. Hyaluronic acid 2.5% is a naturally occurring glycosaminoglycan with inflammation-modulating and bioadhesive properties, which serves as an excellent vehicle for topical drug delivery [44]. Common side effects include dermatitis, pruritus, and xerosis. Recommended dosing is twice per day for 90 days.

Four randomized, double-blind, placebo-controlled trials compared 3% diclofenac in 2.5% sodium hyaluronate (DHA) gel (0.25–0.5 g of 3% DHA twice daily for 60–90 days) vs. hyaluronate gel vehicle (HAV) alone (2.5% HAV twice daily for 60–90 days) in a total of 472-pooled immunocompetent patients with at least 5 AKs located on the head and extremities. Outcomes in all 4 studies evaluated the rate of complete clearance at 30 days posttreatment. Two [45, 46] studies also evaluated the rate of Participant Global Improvement Index (PGII) and Investigator Global Improvement Index (IGII) rated as "completely improved" 30 days after treatment. Analysis showed that compared to the control HAV group, the intervention DHA group showed a statistically significant higher efficacy with respect to complete clearance rates (14.6% vs. 34.9%) as well as higher rates of PGII and IGII rated as "completely improved." In the Rivers et al. study, 97 patients with AK were also treated with DHA or placebo twice daily for 60 days, in which the target lesion number score (TLNS; complete resolution of all target lesions in the treatment areas) was observed in 33% of patients in intervention group vs. 10% patients in placebo group. The cumulative lesion number score (CLNS; resolution of target and new lesions in the treatment area) was achieved by 31% of the patients in the intervention group compared to 8% of the patients in the placebo group. Common side effects included pruritus, contact dermatitis, dry skin, rash, and scaling. None of the studies had histologic verification of the AK diagnosis, and none compared DHA to other modalities used in the treatment of AKs (1a) [37, 45–47].

Two randomized controlled trials evaluated diclofenac against imiquimod. In the first trial, 3% diclofenac HA gel (twice daily for 12 weeks) was compared to 5% imiquimod (twice weekly for 16 weeks) and placebo base cream. Forty-one patients with clinical and histopathological single AK lesions were evaluated clinically every 4 weeks until 6 months for total thickness score (TTS) and PGII. Complete clearance rates for diclofenac, imiquimod, and vehicle at the end of the treatment and at 6-month follow-up were 19.1%, 20%, and 0% and 14.3%, 45%, and 0%, respectively. The average TTS value at 6 months for the diclofenac group was significantly higher than that of the imiquimod group; however, the PGII values were not significantly different. No adverse effects occurred in all groups. ($p = 0.034$, mean difference 0.85, 95% CI 0.36–1.66) (1b/II/A) [48]. The efficacy of imiquimod may be limited in this study due to underdosing as

imiquimod is usually prescribed as three times weekly use rather than twice weekly use in current clinical practice. The second trial compared 3% diclofenac HA gel (once daily for 12 weeks) with 5% imiquimod (three times weekly for 12 weeks) in 49 patients with at least 3 AK lesions. Efficacy was measured by patient and investigator global improvement scores, which were evaluated monthly for 1 year posttreatment. In this study, there were no statistically significant differences found between the two intervention groups with respect to the rate of participants with the PGII and IGII rated as "completely improved": (PGII, 28% DHA vs. 23% IMQ, $p > 0.05$, and IGII, 12% DHA vs. 22% IMQ, $p > 0.05$). There were also no statistically significant differences between the two intervention groups with respect to adverse events (1b) [49].

Ingenol Mebutate

Ingenol mebutate (IM) was approved for use in the United States, Canada, and Europe in 2012 as well as Australia and other countries thereafter [27]. Ingenol mebutate (IM) is a diterpene ester extracted from the sap of the medicinal *Euphorbia peplus* plant. It has two mechanisms of antiproliferative activity: [1] it initially disrupts mitochondrial and cell membranes resulting in rapid lesion necrosis of locally affected cells and [2] it subsequently removes residual tumor cells by selective induction of tumor-specific antibodies and pro-inflammatory cytokines via a neutrophil-mediated antibody-dependent cellular cytotoxic pathway [50–52]. Recommended therapy includes a 3-day course of 0.015% gel for the face and scalp and a 2-day course of the 0.05% gel for the trunk and extremities. The most common adverse effects of ingenol mebutate are local erythema, flaking, scaling, vesiculation, and crusting, which typically peak within the first week and resolve within 1 month without scarring. A small number of patients may experience hyperpigmentation or hypopigmentation after treatment, but the visibility is considered mild and not clinically meaningful by clinicians [50]. Ingenol mebutate and its metabolites have not been detected in blood samples for patients treated with ingenol mebutate 0.05%, suggesting no systemic absorption. The short duration of therapy and tolerable side-effect profile is associated with high rates of adherence to treatment.

In a multicenter, randomized, parallel-group, double-blinded study, 547 adult patients with an average of 4–8 AKs of the face or scalp were randomly treated with ingenol mebutate 0.015% gel or placebo vehicle gel for self-application once daily for 3 consecutive days. Additionally, 458 patients with 4–8 AKs on the trunk or extremities were randomly given ingenol mebutate 0.05% gel or placebo vehicle gel once daily for 2 consecutive days. Outcomes were complete (100%) with partial clearance (75% reduction) of all visible AK lesions and median reduction in lesion numbers on day 57. Ingenol mebutate was statistically significantly more effective for field treatment of AK when compared to vehicle gel at day 57. The rates of complete clearance (cc) and partial clearance (pc) of face/scalp group were higher in patients receiving ingenol mebutate (42.2% cc, 63.9% pc) in comparison with placebo (3.7% cc, 7.4% pc), both with $p < 0.001$. For the trunk/extremities group, clearance rates were also higher in patients receiving IM (34.1% cc, 49.1% pc) in comparison with placebo (4.7% cc, 6.9% pc), both with $p < 0.001$. The median reduction number count was also higher in ingenol mebutate treatment of both face/scalp (83% reduction) and trunk/extremities (75% reduction) groups in comparison to placebo (0% for both face/scalp and trunk/extremities). The study is limited as local skin reactions caused by ingenol mebutate reduce the blinding of the study. No other treatment modalities were used for comparison, making it difficult to interpret its efficacy compared to other established AK treatment modalities (1b) [53].

In a follow-up observational study by M. Lebwohl et al. in 2013, 100 patients with complete clearance of face or scalp lesions and 71 patients with complete clearance of trunk or extremities lesions after treatment with ingenol mebutate were observed 12 months after

treatment to evaluate the recurrence rates and safety associated with ingenol mebutate. The sustained clearance rate after 12-month follow-up was 46.1% (face or scalp) and 44.0% (trunk or extremities). Among patients with complete clearance at day 57, the percentage of reductions in AK at 12 months from the number of baseline AK prior to treatment was 87.2% (face or scalp) and 86.8% (trunk or extremities) (2b) [54].

In a multicentered, randomized, double-blind, double-dummy, vehicle-controlled, sequential-cohort dose-finding study, 222 patients with non-facial actinic keratosis were randomly assigned treatment with ingenol mebutate gel 0.05% for 2 or 3 days, ingenol mebutate gel 0.025% for 3 days, or vehicle gel for 3 days with follow-up evaluation at day 57. Primary outcome was partial clearance rate (75% reduction at day 57). Other secondary outcomes included complete clearance rate, mean reduction of AK lesions, and safety measured as local skin reactions and adverse effects. All three active treatments were significantly more effective than vehicle with regard to partial and complete clearance rates and median percentage reduction in baseline lesions. The therapeutic response was also positively correlated to dosage concentration. Partial clearance rates included 75.4% in the IM gel 0.05% for 3 days group, 61.8% in the IM gel 0.05% for 2 days group, 56% in the IM gel 0.025% for 3 days group, compared to 21.7% of the vehicle group. There were no serious treatment-related adverse effects reported, and there were no discontinuations due to an adverse effect (1b) [50].

Combination therapy of ingenol mebutate with cryotherapy has also been found to be efficacious. In a randomized double-blind vehicle-controlled study, 289 patients with 4–8 discrete AKs on the face or scalp underwent combination therapy with cryosurgery followed 3 weeks later by ingenol mebutate gel 0.015% vs. vehicle gel once daily for 3 consecutive days. Results showed that complete clearance rates were greater after cryotherapy with ingenol mebutate (60.5% at week 11; 30.5% at month 12) in comparison with vehicle (49.4% at week 11; 18.5% at month 12) (1b) [55].

Retinoids

The term retinoid includes both naturally occurring and synthetic derivatives of vitamin A. In the prevention and treatment of skin cancers, retinoids are thought to regulate the differentiation and growth of keratinocytes, interfere in the process of tumor initiation, reduce regulation of proto-oncogenes, increase expression of p53 and pro-apoptotic caspases, and sensitize keratinocytes to apoptosis [56–59]. The use of topical retinoids avoids the systemic toxicity seen with oral therapy, although there may be local adverse effects such as scaling, erythema, burning, and irritation [60]. Most of these adverse effects are seen to reach a peak during the first week and decrease over time [61].

In a randomized double-blind, placebo-controlled, parallel-group study, 79 patients with at least 5 AKs on the face, scalp, and/or upper extremities were assigned to treatment with topical isotretinoin 0.1% cream or vehicle twice daily for 6 months and were clinically assessed every 4 weeks for changes in lesion count in order to assess the efficacy and tolerability of isotretinoin. On the face, there was a statistically significant reduction in the number of actinic keratoses (mean +/− SEM) for patients treated with isotretinoin (3.9 +/− 0.6) compared with placebo (1.7 +/− 0.5) at all assessment points from 16 weeks onward ($p < 0.005$) and at the end of treatment ($p = 0.001$). There was not a significant drug effect seen for lesions on the scalp or upper extremities (1b) [62].

In a prospective RCT, 90 patients with at least 5 AKs on the face and/or scalp were treated with adapalene gel (0.1% or 0.3%) daily as field therapy or its vehicle gel for 4 weeks, followed by twice-daily treatment for 9 months. With adapalene gel 0.1% and 0.3%, the mean number of AKs was reduced by −0.5 ± 0.9 (mean ± SE) and − 2.5 ± 0.9, respectively, whereas with the vehicle gel, there was an increase of +1.5 ± 1.3 ($p < 0.05$) AKs (1b) [63].

Kligman conducted one of the largest multicentered double-blind studies on retinoids with 1265 patients with histologically confirmed AK. In

this study, published in non-peer-reviewed literature, there was a reduction of facial AKs from a mean of 11.2–8.9 (11% reduction) after 6-month use of tretinoin 0.05% cream once or twice daily ($p = 0.001$). This changed to a reduction of 47% after 15-month use ($p = 0.001$) (2b) [64].

Regarding case series on the use of topical retinoids for AKs, Bollag observed a reduction of AKs with tretinoin use. In 60 patients with actinic keratosis, 51 patients with facial lesions, and 9 patients with forearm and hand lesions, tretinoin 0.1% and 0.3% ointment was applied twice daily for 3–8 weeks. In 24 of 51 patients (47%) with keratoses on the face, lesions disappeared completely with no recurrence after 2–6 months. Although forearm and hand lesions did not disappear completely, 7 of 9 patients had a reduction of more than 50% of lesions (4) [65].

In contrast, a few studies have found that long-term use of topical retinoids do not reduce AK counts. In a RCT of 1131 patients, topical tretinoin 0.1% cream applied 1–2 times daily for a mean duration of 3.5 years was found to be ineffective in reducing the number of AKs. The study found no evidence for differences in actinic keratosis counts on the face and ears at any subsequent time point or risk of SCC in situ at 2 years (8 vs. 10%) or 5 years (18 vs. 16%) (1b/II/A) [66]. Campanelli performed a retrospective study in 61 immunocompetent patients who had applied retinaldehyde on photo-exposed body areas, and the total number of AK and skin cancers was counted. Results showed no difference in the use of 0.05% retinaldehyde for 6–142 months. As the study was not controlled, its value is limited (2b) [67].

Most of the studies are case series with small numbers of patients, often without randomization and sometimes without adequate explanation about method. Blind, randomized, and controlled clinical trials with adequate sample sizes are needed to clarify the real benefit of topical and/or oral retinoids [68]. The lack of standardization for topical retinoid treatment and lack of efficacy in larger studies makes topical retinoid treatment a poor choice when more efficacious options are available.

Organ Transplant Patients and Immunosuppression

More than 1 million patients worldwide with end-stage organ disease undergo organ transplantation [69]. Transplant recipients are at increased risk of developing skin cancer, especially squamous cell cancer (SCC) due to chronic immunosuppression. Organ transplant recipients who are on immunosuppressive medications are also up to 250 times more likely to develop AK. In patients receiving immunosuppression following renal transplantation, actinic keratoses have been reported in 38% after 5-year follow-up; however, it has been speculated that with time nearly all these patients will develop actinic keratosis [70]. Effective management of actinic keratoses could help prevent further development of invasive SCC [71].

Sunscreens can diminish the number of AKs by up to 50% in organ transplant recipients. In a prospective, single center case control study, 120 matched adult organ transplant recipients (40 heart, 40 kidney, 40 liver grafted) with AKs were enrolled. Each group had a total of 191 AKs at enrollment. Both groups received equally written and oral information on sun protection measures. Sixty subjects received treatment with a free broad-spectrum study sunscreen (SPF > 50) for daily self-application of 2 mg cm^2 to the head, neck, forearms, and hands. Within the 24-month study interval, 42 of the 120 patients developed 82 new AK (−102 sunscreen group vs. +82 control; $p < 0.01$) and 8 new invasive SCC (0 vs. 8; $p < 0.01$) and 11 BCC (2 vs. 9). In spite of equal numbers of AK at enrollment, the incidence of new AK after 24 months was significantly lower in the intent-to-treat sunscreen group as compared to the control group (89 vs. 273; $p < 0.01$, mean difference 3.07 [1.76–4.36]). The lesion count in the sunscreen group was significantly lower at 24-month visit compared to the initial visit (89 vs. 191; $p < 0.01$, mean difference 1.7 [0.68–2.72]). In the sunscreen group, an overall reduction of 53% in AK numbers as compared to initiation visit was observed after 24 months. In the control group, the AK numbers overall increased by 43%.

With an average of 5.6 applications per week throughout the 24 months, the study sunscreen was generally well tolerated (3b) [72].

A randomized controlled trial specifically addressed the use of imiquimod 5% cream 3 times weekly compared to vehicle alone for 16 weeks in 34 kidney, heart, and liver transplant patients with histologically confirmed AKs. An 8-week follow-up was performed and a punch biopsy was obtained to verify lesion resolution. Complete clearance rates for individual AKs were 62% in IMI group and 0% in vehicle group. In fact, overall lesion clearance rate for vehicle patients was −99%, showing a large increase in overall lesion count from baseline. Common adverse reactions included application site reactions followed by fatigue, headache, diarrhea, nausea, rash, and leukopenia. No patients experienced rejection of the transplanted organ (1b) [69, 73].

A randomized, placebo-controlled trial compared the safety and efficacy of topical diclofenac 3% gel (DHA) to vehicle gel in 32 solid organ transplant patients with at least 3 AK lesions in a contiguous 50cm^2 area located on the bald scalp, face, or hands. Subjects were treated with either DHA or placebo twice daily for 16 weeks, followed by final evaluation and biopsy of treatment area 4 weeks posttreatment. Complete clearance rate was 41% (9/22) in the DHA group vs. 0% (0/6) in the placebo group. Although the results show a trend toward the superiority of diclofenac, due to the very small sample size especially in the vehicle-treated group, short follow-up time, and risk of bias and imprecision, the results are not statistically significant. Side effects included mild erythema and mild to moderate swelling of treatment areas. No graft rejections were detected. In 55% of the previously cleared patients, new AKs developed in the treatment area after an average of 9.3 months. No patients developed invasive SCC within 24 months of follow-up (2b) [74].

One double-blinded, placebo-controlled study compared the efficacy of monotherapy of 0.02% tretinoin cream to a combination of 0.02% tretinoin and calcipotriol and calcipotriol and emollient in 13 adult renal transplant recipients with multiple AKs. Each patient applied the following regimens to four comparable and distinct areas of actinic keratoses on the extremities for 6 weeks: (i) calcipotriol cream 50 μg g^{-1} twice daily; (ii) 0.02% tretinoin cream twice daily; (iii) the combination of calcipotriol and tretinoin cream once daily; and (iv) cremor cetomacrogolis twice daily. The study demonstrated no significant differences in clinical, histological, and immunohistochemical parameters between the four different therapies during a 6-week treatment period (2b) [75].

Due to the high toxicity of high-dose systemic retinoid, Rook compared topical tretinoin alone with the combination of topical tretinoin and the low dose systemic retinoid, etretinate (10 mg) in renal transplant patients. Although results showed more improvement of AKs with the combination regimen, the effectiveness regarding the combination of oral and topical retinoids, versus topical retinoids, is difficult to establish in this clinical trial due to the small number of patients ($N = 11$), the high dropout rate during the study ($N = 4$), the short follow-up period, and the lack of a standard concentration for the topical retinoids in both groups (1b) [76]. Systemic retinoids have been used in the secondary prevention of AKs in renal transplant recipients. A 12-month study found that low-dose acitretin therapy (20 mg daily) is safe, well tolerated, and partially effective in chemoprophylaxis of non-melanoma skin cancer (1b) [77].

Conclusions

Several effective treatment modalities exist for the treatment of AKs. By understanding the different treatment options, physicians may tailor therapy to each patient's needs. Certain factors physicians need to consider when selecting a therapy include the number of AK lesions, the amount of background photodamage, the patient's tolerance to known side effects, and the cosmetic appearance.

An initial RCT by Thompson et al. demonstrated that the regular use of sunscreens not only prevents the development of AKs but also hastens the remission of existing ones and, by implication, possibly reduces the risk of skin cancer in the long term. Several other RCTs and case control studies confirm that sunscreen provides pro-

tection against AKs both in the general population and in high-risk patients [16, 72, 78]. One longer and larger RCT showed that daily sunscreen use reduces the incidence of SCC yet had no effect on BCC. Healthcare providers should continue to recommend sunscreen use in addition to other solar protection methods to reduce the risk of skin cancer.

Cryotherapy lacks rigorous studies investigating the efficacy for treatment of AKs. There are no RCTs comparing cryotherapy to placebo. Non-standardized freezing techniques make it difficult to interpret results. Cryotherapy is generally recommended for single AK lesions and multiple discrete lesions in immunocompetent and immunosuppressed patients. Cryotherapy is not recommended for the treatment of field cancerization. A prospective study showed a 57% complete clearance rate at 3-month follow-up, with the best clearance rates in patients treated with freeze cycles of 20 s or more [18]. A randomized trial comparing cryotherapy to 5-FU and imiquimod revealed that cryotherapy had the poorest initial clinical clearance at 6–8 weeks after treatment of multiple AKs, as well as the worst histological clearance rates and sustained clearance rates [20].

Chemical peels for AKs have the least rigorous studies to support its use. Most of the literature regarding chemical peels comprises case series or cohort studies, with small sample sizes of 16 patients or less. Only one study evaluated patients 1 year later and found a 78% reduction in mean AK count by 12 months. AK counts increased between 12 and 32 months, requiring regular follow-up in patients with AKs.

There are several RCTs and meta-analyses evaluating the efficacy of 5-FU for treatment of AKs, but dosing, follow-up, and cream strength vary between studies. In one RCT, 5-FU had the highest initial clearance (96%) of lesions 6–8 weeks after therapy completion, although a 12-month follow-up showed a sustained clearance rate for individual lesions of only 54% [20]. A meta-analysis of 6 RCTs concluded that overall complete clearance rate with varying strengths of 5-FU was 52.2%. Superior clearance rates were found when 5-FU was applied twice daily for 2–4 weeks as compared to pulse therapy, and 5% 5-FU was more effective than 0.5% [33]. Most studies only have short-term follow-up, and retreatment is recommended since lesions tend to recur by 1 year in studies with longer length of follow-up.

Imiquimod has several rigorous blinded, randomized-controlled trials investigating its efficacy for AKs. Application of 5% imiquimod shows optimal results with 3 times weekly application for 12–16 weeks. A meta-analysis reported 50% complete clearance rates for imiquimod with this regimen; however recurrence rates of at least 25% have been observed when patients were followed up to 16 months [38]. Although complete clearance rates may be lower, a regimen of imiquimod once daily for two 2-week treatment cycles separated by a 2-week treatment-free interval is often utilized [40]. Finally, imiquimod is one of the few modalities tested in organ transplant recipients and there is a complete clearance of 62% at 8-week follow-up [69].

A few RCTs have evaluated the efficacy of diclofenac, and twice-daily application for 2–3 months results in a complete clearance rate of approximately 35%. Diclofenac has been directly compared to imiquimod in two studies, but in both studies optimal dosing regimens were not evaluated. It is difficult to make comparison conclusions from these studies but both diclofenac and imiquimod appear to have efficacy [48, 49].

Ingenol mebutate has the advantage of having a short treatment course as compared to other topical therapies, potentially enhancing adherence. Recommended therapy includes a 3-day course of 0.015% gel for the face and scalp and a 2-day course of the 0.05% gel for the trunk and extremities. There are less RCTs, but complete clearance rate from one large study appears to be around 42% [53]. In one study, sustained clearance after 12-month follow-up was around 45% for the head, trunk, and extremities [54].

While previously described topical therapies for AKs have a consistent proven efficacy compared to placebo, studies for retinoids have variable results. Several small studies found reductions in AKs with topical retinoid use, but the largest study in a peer-reviewed journal of over 1000

patients found tretinoin cream to be ineffective in reducing AKs [66]. With several efficacious treatments available for AKs, retinoids should not be considered a first line therapy.

Because of the potential transition of AKs to cancerous lesions, treatment of AKs is an important component in skin cancer prevention. This is especially true for the transplant population. Several therapies are available for treatment with proven efficacy, but more head-to-head comparisons are needed to determine the best AK treatment strategies. New therapies and combinations of therapies will also likely change the way we treat AKs in the future.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Sunscreen is an effective preventive measure against AKs	A
Cryotherapy is an effective spot treatment for clinically visible AKs, and longer freeze cycles improve efficacy	A
Chemical peels are an effective field treatment for AKs	C
5% 5-FU is an effective field treatment for clinically visible and invisible AKs when applied twice daily for 2–4 weeks; significant side effects may occur	A
0.5% 5-FU is an effective field treatment for clinically visible and invisible AKs when applied once daily to the face or scalp for either 1, 2, or 4 weeks	A
Application of 5% 5-FU twice daily for 3 weeks has superior efficacy than pulse therapy (twice daily for 1 day per week for 12 weeks) for field treatment	B
Combination 0.5% 5-FU + 10% salicylic acid is more effective in AK lesion clearance at 20 weeks compared to diclofenac HA or vehicle twice daily for 12 weeks; more cutaneous side effects occur with 5-FU/SA compared to diclofenac HA	B
Application of 0.5% 5-FU/10%SA once daily achieved greater histological clearance and lower recurrence rates of multiple hyperkeratotic AKs at day 98 compared to cryotherapy treatments 3 weeks apart	C
Imiquimod 5% is an effective field treatment for clinically visible and invisible AKs when applied 3 times weekly for 12–16 weeks	A
Significant side effects may occur and subsequently decrease tolerability and adherence when imiquimod 5% is applied more than 3 times weekly	B
Imiquimod 2.5% and 3.75% creams are both effective field treatment for clinically visible and invisible AKs of the face/scalp when applied once daily for two 2-week treatment cycles separated by a 2-week treatment-free interval and well tolerated; no statistically significant difference in lesion reduction between imiquimod strengths	B
3% diclofenac in 2.5% sodium hyaluronate gel is an effective field treatment for clinically visible and invisible AKs when applied twice daily for 12 weeks; follow-up longer than 30 days is lacking	B
Ingenol mebutate is an effective field treatment for clinically visible and invisible AKs when 0.015% gel is applied to the face/scalp once daily for 3 days or 0.05% gel is applied to the trunk/extremities once daily for 2 days	A
Combination therapy with cryotherapy followed 3 weeks later by ingenol mebutate gel 0.015% once daily for 3 consecutive days is an effective treatment for multiple AK lesions on the face/scalp up to 12 months	B
Topical tretinoin 0.05% is an effective treatment for facial AKs when applied once or twice daily for 6 months; blind, randomized, and controlled clinical trials with adequate sample sizes are lacking	B
Sunscreen is an effective preventive measure for immunocompromised organ transplant recipients	C
Imiquimod 5% cream 3 times weekly is an effective field treatment for clinically visible and invisible AKs in immunocompromised organ transplant recipients	B
Treatment with topical diclofenac 3% gel or topical retinoids in immunocompromised patients cannot be established; blind, randomized, and controlled clinical trials with adequate sample sizes are lacking	C

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Self-Assessment Questions

1. In one study evaluating AKs in patients who did and did not use sunscreen, what was the percent reduction in AKs after 7 months?
   (a) 25%
   (b) 18%
   (c) 10%
   (d) 5%
   (e) 1%

2. In one study evaluating cryotherapy for complete clearance of AKs, how many seconds were necessary to achieve a complete clearance rate of 83%?
   (a) 3 s
   (b) 5 s
   (c) 10 s
   (d) 20 s

3. Twice daily application of 5-FU for 2–4 weeks shows increased AK clearance rates when compared to pulse therapy.
   (a) True
   (b) False

4. AK recurrence rates are equivalent when using imiquimod 5% cream twice weekly compared to 3 times weekly.
   (a) True
   (b) False

5. What is the recommended dosing regimen for ingenol mebutate of the face and scalp?
   (a) 0.015% gel for once daily for 2 days
   (b) 0.015% gel for once daily for 3 days
   (c) 0.015% gel once daily for 1 week
   (d) 0.05% gel once daily for 2 days
   (e) 0.05% gel once daily for 3 days

6. What is the mechanism of action for diclofenac?
   (a) Pyrimidine analog that interferes with DNA synthesis by stopping the conversion of deoxyuradilic acid to thymidylic acid
   (b) Glycosaminoglycan with inflammation-modulating and bioadhesive properties
   (c) Selective cyclooxygenase-2 (COX-2) inhibitor that inhibits the arachidonic acid cascade
   (d) Vitamin A derivative that regulates the differentiation and growth of keratinocytes, reduces the regulation of proto-oncogenes, and increases the expression of p53
   (e) Diterpene ester from the sap of the medicinal *Euphorbia peplus* plant that causes disruption of mitochondrial and cell membranes and results in a neutrophil-mediated antibody-dependent cellular cytotoxic pathway

Correct Answers

1. a: 25%
2. d: 20 s
3. a: true
4. b: false
5. b: 0. 015% gel for once daily for 3 days
6. c: selective cyclooxygenase-2 (COX-2) inhibitor that inhibits the arachidonic acid cascade

Basal Cell Carcinoma

42

Elise Ng, Joanna Dong, and Desiree Ratner

Abstract

The incidence of basal cell carcinoma (BCC) is increasing, and it is therefore important to be able to assess the comparative effectiveness of common treatments. While quality randomized controlled trials are generally lacking, there are systematic reviews comparing treatment modalities using randomized and nonrandomized data. Excision and Mohs micrographic surgery exhibit the lowest recurrence rates and are the putative first-line therapies in treating operable BCC in most patients. Randomized trials have also compared recurrence rates of excision with those of cryotherapy, radiation therapy, and nonsurgical treatment, as well as the comparative efficacy of nonsurgical treatment modalities, including photodynamic therapy and topical therapies. Selection of the appropriate treatment for any given BCC is based on evaluation of patient characteristics and co-morbidities, tumor characteristics such as histology, location, size, and primary or recurrent status, and patient preference. Cost, cosmesis, and safety must also be taken into consideration. An evidence-based summary based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) is provided to assist in the decision-making process.

Keywords

Basal cell carcinoma · Cryosurgery Electrodesiccation and curettage Imiquimod · Mohs surgery · Nonmelanoma skin cancer · Photodynamic therapy Vismodegib · 5-fluorouracil · Dermatologic surgery · Hedgehog pathway inhibitors

Epidemiology

Basal cell carcinoma (BCC) is the most common malignancy in the USA. The exact national incidence is unknown given the lack of national surveillance of nonmelanoma skin cancers (NMSCs). Further, epidemiological projections using insurance claims typically group BCC with other epithelial tumors, including squamous cell carcinoma (SCC). The most recent peer-reviewed analyses of incidence rates in 2012 estimate 2–3 million Americans with BCC annually [1–3]. While BCC has historically been thought to account for 75% of all NMSC, there is evidence of a shift toward a decreased BCC to SCC ratio

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[2, 4]. This trend may be due to biases toward Medicare-based patient sampling in these epidemiology studies, given that SCC is increasingly prevalent in older age groups and BCC remains more common in younger age groups [5]. The change in incidence rates of NMSC over the last 20 years has been variably reported as one that has increased by 17–200%, depending on the population cohort [1, 2, 6, 7]. In 1994, an estimated 750,000 cases of BCC occurred in the USA, suggesting an over twofold increase in BCC incidence rates since then [8]. One systematic review reports an average rate of increase in incidence of 2% annually, with the highest rates in the USA occurring in the states closest to the equator [9]. The worldwide incidence of BCC follows the same trend. In an analysis of comparable national surveys of primarily Caucasian populations, Australia exhibited the highest BCC rates in the world, compared to lower rates found in European countries such as England, Scotland, and Croatia [9].

Chronic sun exposure, both UV-A and UV-B, is the predominant risk factor for developing BCCs. Heavy exposure in the childhood to adolescent years (ages 0–19 years) leads to latent onset of BCCs in adulthood [10]. The cumulative effect, timing, and location of exposure are complex variables contributing to this increased risk [11]. Exposure to iatrogenic UV-A, with or without psoralen use, UV-B, and ionizing radiation, especially before the age of 20, increases the risk of developing BCCs in the original treatment field [12–14]. Other independent risk factors are those that confer greater susceptibility to damage by UV or ionizing radiation: Fitzpatrick skin types I and II, light hair and eyes, genodermatoses (Gorlin syndrome, Rombo syndrome, xeroderma pigmentosum), arsenic exposure, and immunosuppressed states [15–18]. While the average age of diagnosis is 65, the risk steadily increases with age. Notably however incidence rates among young adults less than 40 years of age have increased over the last several years [5]. BCC is more common in men than women, with a ratio of approximately 1.5:1 [6].

Treatment Overview

Various surgical and nonsurgical treatment modalities exist for the treatment of localized BCC. Surgical methods consist primarily of standard excision with post-operative margin assessment, Mohs micrographic surgery (MMS), and electrodesiccation and curettage (ED&C). Nonsurgical options include radiation therapy (RT), cryosurgery, photodynamic therapy (PDT), and topical medications such as imiquimod and 5-fluorouracil (5-FU) cream. For more advanced BCC, the newly developed sonic hedgehog pathway inhibitors, vismodegib and sonidegib, offer a systemic therapeutic option.

Surgical approaches represent the most effective means of curative treatment and are the mainstay of treatment for localized BCC. Standard excision entails surgical removal of the lesion with appropriate surgical margins to the level of the subcutaneous fat. Curettage may be performed prior to excision to delineate the true borders of the tumor more accurately. Microscopic evaluation of the margins is performed post-operatively using traditional permanently fixed vertically oriented sections. Closure of the defect following standard excision utilizes methods that do not shift or alter orientation of the surrounding tissue in the event of a positive margin. Standard excision is typically performed for lesions on the trunk and extremities, where tissue conservation is not of paramount importance.

MMS entails serial excision of tissue layers with interval intraoperative margin evaluation that is performed until negative margins are achieved. Curettage is performed prior to excision by some surgeons. Tissue layers are processed using fresh-frozen tissue processing and oriented horizontally in a manner that allows for complete evaluation of the peripheral and deep margins. Serial excision of tissue layers allows for maximum tissue preservation, while the ability to confirm negative margins prior to closure enables the surgeon to undertake more complex repairs on the same operative day. Given these advantages, MMS is generally considered the

preferred technique for lesions located in cosmetically sensitive anatomic locations.

ED&C is a destructive technique in which tumor tissue is bluntly removed by scraping with a curette to the level of firm, normal dermis, followed by denaturation of the area using electrodesiccation. Three cycles of this process are typically performed. As the technique relies on destruction, one major disadvantage is the lack of histologic margin assessment [19]. ED&C is usually considered for small, low-risk lesions located in non-cosmetically sensitive areas or areas in which wound healing may be difficult. It should not be used for high-risk tumors or in areas with terminal hair growth due to the risk of tumor extension down follicular structures **(5)** [20].

Nonsurgical treatments such as RT and cryosurgery represent destructive treatment modalities. Radiation therapy is administered using varying dosage and fractionation schedules depending on the tumor characteristics and duration of treatment. Cryosurgery involves destruction of tumor tissue through exposure to extreme cold using liquid nitrogen, which is capable of freezing tissue to −50 to −60°C. A range of techniques, such as open and closed spray, can be applied, but there is no consensus regarding the optimal number of freeze-thaw cycles **(4)** [21]. Both RT and cryosurgery are generally reserved for patients who cannot tolerate surgery or for whom surgery is impractical, as both carry the drawback of poorer cosmetic outcomes compared to other treatments. RT is also used as an adjunctive modality post-operatively to reduce the risk of recurrence in high-risk patients. Importantly, RT should be avoided in patients with conditions predisposing to cutaneous malignancy and younger patients for whom long term adverse effects are a consideration [20].

Photodynamic therapy (PDT) involves the application of a photosensitizing agent, usually aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), to the skin followed by exposure to visible light. This activates the photosensitizer, leading to photochemical reactions that generate reactive oxygen species and free radicals that cause cell death. Rapidly proliferating cells are selectively targeted, resulting in destruction of malignant cells. Treatment of BCC requires a red light source operating in the 630-nm range for sufficient penetration. A standardized protocol of two treatment sessions spaced 1 week apart is typically used for MAL-PDT, but treatment schedules with ALA-PDT are less well established [22].

Imiquimod 5% cream is a topical immune response modifier that is FDA-approved for the treatment of primary superficial BCCs not larger than 2 cm in diameter. The current recommended treatment regimen in the USA and Europe is application to the tumor and a 1-cm margin surrounding it five times per week for 6 weeks [23]. Topical 5-FU 5% cream and solution are approved for the treatment of superficial BCC smaller than 2 cm in diameter. This medication is applied twice daily for at least 3–6 weeks to the lesional skin **(2c)** [24]. As with RT and cryosurgery, PDT and topical therapy are reserved for nonsurgical candidates.

Vismodegib and sonidegib belong to a new class of molecules known as sonic hedgehog pathway inhibitors. They block the hedgehog signaling pathway through inhibition of the smoothened receptor. Both are oral medications that are primarily used for the treatment of locally advanced BCC not amenable to surgery or metastatic BCC. Patients with nevoid BCC syndrome who have a high number or incidence of tumors are also candidates for these medications.

Few studies have examined the relative frequency of use for each treatment modality. Available information is based on data for NMSC as a group, not BCC exclusively. In two studies using claims data, standard excision was found to be utilized most frequently, accounting for 35–76% of cases, followed by ED&C, which accounted for 14–32% of cases **(2c, 2c)** [25, 26]. The use of MMS comprises approximately 10% of all cases, but has been on the rise, increasing from 3% in 1995 to 17% in 2010 **(2c)** [27]. Its use has been noted to be as high as 39% in certain areas and settings **(1b)** [28].

Effectiveness of Treatments

Effectiveness of BCC treatment is ascertained by tumor recurrence rate (RR). In early studies of older treatment methods, reported recurrence rates varied widely, in part due to differences in the duration of follow-up. As it became apparent that only 50% of BCCs recur within the first 2 years, with this figure increasing to 82% by 5 years **(2a-)** [29], studies evaluating the efficacy of BCC treatment focused on 5-year recurrence rates (RRs) as the barometer for efficacy. Unfortunately, comparisons between most studies on treatments for BCC are difficult due to differences in patient population, tumor characteristics, technique, study design, and outcome measures.

Excision

Excision is an effective method for treatment of BCC and is considered the standard of care for low-risk lesions in non-cosmetically sensitive areas. Five-year recurrence rates among recent studies range from 3.2% to 8.5% **(2a-, 1b-)** [30, 31]. These rates are lower for lesions on the neck, trunk, or extremities, but are higher for lesions on the face, particularly those greater than 6 mm in diameter, as well as recurrent lesions **(2b, 2b)** [32, 33].

The first systematic review to investigate 5-year RR for standard excision pooled 40 years of data from studies starting in 1947, and found 5-year RR ranging from 1.2% to 23.4%, with a weighted average of 10.1%, for primary BCC, and ranging from 5.0% to 20.2%, with a weighted average of 17.4% for recurrent BCC [29]. However, it should be noted that this analysis included studies from the 1950s, when surgical techniques were not as well developed and standard margins had not been established. It was not until 1987 that Wolf and Zitelli demonstrated that a minimum margin of 4 mm is required to achieve pathologic clearance in 95% of cases of small, well-defined BCC **(2b)** [34].

A subsequent systematic review of all studies between 1970 and 1997 calculated a mean 5-year RR of 5.3% [30], with rates ranging from 3.2% to 8.0% among individual studies. More recent studies have shown similarly variable results. Trials comparing surgical excision using 3-mm margins with curettage-cryosurgery and PDT found a 5-year RR of 8.5% [31] and 1-year RR of 0% **(1b)** [35], respectively. Another comparing surgical excision using 4-mm margins with topical imiquimod found a 3-year clinical cure rate of 98% (**1b**) [36]. A large, randomized trial enrolling 408 high-risk facial lesions reported a cumulative 10-year RR of 12.2% for primary BCC and 13.5% for recurrent BCC after standard excision using 3-mm margins [33].

Curettage prior to excision has been advocated as a strategy to help delineate tumor margins and increase cure rates. One retrospective study of 403 BCCs found that microscopic tumor remained at the margins after curettage in only 14% of specimens, the majority being of morpheaform subtype (**2b**) [37]. Another study of 1983 BCCs found that performing pre-operative curettage was associated with a 26% decrease in surgical failure rate (**3b**) [38].

Electrodesiccation and Curettage

Electrodesiccation and curettage (ED&C) has a long history of use for the treatment of basal cell carcinoma. Early studies in the 1960s and 1970s initially reported very high cure rates of 98–100%, but these were subsequently criticized because of selection bias and lack of adequate follow-up [19]. There is a paucity of recent studies on ED&C, and those with 5-year follow-up data have shown less consistent results. Data also suggest that the efficacy of ED&C may vary based on tumor characteristics and location. Five-year cure rates for primary BCCs have been shown to be as high as 96% (**2b, 2b**) [39, 40] for superficial and nodular subtypes even with curettage alone [39] but as low as 73% when used to treat histologically aggressive tumors (**2b**) [41] and 60–66% for recurrent BCC (**2b, 2b**) [42, 43].

Two systematic reviews have analyzed the literature on ED&C for treatment of BCC. Cure rates from a systematic review of eight studies published between 1963 and 1985 calculated a

weighted average 5-year RR of 7.7% for primary BCC, which rose to 40% for recurrent BCC [29]. Another review of four studies between 1970 and 1997 found 5-year RRs ranging from 5.7% to 18.8% [30].

Multiple studies have shown that efficacy varies with lesion size and anatomic site. In a retrospective review of 2314 primary BCCs treated between 1955 and 1982, the overall RR was found to be 13.2% for primary BCC and 18.1% for recurrent BCC. However, when these tumors were further stratified, the 5-year RR dropped to 3.3% for BCCs located in low-risk sites (neck, trunk, and extremities) regardless of lesion size. For medium-risk sites (scalp, forehead, pre- and post-auricular, and malar areas), tumors less than 10 mm had a 5-year RR of 5.3%, while those 10 mm or larger had a RR of 22.7%. For high-risk sites (nose, paranasal, nasolabial groove, ear, chin, mandibular, perioral, and periocular areas), the 5-year RR was only 4.5% for tumors smaller than 6 mm in diameter, but 17.6% for those 6 mm or larger. Based on these results, the authors concluded that ED&C was effective for BCCs measuring less than 6 mm in diameter and those located on low-risk sites [42].

Julian et al. similarly found a high recurrence rate of approximately 20% in their prospective study of 405 BCCs, of which 60% had a superficial histologic pattern and 71% were located on the head and neck **(1b)** [44]. Consistent with this, a non-randomized, clinical trial of 257 primary BCCs in medium- and high-risk facial sites calculated a worst-case scenario—5-year RR of 20.6% **(2b)** [45]. A recent retrospective study from 2016 found a favorable overall recurrence rate of 6% among 106 tumors treated by a single physician. Of the recurrent tumors, however, 83% were located in high-risk "H-zone" areas (nasolabial fold, nasal alae, orbital area, and auricular area) **(2b)** [46].

An aggressive histologic growth pattern is another factor that has been shown to correlate with a higher treatment failure rate. In a retrospective review of 302 BCCs treated with curettage alone, 85% of which were of the nodular or superficial subtype, Barlow et al. found a favorable 5-year cure rate of 96% [39]. In contrast, a population-based, retrospective study from 2013 that included only tumors with high-risk histology found a 5-year cure rate of only 73% [41].

Operator skill has also been implicated in efficacy of ED&C. One of the earliest studies to examine 5-year RRs following ED&C for treatment of primary BCC was published by Kopf et al. in 1977. This study found that tumors treated by attending physicians had a 5-year RR of 5.7% compared to 18.8% for those treated by inexperienced residents [43].

Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) has been shown to provide the highest cure rates for BCC and is considered the preferred method for high-risk and/or recurrent tumors.

Two systematic reviews from 1989 demonstrated 5-year RRs of 1.0% for primary BCC and 5.6% for recurrent BCC **(2a-)** [29, 47]. Subsequent large studies have confirmed low RRs, generally ranging from 1% to 3% for primary BCC and 4–7% for recurrent BCC **(2b, 2b, 2b, 2b)** [48–51]. In a retrospective study of 720 BCCs treated in the Netherlands between 1992 and 1999, the 5-year RR was 3.2% for primary and 6.7% for recurrent BCC [51]. The largest, prospective, multicenter study on MMS for the treatment of BCC was conducted in Australia and followed 3370 patients for 5 years between 1993 and 2002. This study found 5-year RRs of 1.4% for primary and 4% for recurrent BCCs [49]. Only two randomized, clinical trials involving MMS have been performed, both comparing it to standard excision, and these reported similar results **(2b, 2b)** [52, 53].

Recurrence rates following MMS are low even when patient selection leads to samples enriched for high-risk tumors. A prospective study conducted in the UK of 228 BCCs selected for MMS based on cosmetically sensitive or high-risk location, indistinct borders, or recurrent nature found a 5-year RR of 1.7% for primary and 4.8% for recurrent BCCs [48]. The highest rates of recurrence with MMS were found in a retrospective study of 228 BCCs treated between

1983 and 1992 in Sweden, a country with very limited access to the technique that referred less than 1% of patients for MMS at the time. In this study, all tumors had aggressive histology and the vast majority of tumors were located on the face. The authors found 5-year RRs of 6.5% for primary tumors and 10% for recurrent tumors **(2b)** [54]. A follow-up study that reviewed 587 BCCs treated at the same institution between 1993 and 2003, however, found lower 5-year RRs of 2.1% for primary tumors and 5.2% for recurrent tumors, possibly attributable to improved experience and technique [50].

Risk factors for recurrence following MMS include aggressive histopathologic subtype, prior recurrence, and higher number of stages required for clearance [49, 51]. Patients with CLL have also been shown to be at an increased risk for recurrence. A case control study of 24 patients with CLL for 33 BCCs found a 22% rate of recurrence at 5 years, which was 14 times greater than that of controls **(3b)** [55].

Curettage has been suggested as a useful technique to help delineate margins prior to surgery and increase efficacy. One prospective evaluation of 599 BCCs found that curettage significantly reduces the number of Mohs surgical stages required for BCC clearance **(2b)** [56]. Similar findings were confirmed in a study of 16 BCCs in which histologic evidence of tumor at pre- and post-curettage margins was evaluated **(2b)** [57]. Another prospective, randomized study on the subject found that curettage led to larger final wound sizes and decreased the number of stages required for clearance compared to controls but that this did not change the type of repair that was performed **(1b)** [58].

Cryosurgery

Cryosurgery has primarily been studied for the treatment of low-risk tumors, such as those with well-defined borders, that measure 2 cm or less, or have nodular or superficial histology. A wide range of recurrence rates have been reported, however, and direct comparison between studies is difficult due to variations in technique, including freeze time, number of freeze cycles, margin of normal skin included in the treatment area, and use of pre-procedure curettage [21, 59]. Additionally, most studies were performed more than 15 years ago, and many have short follow-up periods or provide limited details regarding the number of patients achieving 5 years of follow-up time.

Systematic reviews from 1989 and 1999 show recurrence rates from 0% to 7.5% among studies with at least 5 years of follow-up, and mean recurrence rates from pooled analyses range from 3% to 4% [29, 30]. More recent prospective studies have found highly variable rates ranging from 4.5% to 20.6%. A 4.5% recurrence rate was found in a prospective, randomized study that examined the efficacy of one freeze-thaw cycle for the treatment of truncal superficial BCC [60]. In the same study, the authors compared the efficacy of a double freeze-thaw cycle to a single freeze-thaw cycle for 84 facial BCCs and found a 4.7% recurrence rate for the former compared to 20.6% for the latter. Mean time to recurrence was 18 months and the shortest follow-up time was 10 months **(2b)**. In another prospective study of 88 BCCs, in which follow-up time was limited to 1 year, the clinical and histologic recurrence rates were 13% and 15%, respectively **(1b)** [61].

The highest recurrence rate was reported in 1986 by Hall et al., who found that 39% of 44 tumors recurred within 2 years of treatment despite the use of two freeze cycles. It is important to note, however, that at the time of this study, it was standard practice to use treatment temperatures between −25°C and −30°C, which were later realized to be suboptimal **(1b)** [62]. New temperature standards of −50 to −60°C were not adopted until the mid-1980s when research showed that such temperatures were required for destruction of cutaneous cancers [21]. The lowest recurrence rate has been reported by a single provider, who found a 5-year cure rate of 99.0% among 552 cases in a retrospective review. While this may be attributable to operator skill and more aggressive technique, it should also be noted that details regarding outcome assessment and the proportion of patients presenting for 5-year follow-up in this study are unclear [21].

Radiation Therapy

Studies on the use of radiation therapy for the treatment of BCC have utilized various treatment schedules. The 5-year RR for radiation therapy has generally been found to exceed 5%. Two meta-analyses reported recurrence rates of 7.4–8.7% for primary BCC and 9.5% for recurrent BCC **(2b)** [29, 63]. Retrospective studies have found 5-year RRs ranging from 4% to 16% (**2b, 2b, 2b, 2b, 2b, 2b)** [64–69].

A prospective study from over 20 years ago that employed superficial x-rays found a recurrence rate of 4% at 2 years [62]. A more recent study that investigated various forms of radiation therapy, including brachytherapy, contact therapy, and conventional radiotherapy, found an overall 4-year failure rate of 7.5% **(1b)** [70].

Predictors for BCC recurrence after radiation therapy include tumor size and stage and morpheaform subtype. Tumor size greater than 10 mm has been found to correlate with increased rates of recurrence [63, 65, 68]; in one study, size greater than 20 mm was associated with a lower response rate [69]. More advanced tumors similarly tend to demonstrate a poor response to RT, with recurrence rates as high as 56% for Stage III and IV tumors [64, 65]. In a retrospective study of 175 BCCs, morpheaform histology was associated with a 5-year RR of 27% compared to 8.2% for those with nodular histology [67].

Imiquimod

The overall efficacy of imiquimod 5% cream has been well-studied for the treatment of superficial BCC. Several large, randomized, double-blind, vehicle-controlled studies have shown complete histologic clearance rates of 79–88% with an application regimen of once daily for 6 weeks, with rest periods as needed. Post-treatment excision specimens obtained 6–12 weeks after treatment were used for histologic evaluation in these studies (**1b, 1b, 1b)** [71–73]. Two prospective trials examining long-term clinical clearance rates with daily application reported 5-year and 3-year disease-free rates of 80.4% and 84%, respectively (**1b-)** [36, 74]. A meta-analysis of 23 studies on imiquimod for superficial BCC calculated a pooled estimate of 87.3% for tumor-free survival at 1 year (**2a-)** [75]. Tumor thickness greater than 0.40 mm has been associated with a higher recurrence rate **(3b)** [76], while occlusion has not been shown to enhance efficacy **(1b)** [77].

The relative efficacy of various dosing regimens has also been investigated. Complete clearance rates as high as 100% have been reported with twice-daily application, but this regimen has been associated with an unacceptably high rate of adverse effects **(1b)** [78]. Less frequent application results in lower histologic clearance rates of 80–82% for five times per week [71, 72, 78] and 52–76% for three times per week application [71, 77, 78]. Two phase 3, randomized, vehicle-controlled trials demonstrated similar histologic cure rates after five and seven times per week application, prompting a regimen of five times per week to become the FDA-approved dosage [72].

The efficacy of imiquimod 5% cream for nodular BCC has not been as well established. There is some evidence that it may be effective with daily use for 12 weeks. A large, randomized trial comparing standard excision with topical imiquimod found an 81.8% clinical clearance rate at 3 years among 99 nodular BCCs that were enrolled [36]. A smaller study using the same regimen found a 76% histologic clearance rate among 21 patients [79]. Studies utilizing less frequent dosing regimens, however, have shown inferior results for nodular BCC. One multicenter, randomized study employing an application regimen of three times per week for 6 weeks found imiquimod 5% cream to be less effective for nodular BCC compared to superficial BCC, with histologic response rates of 50% and 76%, respectively [77]. Application regimens of twice daily three times per week for 6 weeks **(1b)** [79] and once daily three times weekly for 8–12 weeks **(1b)** [80] have been associated with histologic clearance rates of 42% among 31 patients and 64% among 90 patients, respectively.

The evidence does not support the use of imiquimod for morpheaform BCC. Only one study has included tumors with infiltrative histology. Among

the 13 tumors in this study, a clearance rate of 62% was observed for three times weekly application for 8 weeks and 56% for five times weekly application for 5 weeks **(2b)** [81]. Cure rates lower than those for superficial and nodular BCCs would be predicted given the increased depth and aggressive histologic growth pattern of these tumors, as well as the likelihood of insufficient penetration of this medication.

Photodynamic Therapy

Numerous studies have investigated the efficacy of photodynamic therapy (PDT) for the treatment of primary and nodular BCC. Both aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) PDT have been shown to be effective. A meta-analysis of 13 studies on ALA- or MAL-PDT for the treatment of superficial BCC estimated a tumor-free survival of 84.0% at 1 year [75]. Comparison of results between individual studies is difficult, however, owing to lack of uniformity in treatment regimens, assessment of clearance, and length of follow-up.

Two randomized controlled trials studied MAL-PDT for primary superficial BCC and demonstrated clearance rates as high as 92–97% at 3 months, but recurrence rates were 9% at 12 months and 22% at 5 years **(1b)** [35, 82]. Other prospective studies have similarly demonstrated high short-term clearance rates of 87–93%, but subsequent recurrence rates as high as 18–24% at 24 months **(2b, 2b)** [83, 84]. With longer follow-up, PDT has been associated with 3-year tumor-free survival as low as 58.0% **(1b)** [85]. MAL-PDT has also been studied for nodular BCC. A randomized controlled trial showed a 91% clearance rate at 3 months, but an estimated complete response rate of 76% at 5 years **(1b, 2b)** [86, 87]. Another reported a complete histologic response rate of only 73%, although this was higher, at 89%, for facial lesions **(2b)** [88].

In a review of 12 studies on ALA-PDT, Peng et al. calculated an average complete clearance rate of 87% for superficial BCC versus 53% for nodular BCC [89]. A subsequent prospective, randomized trial that included both superficial and nodular BCCs found an overall 1-year histologic recurrence rate of 25% [61]. A longitudinal study with 10-year follow-up that included BCCs of all subtypes found an overall complete response rate of 75%, with a higher rate of 87% seen among those receiving two treatment sessions **(2b)** [90].

Several studies have observed lower cure rates for nodular BCC compared to superficial BCC following PDT **(2b, 2b)** [83, 84, 91, 92]. Response rates as low as 33% have been observed, though this may be partially attributable to the absence of pre-procedure debulking in this study [91]. Recurrent tumors also fare poorly, with cure rates as low as 40–63% **(4)** [90, 93]. Other factors associated with treatment failure and recurrence include ulceration, tumor thickness, and location on the limbs [91]. Recurrence following PDT generally occurs within the first 3 years after treatment [82, 87, 90]. A higher number of treatment cycles [75], fractionated delivery of PDT **(1b)** [94, 95], and the practice of deep curettage **(4)** [96] may improve treatment response.

5-Fluorouracil

There are few studies on the use of 5-fluorouracil 5% cream for the treatment of BCC, and it has only been studied for superficial BCC. FDA approval was obtained based on an unpublished study of 113 superficial BCC lesions that demonstrated a 93% clearance rate. A subsequent study of 31 tumors on the trunk and limbs found a histologic cure rate of 90% with twice-daily application up to 12 weeks **(2b)** [97]. Of note, the mean time to clinical cure was 11 weeks, substantially longer than the FDA treatment recommendation of 3–6 weeks. The only study evaluating long-term efficacy was a comparative prospective trial of 5-fluorouracil, photodynamic therapy, and imiquimod. This found a 3-year tumor-free survival of 68.2% for 5-fluorouracil, though this study used a shorter application regimen of twice weekly for 4 weeks [85].

Hedgehog Pathway Inhibitors

The effectiveness of the hedgehog pathway inhibitors in treating BCC is supported by well-designed, large-scale clinical trials. The efficacy of vismodegib for the treatment of locally advanced BCC (laBCC) and metastatic BCC (mBCC) was first established in the pivotal ERIVANCE trial, in which patients were treated with oral vismodegib of 150 mg daily **(2b)** [98]. At 18 months of follow-up, the overall objective response rates were 47.6% for laBCC and 33.3% for mBCC; 22.2% of patients achieving complete responses was observed in the former group, but none were seen in the latter. The mean duration of response was 9.5 months for laBCC and 7.6 months for mBCC, while median progression free survival was 9.5 months for both. Disease control was obtained in 83% of laBCC and 94% of mBCC patients **(2b)** [99]. Subsequent phase 2 trials have demonstrated similar response rates ranging from 46.4% to 66.7% for laBCC and 31–37.9% for mBCC **(2b, 2b)** [100, 101].

Vismodegib has also been studied for the prevention of BCC in patients with basal cell nevus syndrome. A prospective study of 41 patients found that vismodegib significantly reduced the rate of development of new operable BCC lesions compared to placebo as well as the number of existing surgically eligible tumors **(1b, 1b)** [102, 103].

The efficacy of sonidegib was established more recently in the multicenter, randomized, double-blind phase 2 BOLT trial, in which patients with laBCC or mBCC received 200 mg or 800 mg of oral sonidegib daily **(2b)** [104]. The benefit-to-risk ratio profile was found to be more favorable in the 200-mg group, leading this to become the recommended dose. In the 12-month follow-up analysis, the overall objective response rate in the 200-mg group was 58% for laBCC and 8% for mBCC. Complete responses were seen in only 5% of patients in the laBCC group, although it has been noted that if the less stringent criteria used in the ERIVANCE trial were applied to this trial, the complete response rate would increase to 20% [105]. The median duration of response was 20.2 months for laBCC and 13.1 months for mBCC, while the median progression-free survival was 21.1 and 11.1 months, respectively. Disease control was obtained in 78% of laBCC and 92% of mBCC patients **(2b)** [106].

The role of hedgehog pathway inhibitors in the neoadjuvant setting has not yet been established. Clinical trials investigating the utility of these medications to shrink tumor size prior to surgery are ongoing. There are also active clinical trials studying the tolerability of alternative dosing regimens in patients with multiple BCCs [107, 108].

Comparative Effectiveness of Common Treatments

Overall, quality randomized control trials (RCTs) comparing treatment modalities in BCC with adequate follow-up of at least 3 years and stringent analytical methods are lacking. Nonetheless, systematic reviews comparing major treatment modalities using available randomized and non-randomized trial data demonstrate that standard surgical excision and MMS exhibit the lowest recurrence rates and are the putative first-line therapies in treating operable BCC in patients without contraindications to the procedure (**2a, 1a-**; Table 42.1) [30, 109]. A number of randomized controlled trials have compared recurrence rates, the primary outcome measure for BCC, of standard surgical excision with that of nonsurgical methods.

The superiority of standard surgical excision compared to cryosurgery, RT, and imiquimod has been well demonstrated in multiple studies. A single-center study randomized 88 patients with 100 superficial or nodular BCCs of the head and neck to surgical excision ($n = 49$) or cryotherapy with pre-procedure curettage ($n = 51$). With median follow-up of 4.29 years, the calculated 5-year probability of recurrence was 8.2% in excision-treated patients and 17.6% in cryosurgery-treated patients, though the observed differences were not statistically significant ($p = 0.10$) [31]. A follow-up study involving 96 of

Table 42.1 Systematic reviews and randomized control trials comparing different modalities for the treatment of basal cell carcinoma

Study type and level of evidence	Treatment comparisons	Conclusion	Reference	Year	Location	Single vs. multicenter	Limitations
Systematic review 2a	Surgical excision, MMS, cryosurgery, ED&C, RT	5-year recurrence rates with cryosurgery and ED&C are higher compared to surgical excision and MMS	Thissen et al. [30]	1999	N/A	N/A	Only one included study on RT and no studies on PDT
Systematic review 1a	Surgical excision, MMS, CS, RT, PDT, 5-FU, imiquimod	Surgery and RT are the most efficacious; Surgical excision and MMS have the lowest recurrence rates	Bath-Hextall et al. [109]	2007	N/A	N/A	Most included trials have 3-year recurrence follow-up
RCT 1b	Surgical excision and cryosurgery (cryotherapy + curettage)	Surgical excision has putatively lower, but not statistically significant, recurrence rates than cryosurgery	Kuijpers et al. [31]	2007	Netherlands	Single	Variable follow-up between 1 and 5 years
RCT 1b	Surgical excision and RT	Surgical excision has significantly higher success rates and cosmetic outcomes than RT	Avril et al.	1997	France	Single	2-mm surgical margin criteria
RCT 1b	Surgical excision and imiquimod 5% cream	Imiquimod is inferior to surgery	Bath-Hextall et al.	2014	UK	Multi	N/A
RCT 1b	Surgical excision and ALA-PDT	ALA-PDT had significantly higher failure rates than surgical excision and should not be used as standard treatment of nodular BCC	Mosterd et al. [114]	2008	Netherlands	Single	Variable follow-up between 1 and 5 years
Non-randomized controlled trial 2b	Surgical excision and ALA-PDT	ALA-PDT non-inferior to surgical excision and has better cosmetic outcomes	Cosgarea et al. [115]	2013	Romania	Single	Non-randomized
RCT 1b	Surgical excision and ALA-PDT	Surgical excision superior to ALA-PDT; Thin tumors ($\leq$ 0.7 mm) significantly less likely to recur after PDT than thick tumors (>0.7 mm)	Roozeboom et al. [116]	2013	Netherlands	Single	N/A

Table 42.1 (continued)

Study type and level of evidence	Treatment comparisons	Conclusion	Reference	Year	Location	Single vs. multicenter	Limitations
RCT 1b	MMS and surgical excision	MMS has lower but not statistically significant recurrence rates than surgical excision	Smeets et al. [53]	2004	Netherlands	Multi	Short follow-up (18 months) for some tumors
RCT 1b	MMS and surgical excision	MMS superior to surgical excision for recurrent BCC	Mosterd et al. [52]	2008	Netherlands	Multi	N/A
RCT 1b	MMS and surgical excision	MMS leads to significantly smaller surgical defect than surgical excision	Muller et al. [111]	2009	Scotland	Single	N/A
RCT 1b	Imiquimod cream, fluorouracil cream, MAL-PDT	Imiquimod is the preferred treatment with the least recurrence rate	Arits et al. [117]	2013	Netherlands	Multi	Short follow-up (12 months)
RCT 1b	Imiquimod cream, fluorouracil cream, MAL-PDT	Imiquimod and fluorouracil are preferred nonsurgical treatments over MAL-PDT	Roozeboom et al. [85]	2016	Netherlands	Multi	Follow-up to 3 years
RCT 1b	ALA-PDT and cryosurgery	PDT non-inferior to cryosurgery	Wang et al. [61]	2001	Sweden	Single	Short follow-up (12 months)

these patients compared cosmetic outcomes of the two treatments after 1 year. Evaluations by independent clinicians and the patients favored surgical excision (**1b)** [110].

Similarly, surgical excision demonstrated superiority over RT in a randomized controlled trial of 347 patients with mean follow-up at 41 months. The 4-year recurrence rate was 0.7% in the surgery group and 7.5% in the RT group ($p = 0.001$), with significantly higher rates of patient and clinician satisfaction with cosmetic outcome in the surgery group ($p < 0.01$) [70]. In comparing surgical excision with 4-mm margins and topical imiquimod 5% cream, a large multicenter randomized investigation of 501 subjects with superficial or nodular BCC demonstrated higher recurrence rates in the imiquimod-treated group (16% vs. 2%, $p < 0.0001$) without a difference in cosmetic outcomes [36].

MMS has only been comparatively investigated with respect to standard surgical excision in controlled studies due to the putative inferiority of nonsurgical methods in treating BCCs of aggressive subtype or in cosmetically sensitive areas. In the first of such trials, 374 patients with 408 primary BCCs of the H-zone of the face or with aggressive histological subtype (morpheaform, micronodular, trabecular, infiltrative, or BCC with squamous differentiation) and 191 patients with 204 recurrent BCCs were randomized to receive MMS or surgical excision with a 3-mm margin for both methods. MMS groups exhibited a lower recurrence rate than surgical excision for primary tumors at 30-month follow-up, 2% vs. 3% ($p = 0.724$), and for recurrent tumors at 18-month follow-up, 0% vs. 3% ($p = 0.119$), although these results were not statistically significant. In this study, overall defect size did not differ signifi-

cantly between the two methods, but in tumors that necessitated more than one standard excision or Mohs stage, MMS had a greatly reduced mean defect size for both primary (4.86 vs. 8.66 cm^2, $p < 0.001$) and recurrent tumors (7.95 vs. 14.52 cm^2, $p = 0.026$) [53]. For these same patients, MMS maintained superior recurrence rates to those of surgical excision after extended 5-year follow-up for primary BCCs (2.5% vs. 4.1%, $p = 0.397$) and recurrent BCCs (2.4% vs. 12.1%, $p = 0.015$), reaching statistical significance in the latter group of participants. This is the first directly comparative prospective randomized controlled study to show significant superiority of MMS over surgical excision in the treatment of recurrent BCCs [52].

While MMS is considered a tissue-sparing surgical technique, few studies have directly compared it to surgical excision along this outcome parameter. Whereas Smeets et al. enforced 3-mm margins for both surgical excision and MMS groups and found no difference in defect size with either technique except under certain tumor conditions, a separate trial comparing MMS with 2-mm margins and surgical excision with 4-mm margins concluded that MMS significantly decreased surgical defect size regardless of tumor conditions. In this study, after randomizing 30 participants with nodular BCC to MMS, the median surgical defect area in the MMS group was 116.6 mm^2 compared to 187.7 mm^2 in the surgical excision group ($p < 0.001$) **(1b)** [111]. Given that the recommended margins for surgical excision for 95% clearance are 4 mm and that most dermatologic surgeons will use margins narrower than 3 mm in MMS, this study may be more representative of tissue-sparing outcome differences, although only nodular BCC was included [34].

Overall, both MMS and surgical excision appear to be equally effective for primary BCCs, and treatment choice in these cases can be differentiated based on patient preference, cost, and physician comfort. MMS is more effective for recurrent BCC. Cosmetic outcome with MMS may be more favorable for tissue sparing based on choice of narrow margins. Imiquimod 5% cream has been investigated as a neoadjuvant or adjuvant therapy to MMS, with variable success in reducing post-MMS surgical defect size **(1b, 1b-)** [112, 113].

While surgical excision and MMS have shown the most consistent efficacy for operable tumors, PDT is an attractive option for inoperable tumors. In a randomized controlled comparison to PDT, 171 patients with nodular BCC received either surgical excision with 3-mm margins or ALA-PDT. Median follow-up was 2.33 years and the predicted 3-year analysis of recurrence was 2.3% and 30.3% ($p < 0.001$), respectively **(2b)** [114]. However, tumor thickness, which was not accounted for in this study, may be an important prognostic indicator of efficacy of PDT in treating BCCs.

A recent study concluding non-inferiority of ALA-PDT for BCC allowed patient selection of treatment, but restricted the PDT group from nodular BCC of greater than 3-mm elevation above skin level. Over a mean follow-up period of 25 months, recurrence rate was 4.16% in the PDT group and 4.34% in the surgery group ($p = 0.64$), with superior cosmetic outcomes in the PDT group at 12 months **(2b-)** [115]. PDT may indeed be effective given appropriate patient selection for tumor thickness. A randomized controlled trial showed a projected 5-year recurrence rate of 35% in superficial BCC tumors greater than 0.7-mm deep compared to 5.6% of tumors less than or equal to 0.7-mm deep ($p = 0.018$) **(1b)** [116].

In recent efficacy comparisons of multiple nonsurgical treatment modalities, imiquimod has demonstrated the greatest superiority. In a randomized controlled trial, 601 patients with superficial BCC were randomized to receive MAL-PDT, imiquimod 5% cream, or fluorouracil 5% cream. Recurrence rates at 12-month follow-up were 27.2%, 16.6%, and 19.9%, respectively. The difference between 5-fluorouracil and the other treatments was not statistically significant, whereas imiquimod had a significantly lower recurrence rate compared to MAL-PDT ($p = 0.021$). Based on these findings, the authors concluded that imiquimod is the treatment of choice of these three treatment modalities, given its lower rate of recurrence and superiority to MAL-PDT.

Cosmetic differences at follow-up were not significant (**1b)** [117]. On an extended 3-year follow-up of these patients, recurrence rates were 42% for MAL-PDT, 30.3% for imiquimod, and 31.8% for fluorouracil, with imiquimod maintaining significant superiority over MAL-PDT (p = 0.001), and fluorouracil non-inferior to either [85]. Although 5-year recurrence rates are lacking for this comparison, these authors suggest that imiquimod and fluorouracil are preferable to MAL-PDT for the nonsurgical treatment of superficial low-risk primary BCCs. Interestingly, post hoc subgroup analysis of these findings found MAL-PDT to be 35.2% more effective than imiquimod in treating superficial BCC of the lower extremities ($p = 0.003$). However, given that these were exploratory findings, conclusions should be made with caution **(1b)** [118].

Cryosurgery has not been extensively compared to nonsurgical therapies in BCC. A phase 3 trial comparing ALA-PDT and cryotherapy (two cycles) in 88 patients with superficial and nodular BCC demonstrated that 25% of PDT-treated lesions and 15% of cryotherapy-treated lesions recurred. This difference was not significant, and PDT was considered non-inferior to cryosurgery [61].

Preoperative Evaluation and Patient Selection

Important preoperative considerations include tumor characteristics such as histology, location, size, stage, and primary or recurrent status. Patient characteristics and co-morbidities must also be considered. Assessment of these factors allows stratification of cases into high-risk and low-risk categories. High-risk tumors are those with risk factors for recurrence, such as aggressive histology, poorly defined borders, recurrent status, location on the face, perineural invasion, and underlying immunosuppression. Procedure selection is based largely upon the presence or absence of such features, in conjunction with patient preference [20].

In general, surgical treatment is considered the standard of care given its superior cure rates. For low-risk tumors, such as well-defined primary lesions with superficial or nodular histology located on the trunk and extremities, standard excision can be considered. However, ED&C should be avoided for lesions located on terminal hair-bearing skin [20]. For high-risk tumors, such as poorly-defined primary or recurrent tumors with aggressive histologic growth patterns located in cosmetically sensitive locations, Mohs surgery can be considered. Standard excision can also be utilized, but wider surgical margins should be employed and it is prudent to delay repairs pending margin evaluation.

For patients who are nonsurgical candidates or who refuse surgery, radiation therapy can be considered, although it is less effective for larger tumors and those with morpheaform histology. Radiation therapy is also used post-operatively for BCCs with perineural invasion. However, RT should be avoided in younger patients, for whom long-term consequences such as later radiation-induced malignancies are a concern, as well as patients who are predisposed to developing ionizing radiation-induced malignancies, such as those with basal cell nevus syndrome and xeroderma pigmentosum [119].

Topical therapies such as imiquimod 5% cream, 5-fluorouracil 5% cream, cryotherapy, and photodynamic therapy are reserved for nonsurgical candidates who cannot undergo RT due to inferior cure rates. Imiquimod and 5-FU are only indicated for tumors with superficial histology. Cryotherapy and PDT can be used to treat superficial or nodular BCCs, though lower cure rates should be expected for the nodular subtype. Topical therapies and PDT offer the advantage of field therapy in select patients.

The hedgehog pathway inhibitors vismodegib and sonidegib are primarily used for locally advanced tumors recurrent after surgery or not amenable to surgical treatment or radiation, as well as for metastatic lesions. Patients with a high tumor burden from basal cell nevus syndrome can also be considered for these medications to decrease the rate of new tumor development as well as the need for surgery. Sonidegib is primarily metabolized by CYP3A and should be avoided in patients taking medications that strongly inhibit or induce that pathway.

For pregnant patients, 5-FU is absolutely contraindicated (pregnancy category X). Vismodegib is category D and topical imiquimod and aminolevulinic acid are both category C. Lidocaine with epinephrine is category B.

Impact of Patient Preference

When selecting the most appropriate therapy, patient and provider preference should be weighed in conjunction with tumor and patient characteristics. Aside from efficacy, factors that may be of concern to patients include cosmetic outcome, convenience, tolerability, and cost. Cosmetic outcome is a particularly strong driver of patient preference and may be just as important in the eyes of the patient as likelihood of recurrence [120, 121]. One discrete choice experiment ascertaining patient preference for imiquimod versus surgery revealed that cosmetic outcome and adverse effects were valued more highly than clearance rate or cost [122].

The treatment modalities that have been associated with the worst cosmetic outcomes are radiation therapy **(1b)** [70, 123] and cryotherapy [31, 61, 110]. Topical therapies, though less effective, are generally associated with the most favorable cosmetic outcomes [61, 115], with imiquimod, 5-FU, and PDT yielding similar cosmetic results [117]. PDT, in particular, has been shown to have superior cosmetic outcomes compared to surgery **(1a-)** [35, 87, 124] and cryotherapy [61, 82]. Moreover, cosmetic results have been observed to improve with time following PDT [35, 84, 86]. While surgical approaches invariably cause scarring, MMS may allow for shorter scars than standard excision. The tissue-sparing nature of MMS was corroborated in a randomized trial, showing that standard excision resulted in a median defect size 1.6 times larger than those of defects following MMS [111].

In terms of convenience and feasibility, treatment options vary in duration and setting. Patients who desire a shorter treatment course and quicker healing time may prefer surgery, ED&C, cryotherapy, or PDT, which may require as few as one to two office visits. Both 5-FU and imiquimod require long, drawn-out treatment courses over weeks, with which patients may not be compliant; however, one advantage is that they can be performed at home. Radiation therapy requires multiple office visits, which may not be practical for patients with difficulties traveling to a physician's office.

In terms of cost, RT and MMS have been found to be most expensive, followed by standard excision and destructive therapies such as ED&C and cryotherapy **(4)** [26, 125–127]. Placement of the non-invasive therapies among the cost spectrum is less clear. Imiquimod is more costly than 5-FU [97, 125, 128], and PDT may exceed the cost of both [128].

Typical Treatment Plan

A 40-year-old woman with no history of skin cancer presents for treatment of a biopsy-proven nodular basal cell carcinoma on her temple. She works as a television news anchor and is extremely concerned about the potential for scarring. Although she has never developed hypertrophic scars in the past, she notes that she has friends who developed unacceptable scarring after skin cancer surgery. She would therefore like to discuss alternative treatment options she read about on the internet, specifically the "creams." Her medical history is unremarkable, and she does not take any medications. Due to her work obligations, she will only be able to take off a maximum of 2–3 weeks for treatment of her BCC.

ED&C, cryotherapy, and radiation therapy would be inappropriate treatment options for this patient given her age, the high-risk location of the lesion, and the importance of cosmetic outcome in this case. She is clearly interested in a non-invasive treatment option. Topical 5-fluorouracil would be inappropriate as it has only been studied for BCC with superficial histology. While imiquimod is similarly approved only for superficial tumors and its role in nodular BCC remains to be determined, there has been one study showing potential efficacy for nodular BCC. Even so, it has lower cure rates than surgery and this option would not be practical for the patient, as a full

course of treatment requires 6 weeks. The option of photodynamic therapy could be discussed, but the patient should be made aware of the high recurrence rates and low cure rates for nodular BCC. Given these considerations, the most appropriate treatment option for this patient would be Mohs micrographic surgery, which would likely provide her with a smaller scar than standard excision.

The treatment course for Mohs micrographic surgery requires an office visit lasting several hours, depending on the number of excision stages required. Repair would likely be performed the same day. She would not want to return to work until the time of suture removal, which would typically be 1–2 weeks after surgery. However, she would likely be able to use make-up and concealer within 3 weeks of the procedure. The probability of complications from surgery would be extremely low in a young, healthy patient such as this one. If she were to develop undesirable scarring, treatment options such as dermabrasion, intralesional corticosteroid injections, and laser surgery could be considered.

Future treatment options may employ the use of laser technology. To date, there have only been small pilot studies suggesting potential efficacy with laser surgery or laser-assisted drug delivery for the treatment of BCC. Their use is considered experimental and larger, controlled studies will be required before these results can be confirmed and these modalities adopted in practice. Lasers that have been investigated for direct treatment of BCC include the pulsed dye laser **(4, 4)** [129, 130], neodymium:yttrium aluminum (Nd:YAG) **(4)** [131], and carbon dioxide **(4)** [132] lasers, which have shown some efficacy in case reports and small case series. Lasers have also been used in conjunction with conventional therapies. A randomized trial of erbium:yttrium aluminum garnet (Er:YAG)-primed MAL-PDT versus traditional MAL-PDT demonstrated significantly lower recurrence rates in the Er:YAG laser group **(2b)** [133]. In a small study that used an ablative carbon dioxide laser to enhance topical 5-fluorouracil applied for 7 days under occlusion, a histologic clearance rate of 71% (10 of 14) was achieved for superficial BCCs **(2b)** [134]. Overall treatment success after 9 months of follow-up was 67% **(2b)** [135]. As with other destructive treatment modalities, lack of definitive histologic evaluation will be a disadvantage; use of reflectance confocal microscopy to evaluate for residual tumor post-treatment has been proposed as a means to mitigate this [132].

Safety

The risks associated with a procedure are an important consideration when weighing therapeutic options. The potential treatment modalities for BCC are each associated with a unique set of adverse events (AEs) (Table 42.2).

Surgical treatment has been established as a safe procedure with a low incidence of serious AEs. In a multicenter prospective cohort study of 20,821 Mohs micrographic surgery procedures, the incidence of AEs was 0.72%, with 0.02% being serious AEs, and no deaths were reported. The most common AEs were infections, followed by dehiscence and partial or full necrosis and bleeding and hematoma. Patients on anticoagulation therapy were at greater risk of bleeding and wound-healing complications. No cases of stroke, myocardial infarction, pulmonary embolus, or death were observed in this study **(2b)** [136], although they have been reported at the case report level, usually in the setting of cessation of antithrombotic therapy [137]. Notably, in a retrospective study of 115 patients aged 90 years and older undergoing 146 MMS procedures, only one complication was identified in the form of chest pain that resolved without hospitalization **(2b)** [138].

In a randomized controlled trial comparing MMS and surgical excision, stratification of safety outcomes by tumor type revealed no difference in postoperative complications between these procedures in treating primary BCCs, but a significantly higher rate of AEs was observed after treating recurrent BCCs with surgical excision (19%) compared to MMS (8%, $p = 0.021$). AEs included wound infections, graft necrosis, and postoperative bleeding for both procedures [53].

Table 42.2 Adverse effects (AEs) associated with treatment modalities for basal cell carcinoma

Treatment modality	Most common AEs	Uncommon or serious AEs
Surgery (excision, Mohs micrographic surgery)	Infection, dehiscence, bleeding, hematoma, hypertrophic scarring	Partial or full necrosis, stroke/myocardial infarction/death (reported with cessation of anticoagulant medications)
Electrodesiccation and curettage	Hypopigmentation, hypertrophic scarring	Infection
Radiation therapy	Acute: localized pruritus, moist desquamation Chronic: dyspigmentation, telangiectasia, atrophy, alopecia, xerosis	Skin necrosis, delayed-onset secondary malignancy Site-specific: lacrimal duct stenosis, ectropion, cataract formation
Cryotherapy	Erythema, edema, pain, blistering, hypopigmentation	Anatomic distortion, necrosis
Imiquimod	Erythema, edema, itching, pain, erosion, crusting, scaling, ulceration, headache	Flu-like symptoms (myalgia, malaise, fatigue, fever)
Photodynamic therapy	Pain, burning, stinging, itching, erythema, edema, erosions, crusting	Infection
5-Fluorouracil	Erythema, erosion	Infection
Hedgehog pathway inhibitors (vismodegib, sonidegib)	Muscle spasms, alopecia, dysgeusia, nausea, fatigue, weight loss, diarrhea	Creatinine kinase elevation, rhabdomyolysis, amenorrhea

The primary AEs associated with ED&C are postoperative hypopigmentation and hypertrophic scarring, although these tend to improve with time [43]. In a retrospective study, curettage alone without electrodesiccation may yield more favorable cosmetic outcomes; hypertrophic scarring was only noted in 0.3% of patients and hypopigmentation was judged to be less significant than traditionally seen with ED&C despite similar efficacy rates [39].

Radiation therapy is associated with acute and chronic AEs. Acute side effects include radiation dermatitis-like symptoms, such as localized pruritus and moist desquamation. Long-term effects include dyspigmentation and telangiectasia, which are seen in more than 65% of patients [70]. Chronic skin atrophy, alopecia, and xerosis also occur commonly. These consequences may lead to an unsatisfactory cosmetic result, which has been shown to deteriorate with time following radiation therapy [63, 64, 70]. In one study that assessed long-term cosmetic outcomes, 60% of physicians and 30% of patients rated radiotherapy scars as poor to fair at 4 years after treatment [123]. Uncommon but serious complications include skin necrosis, which occurs in up to 5% of patients [70], and delayed development of secondary malignancy within the radiation treatment field, a dreaded long-term sequela. Site-specific AEs include lacrimal duct stenosis and cataract formation when radiation is used for eyelid tumors [64, 70]. Fractionation of therapy may decrease the risk of untoward cosmetic effects [69].

One study comparing surgical excision and RT observed greater rates of AEs in the RT-treated group on long-term follow-up. At 4 years posttreatment, surgery-treated patients had remaining physical deformities (25%) and functional contractures (5%), while RT-treated patients had dyspigmentation and telangiectasia (65%) and radiodystrophy (41%). Three patients (n = 173) experienced ophthalmic complications, one each of cataract, ectropion, and lacrimal duct stenosis [70].

The incidence of AEs associated with cryotherapy has not been evaluated in a systematic manner. Well-known common adverse reactions include erythema, edema, pain, and blistering. Delayed events include hypopigmentation, which occurs frequently, and hypertrophic scars, which occur less commonly. Both can lead to an inferior cosmetic result. With the more aggressive treatment regimens utilized in older studies, infec-

tions, pyogenic granuloma, and anatomic distortion from damage to underlying cartilage also rarely occurred **(4)** [59, 139]. One randomized trial found slightly decreased rates of secondary wound infection using cryotherapy (5.9%) compared to surgical excision (8.2%) [31]. Cryosurgery, compared to PDT, has longer healing time and had higher rates of necrosis (7.3% vs. 0%) at 4 weeks posttreatment [61].

The safety of imiquimod has been studied in preclinical and clinical trials. Animal and in vitro studies have shown that imiquimod does not affect fertility and is not teratogenic or tumorigenic [140]. The most common AEs associated with topical imiquimod use are local application site reactions, in the form of erythema, edema, itching, pain, erosion, crusting, scaling, and ulceration. These occur frequently, but range in severity and are dose-dependent. In two randomized, double-blind, controlled studies, 29–43% experienced local skin reactions among those applying the cream five and seven times per week, respectively [72]. In prospective dose-finding studies, application site reactions were present in nearly all patients in the twice-daily application group [71, 78]. Headache occurs in 6–7% of patients [72]. Less common reactions include systemic flu-like symptoms such as myalgia, malaise, fatigue, and fever, which occur in less than 3% of patients [72].

PDT is generally well tolerated and its most common AEs include signs and symptoms associated with photosensitivity reactions, such as pain, burning, stinging, and itching. Post-treatment erythema, edema, erosions, and crusting may also be observed. The incidence of AEs can exceed 70%, but they are usually mild to moderate in severity, local in nature, and transient. Serious AEs are not typically seen [83, 84].

The most common AEs associated with 5-FU are erythema and erosion. When used for the treatment of BCC, levels of erythema are generally moderate in severity, in contrast to the robust erythema seen with the use of 5-FU for actinic keratoses. The majority of patients (>80%) do not experience pain or have scarring; when present, both are usually mild [97].

A large randomized controlled trial of 601 participants compared MAL-PDT, imiquimod, and fluorouracil in treatment of BCCs. The authors reported moderate to severe AEs during the second week of treatment at the following rates: pain (14% vs. 5% vs. 7%, respectively), burning sensation (26% vs. 9% vs. 12%), redness (41% vs. 52% vs. 51%), swelling (4% vs. 21% vs. 7%), erosion (8% vs. 16% vs. 17%), crusts (11% vs. 23% vs. 11%), vesicles and bullae (8% vs. 14% vs. 10%), scaling (5% vs. 3% vs. 6%), pruritus (12% vs. 28% vs. 21%), and tingling (4% vs. 4% vs. 4%). Overall, patients treated with either imiquimod or 5-fluorouracil reported a higher incidence of moderate to severe local swelling, erosions, crust formation, and itching than those treated with MAL-PDT. Influenza-like symptoms and a case of wound infection occurred in 4.8% of the imiquimod-treated group. Two patients (1%) of the 5-fluorouracil-treated group also developed wound infections [117].

AEs occur commonly in patients taking vismodegib and sonidegib and typically occur within the first 6 months [99]. Mild to moderate adverse effects are seen in nearly all patients taking the medications and severe events can occur in up to 52% of patients. These effects may be intolerable, as they led to study discontinuation in 17.3% and 27.8% of patients in the pivotal vismodegib and sonidegib trials, respectively [99, 106].

Vismodegib and sonidegib share similar adverse effects, which are thought to be mechanism-related. The most common adverse effects are muscle spasms, alopecia, dysgeusia, fatigue, nausea, weight loss, and diarrhea. Of these, muscle spasms, alopecia, and dysgeusia occur most frequently, with rates in large phase 2 clinical trials ranging from 49% to 84%, 43–69%, and 38–84%, respectively **(2b)** [99, 100, 141]. Serious AEs found in the sonidegib clinical trial include elevated creatinine kinase and rhabdomyolysis, which occurred in more than 2% of subjects. Amenorrhea in premenopausal patients has also rarely been reported [104, 106]. However, no medication-related deaths have been noted [99, 100, 102, 104, 106, 142].

Postoperative Care and Follow-Up

Clinical monitoring of a patient after treatment is required for two main reasons. The first is to monitor for recurrence at the primary tumor site. The second is to perform surveillance for the development of new skin cancers.

No established guidelines exist to guide appropriate monitoring frequency and duration following basal cell carcinoma treatment. In general, monitoring for recurrence is most crucial in the first 3–5 years, although recurrences beyond 5 years are not rare. In a pooled analysis of studies looking at the treatment of BCC with various modalities, Rowe et al. found that only 50% of recurrences appeared within the first 2 years after treatment; 55% appeared within the first 3 years; and 18% did not appear until 5–10 years later [29]. A large review of tumors published 2 years later similarly found the greatest risk of recurrence to be within the first 4 years [143]. In line with these findings, a retrospective study evaluating the efficacy of MMS found that 75% of recurrences appeared within 3 years of surgery [51]. However, a recent prospective study with 10-year follow-up found that recurrence beyond 5 years is not infrequent and may occur in up to 40% of primary BCCs treated with surgery [33]. Repeat recurrences tend to appear sooner, which has been attributed to the more biologically aggressive nature of recurrent BCCs compared to primary tumors **(2b)** [33, 144]. Based on these findings, a follow-up period of 5 years for primary BCC and 7–10 years for recurrent BCC has been proposed [33].

For patients with a history of BCC, the risk of subsequent NMSC is increased **(2a-, 2a, 2b, 1b)** [145–148]. The risk varies depending on whether the index BCC is a first BCC or not, i.e., whether there is a history of multiple BCCs. A meta-analysis from 2000 calculated a 3-year cumulative risk of 44% for developing a second BCC after initial BCC diagnosis. The risk of developing an SCC following an index BCC was much lower, at 6% [146]. However, this analysis included studies that included patients with a history of more than one BCC and were not exclusive to newly diagnosed patients. A recent prospective cohort study found that the risk of subsequent BCC after the first lifetime BCC is lower than it is after a non-first BCC—12.8% vs. 33.9% at 1 year, 20.0% vs. 51.8% at 2 years, and 26.7% vs. 61.3% at 3 years [148]. This implies that a substantial proportion of patients with a first BCC may never develop another BCC and may not require as frequent and aggressive screening post-treatment as those with a history of multiple BCCs.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Mohs micrographic surgery is the treatment of choice for recurrent BCC	A
Mohs micrographic surgery is superior to standard excision and ED&C for recurrent BCC	A
ED&C can achieve cure rates as high as excision for small, low-risk BCC	B
ED&C is associated with higher risk of recurrence for lesions located on facial sites than on non-facial sites	B
ED&C should not be used for recurrent or infiltrative tumors	B
ED&C should not be used for tumors located on terminal hair-bearing skin	D
Cryosurgery has cure rates that range widely from 1% to 20%	C
Radiation therapy should not be used for patients younger than 60–65 years old	D
Radiation therapy should not be used in patients with conditions predisposing to malignancy	D

Findings	GRADE score: quality of evidence
Imiquimod 5% cream is effective for the treatment of superficial BCC	A
Imiquimod 5% cream may be effective for nodular BCC with more frequent and prolonged use	B
Imiquimod 5% cream has poor efficacy for tumors with infiltrative histology	C
Both MAL- and ALA-PDT are effective for superficial BCC	A
Efficacy of PDT for nodular and infiltrative tumors is not well established	B
5-FU may be effective for superficial BCC on the trunk and limbs with prolonged use	C
Topical therapies are generally associated with superior cosmetic outcomes compared to surgery, radiation, and cryosurgery	A
Vismodegib and sonidegib can be effective for locally advanced and metastatic BCC	A
Vismodegib can significantly reduce tumor burden in patients with basal cell nevus syndrome	A
Vismodegib and sonidegib are associated with a high incidence of adverse effects	A
Vismodegib and sonidegib are not well-tolerated and frequently discontinued by patients	A

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Self-Assessment Questions

1. Which one of these statements regarding the use of imiquimod 5% cream for the treatment of BCC is FALSE?
   (a) Randomized controlled trials have found similar histologic clearance rates with five times per week and seven times per week application for superficial BCC.
   (b) Application of imiquimod 5% cream has been shown to have 5-year clearance rates of approximately 80% for superficial BCC.
   (c) Imiquimod 5% cream has not been studied for nodular BCC.
   (d) Limited evidence shows that imiquimod 5% cream has poor efficacy for BCCs with infiltrative histology.
   (e) Application of imiquimod 5% cream for three times a week rather than five times a week has been shown to be associated with a lower histologic clearance rate.

2. What is the approximate 5-year recurrence rate following Mohs micrographic surgery for primary and recurrent BCC?
   (a) primary: 3–5%; recurrent: 8–10%
   (b) primary: 1–3%; recurrent: 4–7%
   (c) primary: 1–3%: recurrent: 1–3%
   (d) primary: 3–5%; recurrent: 4–7%
   (e) primary: 3–5%; recurrent: 3–5%

3. Which of the following statements is FALSE regarding the treatment of recurrent BCC?
   (a) Excision has similar recurrence rates compared to Mohs micrographic surgery for lesions on the trunk.
   (b) Cure rates have been found to be as low as 40% following treatment with PDT.
   (c) Cure rates have been found to be lower than 70% following treatment with ED&C.
   (d) Topical imiquimod and 5-FU are not recommended for and have not been studied for recurrent BCC.
   (e) Recurrence rates have been found to be as high as 13.5% for lesions on the face following treatment with excision.

4. Which of the following is NOT one of the most common adverse effects of the hedgehog pathway inhibitors vismodegib and sonidegib?
   (a) Dysgeusia
   (b) Muscle spasms
   (c) Alopecia
   (d) Xerosis
   (e) Fatigue

5. Which of the following statements most accurately describes the safety and cosmetic outcome associated with treatment modalities for BCC?
   (a) Imiquimod, PDT, 5-FU, and cryotherapy are all associated with superior cosmetic outcomes that may improve with time.
   (b) Radiation therapy is generally associated with a poor cosmetic outcome, but this tends to improve with time.
   (c) Radiation therapy should be avoided in older patients due to the risk of delayed radiation-induced malignancy.
   (d) Vismodegib and sonidegib can result in complete responses for locally advanced BCC, but are not well-tolerated, and tumors tend to recur following cessation of treatment.
   (e) Studies have shown that patients usually value efficacy over cosmetic outcome and adverse effects.

Correct Answers

1. c: Imiquimod 5% cream has been studied for nodular BCC, but its efficacy is not as well established. There is some evidence that it may be effective with daily use for 12 weeks (as opposed to five times weekly use for 5 weeks as recommended for superficial BCC). With this more frequent and longer treatment regimen, clearance rates of 76% and 82% have been found for nodular BCC in two studies.
2. b: Retrospective and prospective studies have found that 5-year recurrence rates following Mohs micrographic surgery range from 1% to 3% for primary tumors and 4–7% for recurrent tumors.
3. a: Recurrence rates for recurrent tumors following standard excision have been found to range from 5% to 20% in various studies. In one randomized trial of facial lesions, recurrent BCCs had a recurrence rate of 13.5%. These rates are higher than is observed with Mohs micrographic surgery, which has recurrence rates of 4–7% for recurrent tumors.
4. d: The most common adverse effects reported in the vismodegib and sonidegib trials included muscle spasms, dysgeusia, alopecia, nausea, fatigue, and weight loss. Xerosis was not observed as a common adverse effect.
5. d: Imiquimod, PDT, and 5-FU are associated with superior cosmetic outcomes that improve with time, but cryotherapy has been associated with poorer cosmetic outcomes. Radiation therapy has generally been associated with poor cosmetic outcomes and this tends to worsen, rather than improve, with time. It should be avoided in younger patients (those less than 60–65 years of age) due to the risk of delayed development of malignancy. Studies have shown that patients may value cosmetic outcome and adverse effects as highly as, if not more so than, treatment efficacy. Statement d is true: The hedgehog pathway inhibitors have been associated with complete responses for locally advanced BCC, but are generally not well-tolerated, leading to high rates of medication discontinuation. In addition, tumors tend to recur following cessation of treatment. The low tolerability of these medications, combined with the tendency for tumors to recur and potentially develop resistance, poses current challenges to the use of hedgehog pathway inhibitors.

Cutaneous Squamous Cell Carcinoma

43

Nina R. Blank, Kishwer Nehal, and Erica Lee

Abstract

Cutaneous squamous cell carcinoma (cSCC) may be treated surgically, with destructive modalities, or through the use of topical agents. The risk of cSCC metastasis has been shown to increase with tumor size and depth, ear location, and immunosuppression. For cSCC lesions with higher-risk features, excision with postoperative margin assessment and Mohs micrographic surgery (MMS) are considered most effective, with MMS best utilized in locations with minimal excess tissue and/or near vital anatomic structures. While cryosurgery and electrodesiccation and curettage may be used for low-risk cSCC, current evidence supports the use of photodynamic therapy and topical agents for low-risk cSCC in situ only.

Keywords

Nonmelanoma skin cancer · Squamous cell carcinoma · Cutaneous squamous cell carcinoma · Surgical excision · Mohs micrographic surgery · Electrodesiccation and curettage · Cryotherapy · Photodynamic therapy · Imiquimod · 5-Fluorouracil

Epidemiology

Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States, with over 5.4 million people affected and 3.3 million treated in 2012 [1]. The second most common skin cancer after basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), has historically been estimated to represent 20% of all NMSC [2]. Recent reports, however, have pointed to an increasing ratio of cSCC to BCC, possibly secondary to a disproportionate cSCC incidence rise in older age groups [1, 3, 4]. A study estimating NMSC frequency in the US population in 2012 reported equal incidence rates for BCC and cSCC in the Medicare population [1].

Both age and sex affect cSCC incidence, with older age portending greater risk [5–7] and male sex yielding an incidence rate between 2.5 and 2.8 times that of women [8]. Ultraviolet B radiation (290–320 nm) is the most common risk factor for the development of cSCC, through

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Table 43.1 Risk factors for cSCC development

Ultraviolet radiation (UVA, UVB)
Ionizing radiation
Psoralen and UVA (PUVA)
Tanning beds
Phenotype (skin type)
Arsenic exposure
Human papillomavirus
Chronic nonhealing wounds
Sites of chronic trauma
Chronic inflammatory disorders (discoid lupus, lichen planus)
Sites of radiation or chemical exposure
Oculocutaneous albinism
Genodermatoses
Immunosuppression
Chronic lymphocytic leukemia
Organ transplantation
Cigarette smoking
Actinic keratoses

activation of the *ras* pathway and p53 tumor suppressor gene mutations [9]. Thus, those with greatest cumulative exposure to UV radiation (i.e., fair-skinned individuals with outdoor occupational or behavioral exposure and those residing near the equator) are considered to be at greatest risk for cSCC [10–12]. Additional risk factors for cSCC include immunosuppression and ionizing radiation (Table 43.1).

The presence of actinic keratoses (AK) and other NMSC is strongly associated with future cSCC development [10, 13]. AK is considered by many to be a precursor lesion to cSCC. Estimated progression rates of AK to cSCC have ranged between 0.0% and 0.53% per lesion-year, although the reliability of these estimates has been called into question [13]. Despite this uncertainty, AK is often treated for its malignant potential and secondarily for cosmesis with therapies including topical 5-fluorouracil and imiquimod, photodynamic therapy (PDT), and cryotherapy [14].

CSCC variants include verrucous carcinoma, an uncommon entity presenting as an exophytic, verrucous lesion, and keratoacanthoma, which develops rapidly into a crater-like nodule with a central keratotic core. CSCC in situ (cSCCIS) presents with several subtypes, the most common of which are Bowen's disease, or cSCCIS on sun-exposed areas, and Erythroplasia of Queyrat, cSCCIS arising on the glans penis of uncircumcised men.

Treatment Overview

Dermatologic procedures for cSCC and cSCCIS are surgical treatments, including excision with postoperative margin assessment (POMA) and Mohs micrographic surgery (MMS); the destructive modalities electrodesiccation and curettage (ED&C), cryotherapy, and photodynamic therapy (PDT); and the topical agents imiquimod (5%) and 5-fluorouracil (5-FU, 5%). While radiation therapy may have a role in the adjuvant setting or as primary SCC treatment for nonsurgical candidates, details of this modality are beyond the scope of this chapter and will not be discussed in depth.

The intent of any SCC treatment is complete eradication of malignant squamous cells. Appropriate use depends upon invasion status (in situ vs. invasive SCC) and upon clinical and histologic tumor characteristics, more specifically, whether the tumor is considered low or high risk for recurrence. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) delineate "low-risk" anatomic areas to be the trunk and extremities (excluding the pretibia, hands, feet, nail units, and ankles), provided the tumor is < 2 cm in diameter, and the cheeks, forehead, scalp, neck, and pretibia for < 1 cm tumors **(2b)** [15] (Table 43.2).

Nonsurgical modalities were estimated to represent 40.3% of skin cancer treatments performed on Medicare beneficiaries in 2008 [16]. These therapies do not allow histopathologic tumor margin evaluation and are thus generally limited to AK, cSCCIS, and low-risk cSCC in anatomic locations described earlier. ED&C is most commonly performed and involves alternating cycles of tumor tissue curettage down to the dermis with subsequent denaturation through electrodesiccation. This modality is preferred for nonterminal hair-bearing areas due to the risk of infundibular tumor extension inaccessible to ED&C **(5)** [15]. Wounds typically take 4–6 weeks to heal, and the clinical outcome is a white stellate scar that may

Table 43.2 NCCN Guidelines® version 1.2017 squamous cell skin cancer risk factors for local recurrence or metastases

History and physical	Low risk	High risk
Location/size[a]	Area L < 20 mm	Area L > 20 mm
	Area M < 10mm[d]	Area M > 10 mm
		Area H[e]
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(−)	(+)
Site of prior RT or chronic inflammatory process	(−)	(+)
Rapidly growing tumor	(−)	(+)
Neurologic symptoms	(−)	(+)
Pathology		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes	(−)	(+)
Depth[b, c]: thickness or Clark level	<2 mm or I, II, III	>2 mm or IV, V
Perineural, lymphatic, or vascular involvement	(−)	(+)

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[a]Must include the peripheral rim of erythema

[b]If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy

[c]A modified Breslow measurement should exclude parakeratosis or scale crust and should be made from the base of ulcer if present

[d]Location independent of size may constitute high risk

[e]Area H constitutes high risk based on the location, independent of size. Narrow margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with MMS is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high-risk features, other treatment modalities may be considered if at least 4 mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions

Area H = "mask areas" of the face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet

Area M = cheeks, forehead, scalp, neck, and pretibia

Area L = trunk and extremities (excluding the pretibia, hands, feet, nail units, and ankles)

be atrophic or hypertrophic [17–19]. Cryotherapy destroys tumor cells through cycles of liquid nitrogen freezing and thawing. Cell temperature reduction to subzero yields localized tissue destruction and vascular stasis. The treated area typically heals by second intention over 1–3 weeks with erythema, vesiculation, edema, exudation or eschar, and sloughing. Lesions may also permanently hypopigment secondary to melanocyte destruction [17, 18, 20, 21]. PDT requires application of a photosensitizing agent that accumulates preferentially within tumor cells. The most common agents are the topical porphyrin precursor 5-aminolevulinic acid (ALA) and its methyl ester form, methyl aminolevulinate (MAL). Only ALA is available for cutaneous application in the United States. Light-source irradiation of the area then activates the compound, with clinical response involving erythema, edema, and crusting over the week following treatment. These symptoms are expected to resolve within 1–3 weeks, leaving the skin without a scar [17, 18]. Imiquimod acts as a toll-like receptor agonist, inducing a type-2 helper T-cell cytokine cascade that yields cytotoxic T-cell tumor cell

destruction. Fluorouracil is a pyrimidine antimetabolite that directly targets tumor cells by inhibiting DNA synthesis [22]. Both therapies require daily or near-daily application for several weeks and create local erythema throughout the treatment course. The inflammatory response to imiquimod and 5-FU may also involve edema, weeping, crusting or scabbing, and pruritus. Clinical resolution may leave residual blanching erythema or post-inflammatory hypo- or hyperpigmentation [22, 23].

Surgical excision and MMS were estimated to comprise 35.6% and 24.1% of skin cancer treatments in 2008, respectively [16]. Standard surgical excision with POMA may be performed for low- or high-risk tumors in anatomic locations with a 4–6 mm clinical margin. The inability of standard, bread-loaf tissue processing to examine full excision margins justifies wider resection of high-risk lesions to avoid subclinical tumor transection, per NCCN Guidelines **(2b)** [15]. MMS uses en face, frozen histopathologic sections to assess the entire peripheral and deep margin and is thus the desired treatment for high-risk tumors. MMS allows for tissue preservation in aesthetically sensitive and high-risk sites such as the nose, eye, and ear. MMS' higher cost and longer time requirement have led to recommendations of its "appropriate use" to higher-risk anatomic sites such as the head and neck, pretibial surface, and nail unit; aggressive histological subtypes; ill-defined clinical tumors; and recurrent lesions [24].

Effectiveness of Treatments

Despite the high prevalence of cSCC, there are no randomized controlled trials (RCTs) that assess treatment effectiveness for invasive diseases and very few assessing therapy for in situ lesions. The following is a review of mostly observational studies reporting on outcomes such as local recurrence, regional and distant metastasis, and disease-specific death. Local recurrence and metastasis rates have been shown to increase with duration of patient follow-up irrespective of treatment modality **(4)** [25]; this should be considered when comparing studies with differing follow-ups.

Electrodessication and Curettage (ED&C)

ED&C effectiveness data is limited to retrospective studies examining unspecified cSCC recurrence after variable posttreatment follow-up periods. The earliest systematic review of these studies, by Rowe et al. in 1990, reported weighted 5-year ED&C recurrence of 3.7% in tumors described to be less than 1 cm in size **(4)** [25].

The newest systematic review, by Lansbury et al. in 2013, estimated a pooled recurrence rate of 1.7% for 8 studies with variable follow-up **(4)** [26]. Lesions treated with ED&C were small: 5 series with recorded diameters reported lesions < 2 cm in 91%, 94%, 100%, 60%, and 60% of cSCC **(4)** [27–31]. All studies encompassed various anatomic sites excluding Shiffman et al., who reported 3 recurrences (21.4%) leading to 2 metastases (14.3%) among 14 pinna cSCC within 1 year. Recurrent lesions were 2.5 cm, 3 cm, and 3 cm in size. Of the 11 cSCC without recurrence, 1 lesion was > 2 cm **(4)** [30].

Studies have not compared different ED&C techniques. Tromovitch described superior results following two ED&C sequences compared to single-cycle methods **(5)** [32]. Reschly et al. reported on 2 separate retrospective studies: the first treated 106 patients with 2 ED&C rounds and the second, 14 patients with 3 cycles. Both studies reported no recurrences after at least 2 years of follow-up **(4)** [29].

As a fundamentally lower-risk entity, cSCCIS is often studied separately from its invasive counterpart. Although a large 1988 study recorded 18.8% recurrence among 345 cSCCIS 1–5 years after ED&C **(4)** [33], other cSCCIS studies provide substantially lower recurrence rates, at 9.6% after an average of 2.25 years **(4)** [34] and 1.9% after 4 years **(4)** [28].

Cryotherapy

Both prospective and retrospective descriptive studies have examined cryotherapy effectiveness.

Rowe et al. failed to identify studies reaching 5 years of follow-up and thus recorded a short-term recurrence rate of 3.2% after an unspecified time range, with lesions primarily 1 cm or less in size **(4)** [25].

Lansbury et al. compiled 8 studies, also with variable follow-up, to report a pooled recurrence rate of 0.8%. Studies reportedly included low-risk lesions less than 2 cm in diameter **(4)** [26]. The largest study to provide 5-year follow-up data retrospectively reported no recurrences in 134 cSCC in all anatomic locations. Lesions were reported by authors to be <2 cm and amenable to cryosurgery **(4)** [35]. The prospective study with the greatest population also yielded no recurrence after a mean 4.2-year follow-up among 53 face and scalp cSCC, average 8 mm **(4)** [36]. One retrospective study analyzed anatomic sites separately in a cohort of 563 cSCC, 97% of which were < 2 cm. Authors reported a pooled 97.3% cure rate, although the definition of cure was not clearly stated. Locations with "cure rates" less than 97% were the nose (89.8%), eyelids (75%), trunk (93.7%), and scalp (90%) **(4)** [37].

Trials have not analyzed relative effectiveness of various cryosurgery techniques, and no consensus exists for pre-cryosurgery curettage, the number of freeze-thaw cycles, the amount of surrounding tissue requiring freezing, or appropriate thaw time [17, 38]. More prolonged freeze, however, may associate with deeper penetration and higher tissue destruction volume **(5)** [37, 38].

More aggressive cryosurgical treatments have been hypothesized to increase effectiveness in studies of cSCCIS **(5)** [39]. Total freezing times of 30 s and 40 s have yielded recurrence rates at 6.0% or less between 6 months and 5 years **(4)** [40, 41], while a study using a single 20-s freeze reported 21% recurrence at just 1 year **(4)** [42].

Photodynamic Therapy (PDT)

PDT is a newer therapeutic modality with effectiveness data limited to small, prospective studies with variable follow-up.

Initial treatment failure is reported more often following PDT than after ED&C or cryosurgery. Lansbury et al. compiled 14 studies reporting tumor response after PDT, yielding a pooled incomplete excision rate of 28.0%. Of five studies confirming clearance histologically, three revealed clinical examination to be insufficient in evaluating tumor response. Histologic tumor remnants were found in 2 of 10 **(4)** [43], 2 of 2 **(4)** [44], and 6 of 32 **(4)** [45] tumors presumed to have responded completely. Calzavara-Pinton et al. assessed tumor response clinically and found that microinvasive (Clark level II) and invasive (Clark level > III) lesions differed significantly in insufficient clearance, at 8 of 40 (20%) and 17 of 31 (54.8%), respectively ($p < 0.01$) **(4)** [46].

Lansbury et al. reported pooled recurrence rate at 26.4% from 8 studies examining recurrence after apparent initial complete response, none with follow-up reaching 5 years **(4)** [26]. The largest study evaluated outcomes in poor surgical candidates determined based on their general health or if tumors were large or multiple or in surgically difficult areas. Two-year recurrence rates in microinvasive and invasive lesions were 28.1% and 42.9%, respectively, values not analyzed for statistical significance **(4)** [46]. For cSCCIS, a 2003 retrospective study reported 10.5% recurrence for 129 lesions at median 44 weeks **(4)** [47]. Among patients with large lesions and multiple lesions, a 34-month recurrence was 22% **(4)** [48].

Several permutations exist of topical photosensitizer time and type (i.e., ALA vs. MAL) and of light source type, dose, and time; however, no regimens have been studied rigorously for effectiveness in cSCC.

Topical Therapies

Effectiveness data of imiquimod and 5-FU in invasive cSCC is extremely limited. A 2009 systematic review of both treatments found a single study including data for cSCC [22]. In this study, 2/7 (29%) invasive cSCC treated 5 days per week for 12 weeks failed to yield histological clearance **(4)** [49].

Topical therapies are more commonly studied in cSCCIS due to the superficial nature of both the treatment and the tumor. One RCT did compare imiquimod (n = 15) with placebo (n = 16) and found histologic incomplete clearance in 27% of patients 12 weeks after daily imiquimod application for 16 weeks (compared with 0% clearance in the placebo group, $p < 0.001$) **(1a)** [50]. A lower incomplete clearance rate was found in a prospective study among 1/15 (7%) patients applying imiquimod daily for average 12 weeks, mostly to lesions > 1 cm on the legs, examined histologically 6 weeks after treatment **(4)** [51]. The largest long-term imiquimod study was retrospective and included 56 patients treated daily for 9 weeks, with 25% clinical recurrence at 19 months **(4)** [52].

An open-label prospective study of 26 cSCCIS lesions treated twice daily with 5-FU for 8 weeks yielded 15% clinical recurrence after an average follow-up of 4.6 years, with all recurrent tumors in high-risk areas (finger, ear, cheek, penis) **(4)** [53]. Higher 1-year clinical recurrence rates—at 44% and 52%—were found in prospective studies using less rigorous treatment regimens (once daily for 1 week and then twice daily for 3 weeks) **(1b)** [54, 55]. While more intense inflammatory reactions secondary to imiquimod usage have been associated with higher tumor clearance rates, no such correlation has been established with 5-FU **(2a)** [22].

Surgical Excision with Postoperative Margin Assessment (POMA)

A majority of studies evaluating standard surgical excision effectiveness are retrospective. Measures of effectiveness include initial tumor clearance and long-term recurrence.

A 1992 prospective study used MMS to assess tumor clearance in real time using successively larger excision margins. Authors illustrated that wider margins were indicated for higher-risk tumors with greater predilection for subclinical extension. While 95% of tumors required 4 mm margins to clear well-differentiated lesions and lesions <2 cm, less-differentiated lesions and lesions >2 cm required 6 mm margins to reach the same clearance threshold. For 95% clearance of scalp, ear, eyelid, nose, and lip tumors, the 4-mm- and 6-mm-margin patterns emerged for lesions <1 cm and >1 cm **(4)** [56]. Excision margin variations have not been studied head-to-head to compare outcomes. NCCN Guidelines further stipulate that normal-skin margins begin at the periphery of any erythematous tumor rim, which manifests tumor extension **(4)** [15].

Incomplete clearance rates in clinical practice have also been pooled retrospectively. Lansbury et al. assessed 2 prospective and 9 retrospective studies to estimate a failed excision rate of 8.8%, despite variations in surgical margins and in definitions of what constitutes an incomplete excision **(4)** [26]. In the largest prospective study of 469 primary tumors, excision with 2–5 mm margins did not clear tumors in 6.4% of cases **(4)** [57], and lower clearance was seen in auricular lesions compared to other anatomic locations (20.5% vs. 4.8%, $p < 0.001$). Excision of 37 recurrent lesions also had a higher incomplete excision rate of 24.3% compared to the primary tumor rate of 6.3% ($p < 0.001$) **(4)** [57]. The highest incomplete excision rate (25%) was reported in 68 periocular, well-differentiated, and moderately differentiated cSCC tumors excised with 5 mm margins **(4)** [58].

Two systematic reviews determined long-term recurrence rates after standard excision. Rowe et al. reported a weighted 5-year rate of 8.1% in 1990 **(4)** [25]. Lansbury et al. reported pooled recurrence at 5.4% in 2013 and also calculated pooled regional lymph node metastatic rate and disease-specific death rate at 4.4% and 4.1%, respectively **(4)** [26]. A single study with 5-year follow-up retrospectively analyzed 93 cSCC, average size 13.6 mm, and reported no local recurrences but 8 (8.6%) lymph node metastases and subsequent deaths **(4)** [59]. Highest recurrence (13%) and regional metastasis (9%) rates were reported in a study of 54 cSCC on the pinna followed for at least 1 year **(4)** [60].

Among cSCCIS lesions, surgical interventions have shown lowest uniform long-term recurrence. Standard excision led to 2.8% recurrence after mean 31.5 months among 109 cSCCIS in

2008 **(4)** [61] and 4.6% after 1–5-year follow-up of 65 lesions in 1988 **(4)** [33].

Mohs Micrographic Surgery (MMS)

In 1992, Rowe et al. reported weighted 5-year recurrence after MMS at 3.1%. This rate was lowest of the treatments analyzed despite, according to authors, that MMS studies contained "many larger lesions" **(4)** [25]. Lansbury et al. reported similar local recurrence at 3.0% after pooled analysis of 10 prospective and retrospective studies with varied follow-up. Authors also pooled 6 studies to report regional recurrence at 4.2% and 4 studies to yield disease-specific death at 1.1% **(4)** [26].

The largest prospective study followed 615 primary high- and low-risk cSCC over median 43 months and reported recurrence and regional metastasis at 3% and 4%, respectively **(4)** [62]. Auricular tumors yielded significantly greater metastasis risk compared with other sites (9.9% vs. 3.4%, $p = 0.004$) **(2b)** [62]. The largest series with 5-year follow-up prospectively reported recurrence and metastasis rates of 2.6% and 0.0% among 229 high- and low-risk primary tumors, 96.4% on the head and neck **(4)** [63]. A 2010 study of a high-risk cSCC population also had low recurrence and metastasis rates, at 1.3% and 2.2%, respectively **(4)** [64]. For cSCCIS specifically, a 2008 study of 83 lesions yielded 2.4% recurrence after mean follow-up of 26.3 months **(4)** [61].

Comparative Effectiveness of Common Treatments

Caution must be exercised in comparing cSCC treatment outcomes, as individual case series may not be compared given substantial differences between recruited study populations and duration of follow-up.

ED&C and cryosurgery have illustrated the lowest recurrence rates among discrete, single-center studies and pooled analyses; however, these modalities have largely been employed in studies of low-risk lesions. Because these techniques have not been studied in higher-risk cohorts, their relative effectiveness in this population cannot be assessed. PDT has yielded poorest results for both effective tumor clearance and long-term cure among low- and higher-risk invasive cSCC.

MMS has demonstrated high effectiveness in individual observational studies, including those composed of higher-risk lesions. Although no RCTs have compared MMS with standard excision with POMA, pooled analyses from systematic reviews outlined in this chapter have illustrated lower recurrence rates after MMS than after standard excision. However, in a large, prospective cohort study published in 2013, Chren et al. failed to report statistically significant differences in 5-year recurrence between primary cSCC treated with standard excision and MMS. Treatment groups differed substantially when analyzed among all NMSC—tumors treated with MMS were smaller and more likely to lie within high-risk sites. While risk factor-adjusted analyses still failed to detect differences in recurrence, cSCC were not analyzed independently in this analysis **(2b)** [65]. MMS has proven superior to excision in tissue preservation. Van der Eerden et al. showed that among 1504 NMSC, MMS allowed significantly smaller resection defects, after adjustment for anatomic site and primary vs. recurrent disease, compared with standard excision ($3.4cm^2$ vs. $6.3cm^2$). Equivalent effectiveness was maintained at 24-month MMS follow-up and 16-month excision follow-up **(2b)** [66]. This advantage leads to the use of MMS over surgical excision in aesthetically sensitive areas and/or those with a paucity of excess tissue.

Superior effectiveness of MMS has emerged among a number of specific clinical and histologic cSCC subsets, although studies are primarily from the 1990s and earlier. Rowe et al. illustrated MMS' effectiveness in recurrent tumors, with 10% pooled 5-year recurrence vs. 23.3% after standard excision **(4)** [25]. Rowe et al. further demonstrated MMS' high cure rate over non-Mohs modalities in preventing local recurrence at 5 years for tumors located on the

ear (5.3% vs. 18.7%) and on the lip (2.3% vs. 10.5%). Although authors described lower post-MMS recurrence rates vs. non-Mohs modalities for poorly differentiated lesions, those larger than 2 cm in diameter, and those illustrating perineural invasion on biopsy, they did not provide follow-up times for these groups **(4)** [25].

PDT's poor effectiveness in invasive cSCC has limited its evaluation in rigorous studies to low-risk cSCCIS. Within this population, PDT has shown minimal and equivalent 1-year recurrence in RCTs when comparing both ALA- and MAL-PDT with cryotherapy and with 5-FU **(1a)** [23]. CSCCIS patients for whom surgical interventions are infeasible, therefore, may choose PDT over other nonsurgical modalities given the superior cosmesis it affords. Furthermore, broad areas of the skin with multiple cSCCIS lesions may be treated with PDT in a single or repeated session, increasing treatment viability in patients with suspected field cancerization [48].

Procedures for cSCC may be performed in combination such as curettage followed by PDT; however, there are no studies comparing multimodality regimens. Because surgical therapy allows for histologic margin assessment, it is often performed following failures from ED&C, cryosurgery, and PDT to ensure complete tumor extirpation. NCCN Guidelines stipulate that surgery follows any ED&C procedure in which initial curettage yields tumor down to subcutaneous tissue. This event warrants surgical excision due to greater tumor depth of invasion and given that ED&C's effectiveness derives from the physician's ability to distinguish between firm dermis and soft tumor tissue **(5)** [15]. NCCN Guidelines also advocate specifically for the use of MMS in the event that standard surgical excision with POMA fails to clear tumor margins **(5)** [15].

Preoperative Evaluation and Patient Selection

Prognostication in cSCC begins with clinical inspection and palpation of both the involved area and the regional lymph nodes and should be followed with biopsy. Imaging studies play a role in cSCC staging when deep structural involvement—including bone, deep soft tissue, and perineural invasion—or nodal metastasis is suspected. Regional nodal involvement at presentation has been shown to significantly increase mortality risk with a reported hazard ratio of 7.64 ($p < 0.0001$) **(2b)** [67] and commonly coincides with perineural invasion and invasion into subcutaneous tissues **(1b)** [68].

Following assurance that a suspicious lesion is localized to the skin, the practitioner should evaluate patient and tumor features for the classification of the cSCC as either low or high risk and for appropriate tumor staging. NCCN Guidelines for high-risk tumors and AJCC tumor staging are illustrated in Tables 43.2, 43.3**,** and 43.4. Of note, the presence of any risk factor in the NCCN Guidelines is sufficient to place a tumor under the umbrella of "high risk." Because NMSC's ubiquity has rendered it impossible to track in a cancer registry, NCCN has based its prognostic

Table 43.3 AJCC definition of primary tumor (T)

T category		T criteria
TX		Primary tumor cannot be identified
Tis		Carcinoma in situ
T1		Tumor smaller than 2 cm in greatest dimension
T2		Tumor 2 cm or larger but smaller than 4 cm in greatest dimension
T3		Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion[a]
T4		Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion
	T4a	Tumor with gross cortical bone/marrow invasion
	T4b	Tumor with skull base invasion and/or skull base foramen involvement

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[a]Deep invasion is defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

Table 43.4 AJCC prognostic stage groups

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

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cSCC factors on data categorized under NCCN Category 2A, described as lower level but with uniform consensus **(2b)** [15]. AJCC tumor staging for head and neck cSCC uses tumor risk factors shown, through multivariate analysis, to be independently prognostic for poor outcomes. While authors do not assign practice recommendations to different stages, the ability to accurately stage cSCC on the head and neck allows for further risk stratification. Tumors categorized as T1 and T2 without lymph node involvement are staged I and II, respectively. T3 tumors and tumors of any T category (except in situ) with any single regional lymph node involvement are stage III or higher, depending upon lymph node size and presence of extranodal extension **(2b)** [69].

Of special consideration are immunocompromised patients, proven to incur higher risk for cSCC recurrence irrespective of treatment modality. Brantsch et al. reported immunosuppression to associate with more local recurrence and metastasis at average 43 months after MMS, with hazard ratios 3.44 (p = 0.0487) and 4.65 (p = 0.002), respectively **(2b)** [62]. Chren et al. illustrated greater 5-year recurrence in NMSC treated by MMS, ED&C, or standard excision in HIV-infected vs. non-HIV-infected patients (20.8% vs. 2.8%, $p < 0.01$), with MMS comprising a minority of selected therapies in this population **(2b)** [65]. Immunosuppression is thus considered a high-risk criterion regardless of tumor type and location.

A comprehensive understanding of tumor risk allows the dermatologist to engage interdisciplinary collaboration when warranted. Patients with advanced tumors or those requiring lymph node sampling or removal may be referred to head and neck surgery or surgical oncology. High-risk patients who are not surgical candidates may be appropriately managed by radiation oncology. Finally, for those individuals expected to require extensive reconstruction or adjuvant treatment, collaboration with plastic surgery and medical oncology may be necessary.

Impact of Patient Preference

Risk stratification narrows treatment and provider options to those most medically appropriate; however, final therapy selection is a shared decision-making process between the physician and patient. Public demand for accountability and transparency in healthcare has grown over the past several years. Identification of patient concerns and expectations at the consultation opens the door to effective communication and better ensures patient trust and satisfaction throughout the treatment process [70]. Each modality's effectiveness, time requirement, post-procedure recovery, and expected aesthetic and functional outcome should be discussed in the context of the patients' treatment goals.

Patients with low-risk lesions choose between standard excision with POMA, ED&C, cryotherapy, and, in the case of low-risk cSCCIS, PDT and topical agents. Treatment duration and recovery period are considerations that may lead patients to choose one modality over another: ED&C and cryosurgery allow for short procedural times with minimal post-procedure physical limitations. Surgical excision with sutures does not require long wait times but does necessitate activity restrictions. PDT requires the most in-office time due to incubation of the photosensitizing agent, and its recovery period involves short-term avoidance of excessive indoor/outdoor light and diligent sun protection during the

healing process. Topical agents demand several weeks of at-home care and thus require a motivated patient willing to continue medication application despite the expected associated discomfort (erythema, crusting). Treatment discomfort and pain also factor into a patient's treatment decision. Studies generally illustrate more pain secondary to cryosurgery than to ED&C or PDT. In a study of cSCCIS patients, cryosurgery patients were 10.4 times more likely to report any pain than those treated with ED&C ($p < 0.001$) **(2b)** [71]. While PDT may elicit pain specifically during the light treatment, a RCT of 40 cSCCIS patients illustrated less pain following PDT compared with cryotherapy (RR 0.58, 95%CI 0.38 to 0.87, $p = 0.01$) **(1b)** [72], and a systematic review found no statistically significant difference in pain with either MAL- or ALA-PDT compared to 5-FU **(1a)** [23].

Post-procedural cosmetic and functional outcomes have been shown to vary between noninvasive treatments and may thus affect treatment selection. ED&C wounds typically have longer healing times than excisional wounds [19] and tend to leave a white scar that may permanently atrophy or hypertrophy [19]. As cryotherapy areas thaw, pain, swelling, and eschar may persist for several weeks. Like ED&C, both cryosurgery and topical treatments can leave a permanently hypopigmented scar with atrophy or hypertrophy. Although PDT causes erythema, edema, and occasional blistering or crusting, side effects are short-lived and disappear within 1–3 weeks without visible scarring. PDT has demonstrated superiority over cryosurgery and over 5-FU in long-term cosmetic outcome in RCTs **(1b)** [54, 72].

Patients with high-risk lesions are primarily treated with MMS and standard surgical excision with POMA. Dermatologic surgeons perform these under local anesthesia and in the outpatient setting, minimizing the risk of adverse events. The decision to pursue a particular approach is influenced by the time required of the patient as well as the potential aesthetic result. Cosmetic outcome was shown to be very important to patients—though secondary to cancer removal—in a prospective qualitative study of patient experiences after facial skin cancer surgery [73]. MMS requires a time commitment from the patient as the margins are assessed in real time and reconstruction performed the same day. Its ability to minimize removal of healthy tissue, however, can yield superior cosmesis. Margin status is delayed with surgical excision and POMA, and should pathology reveal the tumor to be incompletely removed, the required re-excision has potential to leave a larger scar. Asgari et al. illustrated that while there was no difference in immediate posttreatment satisfaction between MMS and surgical excision with POMA, MMS yielded greater long-term satisfaction 1 year after treatment **(2b)** [74].

Typical Treatment Plan

A 71-year-old, immunocompetent man presented with a 0.8 cm keratotic papule with poorly defined borders on the left mid-cheek, without evidence of regional adenopathy. Biopsy determined the tumor to be a moderately differentiated cSCC, 1 mm in depth, and without perineural or lymphovascular involvement. Although the small lesion lacked pathologic high-risk criteria and lay outside the high-risk "mask" area of the face, its ill-defined borders placed it within the NCCN Guidelines "high-risk" category for recurrence [15]. Its location on the cheek rendered it appropriate for the use of MMS, per published criteria [24]. The patient, a surgical candidate, was thus given the options of surgical excision with POMA and MMS.

The patient and dermatologist determined together that MMS would be the optimal therapy. The patient understood that both surgical modalities carried similar and low risks of recurrence and that MMS could require a full day in the office compared with standard excision's shorter procedure time. The patient expressed, however, that he was more comfortable knowing margin status prior to wound closure. The potential for a larger surgical defect given his tumor's risk for

subclinical extension further concerned the patient for cosmetic reasons, prompting him to elect for MMS given its capacity for tissue sparing.

The patient returned to the office for MMS a week later. He underwent the first MMS stage under local anesthesia, was provided a temporary bandage, and waited in the patient waiting area until his frozen pathology results returned. Given a positive margin in one quadrant of the excised specimen, a second stage was taken from the positive area and was subsequently negative. The Mohs surgeon proceeded to close the wound primarily. The patient was given a pressure dressing and post-procedure instructions.

At the suture removal visit, the patient reported that although his sleep was made difficult due to the location of his wound, his pain was well controlled with acetaminophen. He was instructed to continue skin exams with his dermatologist and return in a few months for follow-up of the scar. On his return, he reported that the residual redness from the scar resolved after a few weeks and that he was able to resume his usual exercise routine shortly after suture removal.

Safety

Although there is a paucity of data confirming frequency of adverse events (AE) among treatments commonly used for cSCC and cSCCIS, these therapies are generally regarded as both safe and well tolerated.

ED&C

AE secondary to ED&C include electrical burns and infection, although few studies have evaluated frequency of these outcomes. In a prospective study, 2 of 44 (4.5%) cSCCIS patients treated with ED&C developed infection sufficient to require oral antibiotics **(4)** [71]. Interference of the electrodesiccation device with implantable cardioverter-defibrillators (ICDs) has also been reported. One study calculated an AE rate in 0.8 ICD patients/100 years of surgical practice following electrosurgery for any condition. Negative outcomes due to electrosurgical interference included syncope, altered mental status, and palpitations. In this study, no significant morbidities or mortalities were reported **(4)** [75].

Cryotherapy

Cryotherapy has also generally proven safe in treatment of NMSC, with AE limited to those of wound healing, including ulceration and infection. In a prospective study, 4 of 36 (11.1%) cSCCIS patients treated with cryosurgery developed infection that required oral antibiotics **(4)** [71]. Another prospective study described post-procedural ulceration in 5 of 20 (25%) cSCCIS lesions treated with cryotherapy, leading to cellulitis requiring systemic antibiotics in 2 patients (10%). Authors reported that 16 of 20 lesions were on the legs but failed to specify anatomic sites of lesions that ulcerated **(4)** [72]. Holt described a series of 395 NMSC patients treated with cryosurgery and reported a number of AE. Three patients (0.8%) developed frank hemorrhage controlled with absorbable hemostatic sutures. The author also noted that 2 of 30 (6.7%) cases on cartilaginous sites developed scar notching due to partial necrosis of underlying cartilage **(4)** [40].

PDT

PDT is well tolerated with an excellent safety profile. Expected side effects secondary to PDT include pain, erythema, burning, irritation, and itching [54]; however, more serious events such as ulceration, infection, or bleeding have rarely been reported. A prospective evaluation of 55 patients with cSCCIS and SCC did not report any local or systemic AE (0%) outside of expected intra-procedure complaints **(4)** [46]. Wolfe and colleagues reported 4 cases of cellulitis in > 700

patients treated with PDT for AK **(4)** [76]. All patients exposed to light sources such as that required for PDT should wear protective glasses to prevent retinal damage, and patients exposed to sunlight during the 48 h after treatment risk severe phototoxicity with ultraviolet exposure.

Topical Therapies

Imiquimod yields a predictable, localized inflammatory reaction that may involve transient itching, edema, weeping, or crusting. Exuberant inflammatory responses may cause erosion or ulceration. A systematic review of imiquimod use in NMSC estimated that 3% of subjects experienced reactions of sufficient intensity to warrant treatment discontinuation **(2a)** [22]. Systemic findings, likened to a "flu-like" illness including malaise and fatigue, are rare and likely secondary to pro-inflammatory cytokines entering systemic circulation [77]. Fluorouracil also produces erythematous local reactions, ranging from mild to severe and possibly involving pain, irritant dermatitis, pruritus, and ulceration. In one study of 5-FU in cSCCIS (applied once daily for 1 week; twice daily for weeks 2–4), severe eczematous reactions developed in 7/33 lesions (21%), and ulceration occurred in 3/33 (9.1%) lesions with resultant prominent scarring **(4)** [55]. A systematic review found that 5% of subjects across 5-FU studies in NMSC discontinued therapy **(2a)** [22].

Surgical Therapies

AE following MMS and standard excision are those inherent to any local surgical procedure. AE incidence has been reported more often for MMS than for standard excision. In a 2013 multicenter prospective cohort study of 20,821 cases, 149 AE (0.72%), including 4 serious events (0.02%) were reported. Common AE were infections (61.1%), partial or full dehiscence and necrosis (20.1%), and bleeding/hematoma (15.4%) **(4)** [78]. In another prospective study of 1358 cases treated with MMS, the overall complication was 1.64%. A majority of complications involved difficulties with hemostasis; none were sufficient even to involve the assistance of another specialist, let alone require hospitalization **(4)** [79]. A prospective study of 1000 consecutive patients treated with either MMS for NMSC (n = 968) or modified MMS ("slow Mohs," n = 32) for lentigo maligna specifically evaluated the rate of surgical site infection without prophylactic antibiotics. Authors determined the rate to be 0.7% (8/1115 tumors) **(4)** [80]. Yet another 1000-patient prospective study using clean surgical technique in MMS for NMSC found an overall rate of infection of 0.91% (11/1204 tumors), with 3 of 11 infections as complications of hematomas **(4)** [81].

Relative Safety

Few studies have compared adverse events for cSCC therapies directly. One RCT compared total adverse events in MAL-PDT, cryotherapy, and 5-FU and reported total AE numbers that did not differ significantly **(1b)** [54]. Another RCT did, however, report statistically significantly fewer adverse events in an ALA-PDT group compared with 5-FU (0/33, 0% vs. 12/33, 36.4%, $p < 0.001$) **(1b)** [55]. Ahmed et al. described cSCCIS patients treated with either ED&C or cryotherapy and reported higher post-procedure infection among cryotherapy patients (4/36, 11.1% vs. 2/44, 4.5%), with all 6 infections arising on the lower legs **(4)** [71].

Postoperative Care and Follow-Up

A diagnosis of cSCC mandates careful, structured posttreatment surveillance both for tumor recurrence and for the development of new malignancies, with greatest vigilance required throughout the first 5 years after treatment.

As illustrated through Rowe et al. and Lansbury et al.'s systematic reviews in 1992 and 2013, respectively, 70–90% of cSCC recurrences and metastases have been reported in case series

and cohort studies to develop within 2 years of initial therapy. Both reviews concluded that 95% of these outcomes occur within 5 years **(4)** [25, 26].

Several studies have illustrated the greater NMSC and melanoma risk incurred by cSCC development. Mean 3-year cumulative risk of subsequent cSCC after index cSCC has been reported at 18%, corresponding to an estimated tenfold greater risk compared with the general population **(2b)** [82]. Adding to this risk, authors found mean 3-year cumulative risk of developing BCC after initial cSCC diagnosis to be 43% based upon 1 retrospective cancer registry-based study **(4)** [82]. Finally, the risk of melanoma is substantially elevated among those with personal NMSC history, on the order of eight times more risk than the general population **(2a)** [83].

Based upon these facts, the NCCN suggests follow-up based on tumor risk profile, with full skin and lymph node examination every 3–12 months for 2 years after treatment, when the majority of recurrences occur. In the 3 years following, patients should be examined every 6–12 months. Finally, a practitioner should examine the patient annually for life, in order to responsibly assess for the development of new malignancies [15].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
The risk of cSCC metastasis increases with tumor size, depth, location on the ear, and immunosuppression	B
Surgical excision with postoperative margin assessment and Mohs micrographic surgery (MMS) are the most effective treatments for high-risk lesions	C
MMS is effective for lesions in locations with minimal excess tissue and/or near vital anatomic structures	C
There is insufficient evidence to support cryosurgery or ED&C in high-risk cSCC	C
Photodynamic therapy and topical therapies should be limited to low-risk cSCCIS	B
Clinical follow-up is based on tumor risk with visit frequency highest in the first 5 years	C

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Self-Assessment Questions

1. High-risk anatomic locations for cSCC include:
   (a) Central face
   (b) Neck
   (c) Ear
   (d) All of the above
   (e) a + c only

2. A 61-year-old, healthy male presents with a 1.3 cm keratotic plaque on the right leg diagnosed as cSCC. The lesion was treated with ED&C several years prior. Which of the following would be the *most* appropriate treatment?
   (a) ED&C
   (b) MMS
   (c) Aggressive cryotherapy
   (d) Combination treatment with photodynamic therapy and curettage
   (e) Any of the above options would be appropriate

3. A 68-year-old woman presents with a 0.5 cm, well-demarcated, scaly papule on the right shoulder. Biopsy reveals well-differentiated cSCC, 1 mm in depth, without evidence of perineural or lymphovascular invasion. Which of the following would be an appropriate treatment?
   (a) ED&C
   (b) Surgical excision with 4–6 mm margins and POMA
   (c) MMS
   (d) All of the above
   (e) a + b only

4. Which of the following statements is true?
   (a) There is no consensus on best techniques for performing cryosurgery on cSCC
   (b) MMS' ability to spare tissue renders it useful for lesions on or near vital anatomic structures (i.e., nose/ear) for preservation of function and cosmesis
   (c) Of all therapies for cSCCIS, photodynamic therapy is least likely to leave permanent scarring
   (d) All of the above
   (e) b + c only

5. According to the NCCN, patients treated for cSCC should be followed with:
   (a) Full skin and lymph node examination every 3–12 months, indefinitely
   (b) Full skin and lymph node examination every 3–12 months for 2 years, every 6–12 months for 3 years, and yearly thereafter
   (c) Examination of the treated site every 3–12 months for 2 years, every 6–12 months for 3 years, and yearly thereafter
   (d) Full skin examination yearly
   (e) CSCC patients need not be followed after definitive treatment

Correct Answers

1. e: a + c only. The central face and ear are part of the "mask area" of the face, considered high-risk for local recurrence or metastasis independent of size.
2. b: MMS. Recurrent tumors are considered "high risk" for future recurrence and metastasis regardless of anatomic location. Of all therapies listed here, MMS is most appropriate high-risk lesions.
3. e: a + b only. This clinically and histologically low-risk tumor is in an anatomic location with sufficient excess tissue for linear reconstruction; therefore, ED&C and standard surgical excision are sufficiently effective therapies. MMS would be effective in permanently eradicating this tumor, but the method's costliness and greater time requirement render it appropriate for use only for higher-risk lesions and anatomic sites.
4. d: All of the above. Each of these statements is true.
5. b: Full skin and lymph node examination every 3–12 months for 2 years, every 6–12 months for 3 years, and yearly thereafter. Ninety-five percent of cSCC lesions recur or metastasize within 5 years after treatment, with a majority of these outcomes occurring within the first 2 years. Posttreatment surveillance should thus be most frequent within the first 2 years after treatment. Furthermore, patients treated for cSCC are at higher risk for NMSC and melanoma development than the general population and should thus receive full skin and lymph node examinations during follow-up visits.

Melanoma in Situ

44

Katherine T. Steele and Christopher J. Miller

Abstract

Melanoma in situ, defined as melanoma entirely restricted to the epidermis and its accompanying epithelial adnexal structures, is increasing in incidence. Detection and treatment of MIS is important, due to the risk of occult invasion or progression to invasive melanoma. There is a lack of high-quality evidence regarding the optimal treatments for MIS. The majority of MIS in the United States are treated with surgical modalities including conventional wide local excision, staged excision, and Mohs micrographic surgery (MMS). Conventional wide local excision effectively treats most well-defined primary melanomas on the trunk and extremities, but the technique has greater than a 10% risk of positive margins and local recurrence for MIS on the head, neck, hands, feet, and pretibial leg. Staged excision with microscopic margin evaluation via formalin-fixed paraffin-embedded sections and MMS achieve local clearance rates of > 98% for in situ and invasive melanomas arising in chronically sun-damaged skin. Anatomic location and history of previous treatment identify melanomas that may benefit from staged excision or MMS to detect subclinical spread of tumor prior to reconstruction.

Keywords

Local · Excision · Head · Neck · Staged excision · Surgery

Epidemiology

In 2017, in the United States, 74,680 cases of melanoma in situ (MIS) were expected to be diagnosed, compared to 87,110 invasive melanomas (1b) [1]. The incidence is increasing more rapidly for MIS versus invasive melanoma (2b) [2]. By definition, MIS is entirely restricted to the epidermis and its accompanying epithelial adnexal structures. MIS is a heterogeneous diagnosis with overlapping clinical and histologic subtypes. Superficial spreading MIS, which occurs most commonly on the trunk and extremities, is characterized histologically by prominent melanocytic nests and relatively less solar elastosis. Lentigo maligna, which occurs most commonly on chronically sun-exposed skin of the head and neck and distal limbs, is characterized histologically by a proliferation of atypical melanocytes at the base of the epidermis in solar elastotic skin. Acral lentiginous MIS, which occurs on the palms, soles, and digits, is characterized histologically by a proliferation of melanocytes arranged as single cells along the basal layer of the epidermis. Oral mucosal and genital melanomas in situ are examples of other less common

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subtypes. Although the clinicopathologic features differ among these subtypes, surgical excision is the mainstay therapy for all of them. Therefore, this chapter will address all subtypes as a group, simply called MIS.

Detection and treatment of MIS is important, due to the risk of occult invasion (2b) [3, 4] or progression to invasive melanoma (1b) [5, 6]. Whereas 9,730 deaths were expected to occur in patients with invasive melanoma in 2017 (1b) [1], rates of metastasis and death from MIS were rare, but not zero (1b) [3, 7]. A diagnosis of MIS increases the risk to develop subsequent invasive melanomas of any stage (1b) [8].

While acral, oral, and genital MIS have unique epidemiology, general risk factors for MIS include light skin, hair, and eye color, ultraviolet light exposure, multiple nevi, and a personal or family history of melanoma (1b) [9]. The majority of MIS occur above the waist, but lower extremity location is more common in women (21%) than men (6%) (2b) [2]. The anatomic distribution of MIS shifts with age. Trunk and extremity location is most common in people <50 years old, whereas head and neck location is more common in people >70 years old (2b) [2].

Treatment Overview

Introduction

Surgical excision with clear microscopic margins is the mainstay treatment for MIS (2a) [10]. At least 94% of melanomas in the United States are treated with a method of surgical excision (2b) [11]. Topical imiquimod is a relatively new and less common treatment option, typically reserved to treat lentigo maligna in patients who are not able to undergo surgery (2a) [12].

Methods of Surgical Excision

Methods of surgical excision are divided into three categories: conventional wide local excision, staged excision with microscopic margin evaluation via formalin-fixed paraffin-embedded sections (FFPE), and Mohs micrographic surgery (MMS) with same-day frozen section microscopic margin evaluation (2a) [13].

Conventional Wide Local Excision

Conventional wide local excision removes the clinically visible MIS with a margin of clinically normal skin. No randomized control trial has compared different surgical margins for MIS, so consensus opinion and evidence from case series guide practice. In 1992, expert consensus recommended 0.5 cm surgical margins for MIS (5) [14]. Numerous case series subsequently demonstrated the insufficiency of 0.5 cm margins for up to half of MIS (2b) [15–19]. In a case series of 1120 MIS treated with Mohs surgery, Kunishige et al. demonstrated that a minimum of a 9 mm surgical margin is necessary to clear 97% of MIS (2b) [20]. Based on existing evidence, expert consensus now recommends surgical margins ranging from 0.5 to 1.0 cm, using the wider end of the range particularly for lentigo maligna (2a) [10, 21]. Peripheral excision margins are based on clinical margins taken at the time of surgery, not the gross or histologic margins measured by the pathologists [10]. This distinction is important, because the size of the clinical and pathologic margins correlates in only 12% of the excisions (2b) [22]. While there is no consensus on the depth of the excision (2b) [23–25], extending the excision to the fascia ensures complete removal of MIS extending down adnexa.

The excised specimen is fixed in formalin, with or without orienting sutures, and a pathology lab accessions the gross characteristics and divides the specimen into vertical breadloaf sections. Based on these formalin-fixed paraffin-embedded vertical sections, which sample less than 1% of the surgical margin (2b) [26, 27], a pathologist determines the adequacy of the microscopic margins. If tumor is present at the margins, the pathologist can roughly estimate the location of the residual tumor, as long as the surgeon placed orienting sutures on the initial specimen. The average turnaround time for tissue processing and microscopic margin evaluation is

3–5 days. The surgeon reconstructs the wound immediately after excision and before the microscopic margin evaluation, which risks the need for more surgery if margins are positive. Reconstruction may be delayed until the margins have been evaluated, but this is a form of staged excision.

Staged Excision with Microscopic Margin Evaluation via Formalin-Fixed Paraffin-Embedded (FFPE) Sections

For MIS at increased risk for upstaging or positive margins from conventional wide local excision, staged excision with microscopic margin evaluation via formalin-fixed paraffin-embedded sections may be utilized. Examples of staged excision techniques include the square procedure (4) [28], the spaghetti technique (2b) [29], slow Mohs (4) [30], staged excision with radial vertical sections (2b) [31], and mapped serial excision (2b) [32]. Comprehensive descriptions of each method are beyond the scope of this chapter, and readers are referred to primary sources and excellent review articles for more information (2a) [33].

While the various staged excision techniques may differ in the methods of tissue processing and the percentage of the margin examined, they all involve a pathologist's microscopic margin evaluation via formalin-fixed paraffin embedded sections prior to reconstruction. The surgeon, usually a Mohs or dermatologic surgeon with extensive knowledge of tissue processing, outlines the clinical margin of the tumor and a surgical margin of clinically normal skin. The size of the surgical margins varies by the surgeon and clinical circumstance. The initial excision is performed (contents of the initial excision vary among the techniques), and the patient returns home with a bandage until the microscopic margins have been examined.

The tissue is fixed in formalin and delivered to a histopathology lab, where it is inked and processed for microscopic examination. Melanocytic immunohistochemical stains may or may not be used. The surgeon must communicate with the laboratory personnel to maintain orientation of the tissue relative to the patient and to ensure accurate tissue processing. A pathologist interprets the microscopic margin and communicates the results to the surgeon, usually one to several days after the excision. If the margins are positive, the patient returns for a targeted excision of the residual tumor, then returns home during another round of tissue processing and margin determination. The process continues until margins are clear and the wound is reconstructed.

Tissue processing time and coordinating schedules of the numerous people involved in the care create several logistical challenges. The surgeon and patient will not be sure when the margins are clear, so timing of additional stages and/or reconstruction is uncertain. Dermatopathology labs are frequently unaccustomed to *en face* sections, so errors can occur without careful communication between the surgeon and pathology lab. Since a dermatopathologist interprets the margins, which are often challenging, the surgeon and dermatopathologist must have excellent communication about the clinical relevance of the histopathologic findings.

Mohs Micrographic Surgery (MMS)

Between 2003 and 2009, 3.5% (6872/195,768) melanomas (both invasive and MIS) were treated with MMS, and the utilization rate for MMS increased by 60% during that period [11]. Like staged excision, MMS is used to treat MIS at increased risk for upstaging or positive margins from conventional wide local excision. MMS allows same-day microscopic examination of the entire surgical margin, and pathology is interpreted by the Mohs surgeon, rather than a separate pathologist. The visible tumor is excised with a margin of clinically normal skin. Hash marks are made on the skin surface to maintain orientation relative to the patient. The surgeon grossly sections the excision specimen into pieces that will fit on a microscopic slide. The free cut edges of all grossly sectioned specimens are inked, and a surgical map is drawn to represent the method of gross sectioning and inking. The tissue is frozen, rather than formalin-fixed,

and microscopic frozen sections are cut from 100% of the complete peripheral and deep margins.

For melanoma, the frozen tissue sections are stained with both hematoxylin and eosin and a melanocytic immunohistochemical stain, such as MART-1 or MITF. The Mohs surgeon evaluates the pathology. If tumor is detected at the margin, the Mohs surgeon indicates the precise location of residual cancer on the specimen map. Targeted excision, or a second "stage," is performed around the residual tumor. Again, the free cut edges of the specimen are inked, a map of the specimen is created, and the frozen sections of the entire peripheral and deep margin of the specimen are examined by the Mohs surgeon. The process continues until clear margins are achieved. The average turnaround time for each stage is 1–2 h. Reconstruction is done usually on the same day immediately after confirming clear margin status.

Imiquimod

Imiquimod cream, which induces an immune response to atypical melanocytes, has been used as off-label primary treatment for MIS in patients who are poor surgical candidates since the year 2000 [12]. The cream is used primarily for lentigo maligna subtype of MIS (2a) [34]. Although the Food and Drug Administration has not approved imiquimod for the treatment of melanoma, consensus guidelines include consideration of the topical imiquimod as an *adjuvant* therapy for selected patients with MIS extending to the margins after surgery [10]. However, several publications document the use of imiquimod as a primary therapy for MIS.

Treatment regimens vary widely in the frequency and duration of application and margins around the clinically visible tumor. The typical treatment regimen involves application to the tumor by the patient at a frequency of 5 days per week over a total duration of 12 weeks (2a) [35]. Treatment with > 60 total applications or with >5 applications per week is associated with a higher likelihood of histologic clearance [12]. No randomized, prospective trials have compared the efficacy of imiquimod and surgery (2b) [36]. Concerns with monotherapy treatment of MIS with imiquimod include failure to respond and removal of skin surface pigmentation, which can disguise progression of MIS to invasive melanoma.

Effectiveness of Treatments

Introduction

Local recurrence is the ultimate measure of effectiveness of treatment for melanoma. Reconstruction with positive margins is another important metric, because subsequent surgeries involve more challenging margin assessment and more complex reconstruction (2b) [37]. Most studies evaluating rates of positive margins and local recurrence after conventional WLE group MIS with invasive melanoma. While precise rates for MIS may be lacking, aggregate data for invasive and in situ melanoma likely represent both groups. Invasive melanomas with a component of MIS are known to have an increased risk for positive excision margins, and MIS is the most common cause of positive margins (2b) [38]. Additional support for the relevance of aggregated data is the fact that the frequency of subclinical spread, which is the primary cause of positive margins and local recurrence, does not differ between invasive and in situ melanoma [37].

Conventional Wide Local Excision

Published Rates of Positive Margins After Conventional Wide Local Excision of Melanoma

Reconstruction is done prior to microscopic margin assessment with conventional wide local excision; therefore, this surgical technique risks reconstruction before complete excision of the MIS. The risk for positive margins after conventional wide local excision of melanoma is 2% for melanomas of the trunk and proximal extremities, compared to 12% for tumors on the head, neck, hands, feet, and pretibial leg (2b) [39].

Table 44.1 Published rates of positive margins after conventional wide local excision of melanoma (Miller et al. [39])

Reference	Rate of positive margins	Anatomic locations
Mangold et al. [38]	6% (34/543)	Head and neck: 14% (19/135) Lower extremity: 7% (9/129) Trunk: 2% (4/164) Upper extremity: 2% (2/115)
Berdahl et al. (2b) [40][b]	23% (9/40)	Upper face[a]
Christophel et al. (2b) [41][b]	12% (48/412)	Nose: 15% (6/39) Eyelid: 17% (2/12) Cheek: 14% (15/109) Ear: 6% (5/79) Neck: 10% (5/52) Forehead: 19% (5/27) Lips: 0% (0/2) Temple: 12% (3/25) Scalp: 10% (7/67)
Hou et al. (2b) [42]	8% (22/269)	No location breakdown
Parrett et al. (2b) [43][b]	5% (4/76)	No location breakdown
Sullivan et al. (2b) [44][b]	6% (7/117)	Cheek: 14% (5/36) Forehead: 4.34%(1/23) Neck: 33%% (1/3) Other sites: 0% (0/55)
Rawlani et al. (2b) [45][b]	9% (7/79)	No location breakdown

[a]Upper face defined as the forehead, periorbital region, nose, cheeks, and midfacial region superior to the nasolabial fold

[b]All melanomas were located on the head and neck

Several studies with published rates of positive margins after excision of melanomas (both invasive and MIS are included) are listed in Table 44.1.

Published Rates of Local Recurrence After Conventional Wide Local Excision of Melanoma

Anatomic location on the head and neck is an independent risk factor for local recurrence after conventional wide local excision of melanoma (2b) [46–48]. Noncompliance with recommended excision margins is also an independent risk factor for local recurrence (2b) [47]. Of 3128 head and neck melanomas reported to be treated with conventional wide local excision, 261 (8.3%) developed local recurrence. By comparison, only 1.7% (144/8409) trunk and extremity melanomas developed local recurrences after conventional wide local excision (Table 44.2).

Staged Excision with Microscopic Margin Evaluation via Formalin-Fixed Paraffin-Embedded (FFPE) Sections

Unlike conventional wide local excision, staged excision with microscopic margin evaluation via FFPE delays reconstruction until clear microscopic margins have been confirmed. Therefore, this technique should theoretically have little to no risk of reconstruction before complete excision. The effectiveness of the technique is best demonstrated by numerous references that publish low local recurrence rates (Table 44.3).

Mohs Micrographic Surgery

Like staged excision, MMS reserves reconstruction until clear microscopic margins have been achieved. Therefore, this technique should theoretically have little to no risk of reconstruction before complete excision. The effectiveness of the technique is best demonstrated by numerous references that publish low local recurrence rates (Table 44.4)

Imiquimod

Efficacy of imiquimod is difficult to assess, due to small case series, variable frequency and duration of treatment periods, short follow-up periods, and inadequate methods for assessing recurrence. Clinical assessment is unreliable to determine treatment effectiveness, because the presence or absence of visible pigment does not necessarily correlate with histologic disease (2b) [92]. Based on 347 tumors from 45 studies,

Table 44.2 Published standard excision local recurrence rates of melanoma in studies that allowed delineation of recurrence location between head or neck lesions and trunk or extremity lesions

Reference	LR/total patients	LR rate, %	Follow-up, y	Definition of LR
Trunk and extremity melanomas				
Heaton et al. (2b) [51]	29/234	12.4	2.3	≤ 3 cm from WLE surgical scar
Agnese et al. (2b) [52]	21/624	3.4	2.8, median	NS
Balch et al. (2b) [53]	22/676	3.3	10, median	≤ 2 cm from the scar or graft
Neades et al. (2b) [54]	6/356	1.7	10, median	In the scar or graft
Moehrle et al. [47]	40/3376	1.2	5, median	In the scar or graft
Cohn-Cedemark et al. (2b) [55]	26/3143	0.8	8, median	In the scar or graft
Head and neck melanomas				
Harish et al. (2b) [57][a]	12/56	21.4	3.1, median	NS
Osborne and Hutchinson (2b) [58]	16/81	19.8	3.5	NS
Berdahl et al. [40]	5/40	12.5	3.1, mean	NS
Jones et al. (2b) [59]	6/50	12.0	3.1, median	NS
Fisher et al. (4) [56]	104/900	11.6	NS	NS
Bogle et al. (2b) [60]	4/35	11.4	3.5, mean	NS
Heaton et al. [51]	5/44	11.3	2.3	≤ 3 cm from WLE surgical scar
Ravin et al. (2b) [61][b]	21/199	10.6	3.3, median	NS
Balch et al. [53]	6/64	9.3	10, median	≤ 2 cm from the scar or graft
Pitman et al. (4) [62]	2/22	9.1	3.2, mean	NS
Coleman et al. (4) [63]	2/23	8.7	3, mean	NS
Gibbs et al. (2b) [64]	11/168	6.5	NS	In the scar or graft
Neades et al. [54]	5/78	6.4	10, median	In the scar or graft
Agnese et al. [52]	8/131	6.1	2.8, median	NS
Tsang et al. (2b) [65]	1/18	5.5	6, median	NS
Moehrle et al. [47]	29/584	5.0	5, median	In the scar or graft
Cohn-Cedermark et al. [55]	22/563	3.9	8, median	In the scar or graft
Sullivan et al. (2b) [66]	2/72	2.8	5.2, mean	NS

Adapted from Etzkorn et al. (2b) [49]; Dawn et al. (2a) [50]
Studies are arranged in descending order of LR rates
LR Local recurrence, *NS* not specified, *WLE* wide local excision
[a]Eyelid melanomas
[b]Ear melanomas

Table 44.3 Local recurrence rates of melanoma for staged excision techniques

Reference	LR/total patients	LR rate, %	Follow-up, mean months (range)
Square procedure and associated variations			
Johnson et al. [28]	0/35	0	NR, "1–3 years after first patient"
Anderson et al. (4) [68]	1/150	0.67	NR, "less than 5 years"
Agarwal-Antal et al. [15]	0/92	0	NR, "4 years after first patient"
Mahoney et al. (4) [69]	0/11	0	4.7 (1–13.4)
Jejurikar et al. (2b) [70]	0/51	0	31.8 (16–46)
Demirci et al. (2b) [71]	1/40	2.5	49 (9–112)
Abdelmalek et al. (2b) [72]	4/239	1.7	32.3 (2–96)

Table 44.3 (continued)

Reference	LR/total patients	LR rate, %	Follow-up, mean months (range)
Spaghetti technique and associated variations			
Möller et al. [29]	0/29	0	14 (1–36)
Bosbous et al. (2b) [73]	1/59	1.7	27 (1–122)
Gaudy-Marqueste et al. (2b) [74]	1/21	4.7	25.4 (0–72)
De Vries et al. (2b) [75]	4/100	4.0	60 (NR)
Slow Mohs			
Dhawan et al. [30]	0/1	0	12 (NA)
Cohen et al. (2b) [76], (2b) [77]	1/45	2.2	57 (15–106)
Clayton et al. [18]	1/106	0.9	22 (NR)
Lee and Ryman. (2b) [78]	3/31	9.7	42 (12–89)
Staged excision with radial vertical sections			
Bub et al. [31]	3/62	4.8	57 (9–139)
Connolly et al. (2b) [79]	4/100	4	60 (0–144)
Mapped serial excision			
Hill and Gramp [32]	1/66	1.5	25 (10–48)
Huilgol et al. (2b) [80]	4/161	2.5	38 (5–100)
Walling et al. (2b) [81]	3/41	7.3	95 (6–240)
Malhotra et al. (2b) [82]	4/141	2.8	32 (1–100)

Adapted from Mayo et al. [67]
LR Local recurrence, *NR* not reported, *NA* not applicable

Table 44.4 Local recurrence rates of melanoma in situ after Mohs micrographic surgery

Reference	LR/total patients	LR rate, %	Follow-up, mean months (range)
Mohs without immunostains			
Hou et al. [42]	3/154	1.9	94.8
Bene et al. (2b) [84]	2/143	1.4	50
Zitelli et al. (2b) [85]	1/184	0.5	60
Bienert et al. [19]	0/76	0	33 (8–72)
Temple and Arlette (2b) [86]	0/202	0	29.8 (0.25–114.6)
Mohs with immunostains			
Newman et al. (2b) [87]	5/460	1.1	34
Bhardwaj et al. (2b) [88]	1/200	0.5	38.4 (6–58)
Valentin-Nogueras et al. (2b) [89]	4/863	0.5	44.8 (0–114.5)
Bricca et al. (2b) [90]	1/331	0.3	58 (0–238.8)
Kunishige et al. [20]	3/1120	0.3	56.4 (0.24–282)
Etzkorn et al. [49]	2/597	0.3	33.6 (0–104.2)
Stigall et al. (2b) [91]	1/882	0.1	60.2 (1–340)
Zalla et al. [16]	0/46	0	16 (1–32)

Adapted from Shin et al. (2a) [83]; Higgins et al. (2b) [34]
LR Local recurrence

histologic and clinical clearance rates were 76.2% and 78.3%, respectively [12]. Considering available data, the local recurrence rate after imiquimod is approximately 25%, with reported rates ranging from as low as 4.2% to as high as 50% (Table 44.5) [92].

Comparative Effectiveness of Common Treatments

Surgery is highly effective to treat MIS. The relative effectiveness of the different surgical procedures depends on tumor selection (Table 44.6).

Table 44.5 Studies of the use of topical imiquimod for treatment of lentigo maligna

Reference	Sample size	NR + LR /total patients	Recurrence rate, %	Follow-up, mean months (range)	Determination of clearance
Spenny et al. (4) [93][a]	12	2/12	16.7	18.3	Clinical + histopathological
Van Meurs et al. (4) [94][b]	10	5/10	50	31, median (11–56)	Histopathological
Powell et al. (2b) [95][a]	48	11/48	22.9	48.6 (25–72)	Histopathological
Ly et al. (2b) [96][b]	38	18/38	47.4	Excised at 4 months	Histopathological
Wong et al. (2b) [97][a]	27	7/27	25.9	NS (4.6–40.8)	Clinical + histopathological
Fleming et al. (4) [98][b]	6	4/6	33.3	Excised at 2 months	Clinical + histopathological
Powell et al. (4) [99][b]	12	2/12	16.7	6, median (3–18)	Histopathological
Naylor et al. (2b) [100][b]	28	2/28	7.1	12, median	Histopathological
Cotter et al. (2b) [101][a]	40	10/40	25	18 (12–34)	Histopathological
Kirtschig et al. (2b) [102][b]	24	1/24	4.2	39 (21–70)	Clinical + histopathological
Total	245		24.5		

Adapted from Kai et al. [92]
$I^2 = 62.6\%$, $P = 0.004$, Q test statistic = 24.06, df = 9
NR Nonresponders, *LR* Local recurrence, *NA* not applicable, *NS* not specified
Recurrence rate = nonresponders + local recurrence / total patients
[a]Retrospective
[b]Prospective

Table 44.6 Comparison of outcomes for different treatments of melanoma in situ

	Conventional WLE		Staged excision	MMS	Imiquimod
Positive margins	2%	Trunk and proximal extremities	N/A	N/A	N/A
	12%	Head, neck, hands, feet, pretibial leg, genitalia			
Local recurrence rates	2%	Trunk and proximal extremities	<2%	<2%	25%
	12%	Head, neck, hands, feet, pretibial leg, genitalia			

WLE wide local excision, *MMS* Mohs micrographic surgery

For MIS of the trunk and proximal extremities, conventional wide local excision is highly effective, with an approximately 2% rate of positive margins [39] or local recurrence [49]. Up to 17% of MIS of the trunk and proximal extremities may have subclinical extension more than 5 mm beyond the clinically visible margin, and a margin of at least 9 mm is necessary to ensure complete removal of 97% of MIS [91]. Therefore, to ensure complete removal, excision of trunk and extremity MIS should involve a clinical margin on the wider end of the 0.5–1.0 cm range recommended by consensus opinion. Staged excision and MMS are also highly effective for MIS of the trunk and proximal extremities [49, 91]; however, these techniques should be reserved for a select subset of MIS at high risk for upstaging or positive margins after conventional wide local excision. Risk factors for upstaging include extension of tumor to the base of the preoperative

biopsy, the need for multiple preoperative scouting biopsies due to ill-defined clinical margins, and older patient age (2b) [103]. Risk factors for positive margins after conventional wide local excision include: noncompliance with recommended surgical margins, histologic regression on the diagnostic biopsy, the need for multiple preoperative scouting biopsies to assess ill-defined margins, and increased patient age [39].

For MIS of the head, neck, hands, feet, pretibial leg, and genitalia, staged excision or MMS improves surgical outcomes. Conventional wide local excision for MIS in these anatomic locations has an increased risk for poor outcomes, including a 12% rate of upstaging [103], a 12% rate of positive margins [39], and a 12% rate of local recurrence [49]. Location of melanoma in these anatomic areas is one of the major risk factors for upstaging or positive margins after conventional wide local excision [39, 103]. Both staged excision and MMS allow detection of upstaging, which may be important to optimize patient counseling and utilization of sentinel lymph node biopsy prior to reconstruction, to ensure complete removal of MIS prior to reconstruction, and to decrease the risk of local recurrence to less than 2%. Ensuring complete tumor removal prior to reconstruction and decreasing the risk of local recurrence is important to minimize complexity of the surgery [37] and to restore normal appearance in the anatomic locations valued most highly by patients for their cosmetic and functional roles (2b) [104]. Staged excision and MMS are equally effective; therefore, the choice between the two procedures depends on the expertise of the treating surgeons and institutional and patient preferences.

Compared to greater than 98% local clearance rates after properly selected surgeries, imiquimod has inferior local clearance rates of 76% [12], and local recurrence rates of approximately 25%, but ranging as high as 50% [92]. Due to the markedly inferior outcomes with imiquimod, its use should be reserved strictly for patients in whom surgery is not an option. Consultation with an experienced surgeon is recommended to determine the feasibility of surgery.

Procedure Selection

Preoperative Evaluation and Patient Selection

The most important test for preoperative evaluation for MIS is the diagnostic biopsy. One potential pitfall is a biopsy that only partially samples the melanoma. Partial biopsies are common for melanocytic lesions with uncertain clinical diagnosis, large size, and location in cosmetically or functionally important areas (2b) [105, 106]. Partial biopsies increase the risk that the residual lesion will harbor more advanced melanoma (2b) [107], which can affect patient counseling about prognosis, surgical margins, and indications for sentinel lymph node biopsy [103]. If biopsy of the entire clinically visible lesion is not possible, sampling as much of the lesion as possible prior to definitive excision improves microstaging accuracy.

Another potential pitfall of preoperative biopsy is interpretation of intraepidermal melanocytic lesions with equivocal diagnostic features. Histologic features of MIS overlap with junctional dysplastic nevi and atypical intraepidermal melanocytic proliferation. Discordances in pathologic interpretation are relatively common and can impact diagnosis, staging, prognosis, and surgical management (2b) [108–110]. Interpretation of biopsies of melanocytic lesions at expert melanoma centers may improve diagnostic accuracy (2b) [108, 111].

After a biopsy confirms the diagnosis of MIS, a total body skin exam should be performed, because patients with MIS have an increased risk for additional primary melanomas and other skin cancers [8]. A lymph node examination of the draining basins should be performed, since metastasis and death from MIS can rarely occur [3, 7]. Enlarged lymph nodes suspicious for metastasis should be sampled for pathologic diagnosis. Sentinel lymph node biopsy is not indicated for MIS.

The choice of surgical technique for MIS varies according to the clinicopathologic characteristics of the MIS, the expertise and resources of

Table 44.7 Comparison of logistics of different surgical treatment options for melanoma

	Conventional WLE	Staged excision	MMS
Who excises the tumor?	Surgeon	Surgeon	Mohs surgeon
Who examines the margin under the microscope?	Dermatopathologist	Dermatopathologist	Mohs surgeon
How is tissue processed?	Formalin-fixed paraffin-embedded sections	Formalin-fixed paraffin-embedded sections	Frozen tissue sections with melanocytic immunostains
Typical delay between excision and microscopic margin evaluation	2–5 days	1–3 days	1–2 h
Percentage of surgical margin examined under the microscope	<1% [26, 27]	Up to 100%, depending on method	100%
Ability to perform same day microscopic margin assessment and reconstruction	No	No	Yes

Adapted from Shin et al. [83]
WLE wide local excision, *MMS* Mohs micrographic surgery

the surgeon, and the preferences of the patients. Conventional wide local excision is highly effective for clinically well-defined MIS on the trunk and proximal extremities. Staged excision techniques and MMS are indicated for MIS at increased risk for subclinical spread and complications from conventional surgery, such as pathologic upstaging, positive margins, local recurrence, and reconstructive surgery prior to complete tumor removal. Clinical factors that increase the risk of complications from conventional surgery of MIS and are potential indications for staged excision or MMS include location on the head, neck, hands, feet, and pretibial leg; recurrence after previous treatment; preoperative size >1 cm; and older patient age (2b) [37, 112]. Table 44.7 summarizes key differences between conventional wide local excision, staged excision, and MMS.

Impact of Patient Preference

When deciding among treatment options, patients place highest value on achieving the highest possible cure rate and avoiding reconstruction until complete removal of the cancer has been confirmed (2b) [113]. Patients also place high value on restoring normalcy to the face and hands [104]. Ensuring complete tumor removal prior to reconstruction is especially important in cosmetically and functional important locations, because subsequent surgeries to address positive margins or local recurrence are more complex [37]. Based on these patient preferences, staged excision or MMS should be strongly considered for MIS on the head, neck, hands, feet, pretibial leg, and genitalia, due to the superior local cure rates and assurance that the reconstruction will be performed only after confirming clear microscopic margins. Conventional wide local excision is sufficient for the vast majority of primary MIS of the trunk and proximal extremities. MIS that has recurred on the trunk and proximal extremities after previous treatments may benefit from staged excision or MMS. When staged excision or MMS is indicated, the choice between the two depends on the expertise of the local surgeons and the patients' desire to confirm clear microscopic margins and reconstruct in single versus multiple visits.

Typical Treatment Plan: Case Discussion

Case 1 A 51-year-old woman presents with a new pigmented lesion on the left prescapular back. Based on the lesion's asymmetric shape,

ill-defined borders, irregular color, and large and evolving size, the lesion is biopsied with a 1–2 mm narrow excision. Histology of the biopsy demonstrates MIS, characterized by a proliferation of atypical melanocytes with confluence along the basal layer of the epidermis, nesting, pagetoid spread, and extension down hair follicles. The patient returns for a wide local excision with 0.5–1.0 cm margins. The surgeon consents the patient preoperatively and excises the MIS with a 1.0-cm margin to the muscular fascia in order to maximize the likelihood of complete removal. The wound is closed immediately with a primary closure. The specimen is sent in formalin to a pathology laboratory. Three to five days later, the surgeon receives a pathology report confirming that the MIS has been completely removed. The lesion does not require any additional treatment. The patient is counseled to return at least annually for skin examinations and to perform regular self-skin and lymph node examinations, due to her increased risk for additional primary melanomas.

Case 2 A 75-year-old man presents with a growing pigmented lesion on the tip of the nose. On clinical examination, the lesion has variegated shades of brown and light tan color. Actinic keratoses and a scar from previous surgery of a basal cell cancer are adjacent to the pigmented lesion. A shave biopsy of the darkest portion of the lesion is performed. Histology of the biopsy demonstrates lentigo maligna, characterized by a near confluence of single atypical melanocytes along the basal layer and pagetoid melanocytosis. The patient returns for MMS with MART-1 frozen section immunostains. The clinically visible tumor is outlined, and the lesion is excised with a 5 mm margin of clinically normal skin to the depth of the perichondrium. Hash marks are made on the excision specimen to maintain orientation relative to patient, and a map of the specimen is drawn. A bandage is placed over the wound, and the patient waits while the tissue is processed, and the Mohs surgeon interprets the microscopic margins. Within 1.5 h, the Mohs surgeon confirms the presence of MIS in the breadloafed vertical section of the debulking excision and detects MIS along 25% of the microscopic margin. The bandage is removed, and the surgeon excises an addition 3–5 mm of clinically normal tissue around the residual MIS. Again, hash marks are made on the excision specimen to maintain orientation relative to the patient, and a map of the specimen is drawn. A bandage is placed over the wound, and the patient waits while the tissue is processed, and the Mohs surgeon interprets the microscopic margins. Within another 1.5 h, the Mohs surgeon confirms that the margins are clear. Reconstruction with a paramedian forehead flap is performed immediately after confirming clear margins. The lesion does not require any additional treatment. The patient is counseled to return at least annually for skin examinations and to perform regular self-skin and lymph node examinations, due to his increased risk for additional primary melanomas.

Safety

The actual procedures have similar safety profiles, except for variations in type of anesthesia. MMS is typically performed with excellent safety under local anesthesia, regardless of the location of the tumor (2b) [114–116]. Conventional wide local excision and reconstruction after staged excision of MIS of the head and neck may be more likely to be performed under general anesthesia, which can increase complication rates (2b) [117].

Differences in the safety profiles of procedures for MIS depend primarily on complications from positive margins or local recurrence. Positive margins or local recurrence increase the complexity of subsequent procedures [37]. Local recurrences may have a more advanced stage than primary melanoma, potentially giving patients a worse prognosis (2b) [118]. To avoid complicated procedures and melanoma progression, surgeons should choose surgical procedures that ensure complete removal prior to reconstruction.

Postoperative Care and Follow-Up

MIS has low risk for metastasis, so postoperative surveillance focuses on physical examination of the scar for local recurrence and total body skin examinations to look for additional primary tumors. The risk for metastasis and death from MIS is not zero [3, 7]; therefore examination of draining lymph nodes of previously treated MIS is also indicated. A diagnosis of MIS increases the risk to develop subsequent invasive melanomas of any stage [8].

Patients who undergo skin cancer screening have melanomas detected at earlier stages than unscreened patients (2b) [119]. Consensus guidelines recommend at least lifetime annual screening [10], which may be adjusted more or less frequently according to the patient's risk.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: Quality of evidence
There is a lack of high-quality evidence for the treatment of MIS [120]	N/A
Conventional wide local excision is effective to treat well-defined primary melanomas on the trunk and extremities [103]	A
Conventional wide local excision of MIS on the head, neck, hands, feet, pretibial leg has >10% risk of positive margins and local recurrence [39]	B
Risk factors for subclinical spread include anatomic location on the head, neck, hands, feet, pretibial leg; persistence or recurrence after previous treatment; size >1 cm; and patient age ≥ 60 [112]	B
Staged excision with microscopic margin evaluation via formalin-fixed paraffin-embedded sections achieves 98% + local clearance rates for in situ and invasive melanomas arising in chronically sun-damaged skin on the head and neck [121]	B
MMS with frozen section MART-1 immunostains achieves 99% local clearance rates for in situ and invasive melanomas in chronically sun-damaged skin [49, 89]	B
Anatomic location and recurrence status identify melanomas that may benefit from staged excision or MMS to detect subclinical spread of tumor prior to reconstruction [37]	B
Imiquimod monotherapy of melanoma results in local recurrence rates of 25% [92]	B

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Self-Assessment Questions

1. A 44-year-old healthy female presents with a new 0.9 cm dark brown macule with asymmetric shape and uneven pigmentation on the right upper back. A shave biopsy of the lesion is performed and is consistent with MIS. Which management option would be the *least* appropriate?
   (a) Conventional wide local excision
   (b) Mohs micrographic surgery
   (c) Staged excision
   (d) Imiquimod monotherapy, five times per week for 6 weeks
   (e) Slow Mohs

2. A 68-year-old male with a personal history of melanoma in situ on the right cheek presents with a 1.2 cm pigmented patch on the left dorsal hand. He reports that this lesion was previously treated with imiquimod cream but persisted. Biopsy of the lesion is consistent with MIS. Which of the following is **not** a risk factor for subclinical spread of MIS in this patient?
   (a) Age ≥ 60 years
   (b) Personal history of melanoma
   (c) Size >1 cm
   (d) Location on the dorsal hand
   (e) Persistence after prior treatment

3. Conventional wide local excision for treatment of MIS of the trunk and proximal extremities is associated with a local recurrence rate of 2%. By contrast, conventional wide local excision for treatment of MIS of the head, neck, hands, feet, pretibial leg, and genitalia is associated with a local recurrence rate of:
   (a) 9%
   (b) 12%
   (c) 17%
   (d) 24%
   (e) 33%

4. A 74-year-old male has a history of melanoma in situ on the vertex scalp diagnosed 3 years ago and treated with conventional wide local excision. He presents to your clinic for evaluation, and exam shows an 8 mm hyperpigmented macule within the surgical scar on the vertex scalp. Biopsy is performed and is consistent with a recurrent MIS. Which of the following treatments have been shown to have the highest local clearance rates (≥98%) in patients with recurrent MIS located on sun-damaged skin of the head and neck?
   (a) Conventional wide local excision
   (b) Staged excision
   (c) Imiquimod
   (d) Mohs micrographic surgery
   (e) Both B & D

5. A 53-year-old female presents with a 0.7 cm dark brown macule on the left upper arm. Biopsy is consistent with lentigo maligna. After a discussion of treatment options, you decide to proceed with conventional wide local excision for definitive treatment of this lentigo maligna. What surgical margin is necessary to achieve a 97% clearance rate?
   (a) 0.3 cm
   (b) 0.5 cm
   (c) 0.9 cm
   (d) 1.5 cm
   (e) 2.0 cm

Correct Answers

1. d: Imiquimod monotherapy, five times per week for 6 weeks. Imiquimod monotherapy of melanoma results in local recurrence rates of 25% [92], whereas properly selected surgical modalities are associated with less than 2% local recurrence rates. Given this patient's young age, good health status, and location of the tumor on the trunk, she has no contraindications to surgical treatment for this MIS. Given the markedly inferior outcomes with imiquimod, its use should be reserved strictly for patients in whom surgery is not an option.
2. b: Personal history of melanoma. Risk factors for subclinical spread include anatomic location on the head, neck, hands, feet, pretibial leg; persistence or recurrence after previous treatment; size > 1 cm; and patient age ≥60 [112]. While personal history of melanoma increases a patient's risk of developing another melanoma, this has not been shown to be a risk factor for subclinical spread of melanoma.
3. b: 12%. Conventional wide local excision is effective to treat well-defined primary melanomas on the trunk and extremities, resulting in a local recurrence rate of less than 2%. Conventional wide local excision for MIS located on the head, neck, hands, feet, pretibial leg, and genitalia has an increased risk for poor outcomes, including a 12% rate of upstaging [103], a 12% rate of positive margins [39], and a 12% rate of local recurrence [49].
4. e: Both b & d. Both staged excision with microscopic margin evaluation via formalin-fixed paraffin-embedded sections and MMS with frozen section MART-1 immunostains achieve 98% + local clearance rates for in situ and invasive melanomas arising in chronically sun-damaged skin on the head and neck [49, 89, 121]. When staged excision or MMS is indicated, the choice between the two depends on expertise of the local surgeons and the patients' desire to confirm clear microscopic margins and reconstruct in single versus multiple visits.
5. c: 0.9 cm. In a case series of 1120 MIS treated with Mohs surgery, Kunishige et al. demonstrated that a minimum of a 9 mm surgical margin is necessary to clear 97% of MIS [20]. Based on existing evidence, expert consensus now recommends surgical margins ranging from 0.5 to 1.0 cm, using the wider end of the range particularly for lentigo maligna [10, 21].

Merkel Cell Carcinoma

45

Iris K. Noh and Christopher K. Bichakjian

Abstract

Merkel cell carcinoma (MCC), also referred to as primary cutaneous neuroendocrine carcinoma, is a rare but potentially aggressive cutaneous malignancy. First described in 1972 as trabecular carcinoma, MCC is believed to arise from Merkel cells which function as mechanoreceptors in the skin (Tang and Toker, Cancer 42(5):2311–2321, 1978; Toker, Arch Dermatol 105(1):107–110, 1972).

Keywords

Merkel cell carcinoma · Merkel cell polyomavirus · Immunotherapy · Radiation therapy · Sentinel lymph node biopsy

Introduction

Merkel cell carcinoma (MCC), also referred to as primary cutaneous neuroendocrine carcinoma, is a rare but potentially aggressive cutaneous malignancy. First described in 1972 as trabecular carcinoma, MCC is believed to arise from Merkel cells which function as mechanoreceptors in the skin [1, 2].

Currently, conclusive evidence regarding the optimal management of MCC is limited due to the rarity of this tumor, and lack of prospective, randomized trials and other high-level evidence. The objective of this chapter is to provide those involved in the care of patients with MCC with the best evidence-based recommendations regarding diagnosis, staging, treatment, and follow-up.

A primary reference for this chapter will be the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, MCC section (5) [3]. This represents a "best practices" consensus document regarding the management of MCC from a panel of recognized national experts in dermatology, surgical oncology, otorhinolaryngology, dermatopathology, medical oncology, radiation oncology, and hematology/oncology. Although this theoretically is level 5/Grade D evidence, it represents a hybrid of recommendations that is primarily based on the highest level of medical evidence available and secondarily on expert opinion.

Epidemiology and Clinical Characteristics

MCC typically presents as a red to violaceous, firm, and non-tender nodule. In one study, a majority of lesions (56%) were presumed benign at biopsy, with epidermoid cyst as the most likely

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diagnosis [4]. The differential diagnosis for MCC may include basal cell carcinoma, squamous cell carcinoma, cyst, pyogenic granuloma, lymphoma, or lipoma. Sun-exposed areas of the body are the most common locations for presentation, with the head and neck region and extremities accounting for 70–90% of all cases [4–6].

The majority of individuals diagnosed with MCC are Caucasian (96%) and at least 60 years of age, with a median age at diagnosis of 76 years. Most studies report a slight male predominance [6, 7]. The US Surveillance, Epidemiology, and End Results registry reports an annual incidence rate of 0.79 per 100,000 persons (approximately 1600 cases annually in the US) and a mortality rate of 0.43 per 100,000. This represents a greater than threefold increase in MCC incidence and mortality from 1986 to 2011, which is likely due in part to a growing aging population [8].

The association with immunosuppression is well documented and seen in approximately 8–15% of individuals diagnosed with MCC [4, 5, 9]. Common underlying causes for the immunosuppressed status may be iatrogenic (e.g., solid organ transplant recipients or individuals with autoimmune disorders) or related to comorbidities such as chronic lymphocytic leukemia or HIV infection [4, 9–13].

Pathogenesis

Recent evidence suggests two distinct tumorigenic pathways for MCC, either ultraviolet- (UV) or viral-dependent. The preferential anatomic distribution of tumors on sun-exposed body surfaces and high proportion of fair-skinned individuals diagnosed with MCC have long suggested UV exposure as an important etiologic factor [6, 14]. Recent studies have identified virus-negative MCC tumors with a high mutational burden characterized by a prominent UV-signature pattern of mutations [15, 16].

In 2008, Feng et al., identified a novel Merkel cell polyomavirus (MCPyV) and described clonal integration of viral DNA in 80% of MCC tumors [17]. MCPyV is commonly acquired as a self-limited childhood infection, and seroprevalence has been reported to range between 59 and 94% among adults in the general population [18, 19]. In MCPyV-positive tumors, MCC tumorigenesis may be promoted as the result of specific truncating mutations of viral T antigens, integration of viral DNA into the human host genome, and inhibition of tumor suppressors such as retinoblastoma (RB1). In support of a dichotomy in MCC tumorigenesis, MCPyV-positive tumors were found to have a low mutational burden and lacked a UV signature [15, 16]. While conflicting evidence exists, some studies suggest that MCPyV-negative tumors may represent a more aggressive subtype associated with a worse prognosis [20].

Diagnosis

Excisional biopsy is preferred for the most accurate diagnosis and microstaging information. Narrow margins are recommended to minimize the risk of inaccurate lymphatic mapping, if a subsequent sentinel lymph node biopsy (SLNB) is indicated [3].

MCC is histologically composed of small round blue cells and can resemble small cell lung cancer (SCLC), melanoma, or lymphoma on standard hematoxylin and eosin (H&E) staining. Additional cytokeratin (CK)-20 and thyroid transcription factor (TTF)-1 immunohistochemical stains should be performed and are best interpreted by an experienced dermatopathologist (4) [21, 22]. CK-20 is a very sensitive (90–100%) but not specific marker for MCC. Up to 33% of SCLCs and 4% of extrapulmonary small cell carcinomas can also stain positively for CK-20. Therefore, staining with TTF-1, which is consistently absent in MCC but expressed in 83–85% of SCLC, is highly recommended. Of note, negative TTF-1 staining supports but does not alone confirm the diagnosis of MCC, since TTF-1 also variably stains extrapulmonary small cell carcinomas (3–42%) [22]. Other immunohistochemical markers with high sensitivity for MCC are synaptophysin, neuron-specific enolase, chromogranin A, neurofilament protein, KIT receptor tyrosine kinase (CD117), BER-EP4, and CAM 5.2 [23]. MCC is invariably negative for S-100 and leukocyte common antigen (CD45), thus distinguishing it from small cell melanoma and lymphoma, respectively.

Staging

Staging is required to help assess prognosis, aid in the counseling of patients, and guide treatment. Because the presence or absence of lymph node metastasis is the most consistent predictor of survival, SLNB is considered standard of care for optimal staging. Numerous studies have confirmed the value of SLN status as a prognostic tool. The incidence of sentinel lymph node (SLN) positivity in patients with MCC without clinical evidence of nodal metastasis has consistently been reported in the 20–50% range regardless of primary tumor size (2b, 4) [24–27]. Immunohistochemical analysis of the SLN with CK-20 and pancytokeratins (AE1/AE3) is critical for acceptable sensitivity and specificity in identifying micrometastatic MCC (4) [28, 29]. Among clinically node-negative patients with localized MCC, 5-year survival rates are consistently better among individuals with pathologically negative nodes (76–97%), compared to those with pathologically positive nodes (42–62%) (2b) [30]. In one study of 364 patients who underwent complete resection of the primary MCC, regional recurrence was 6% in patients with clinically and pathologically negative lymph nodes compared to 21% in patients with only clinically negative lymph nodes who did not undergo pathologic lymph node staging (2b) [31].

The recently published 8th edition of the American Joint Committee on Cancer staging system for MCC is based on the analysis of a total of 9387 MCC cases from the National Cancer Database (2b) [7, 32]. The updated MCC staging system separates pathological from clinical staging to create consistency with all other AJCC staging systems. Approximately 65% of patients with MCC present with stage I or II disease, 26% with stage III, and 8% with stage IV. Stages I and II represent localized disease, in which stage I signifies a low-risk primary tumor measuring ≤2 cm in diameter and stage II a high-risk lesion >2 cm. Stage II is further subdivided to differentiate between primary tumors >2 cm (IIA) and tumors that invade fascia, muscle, cartilage, or bone (IIB).

Stage III represents regional disease; specifically, stage group IIIA includes occult nodal metastasis identified after SLNB or lymph node dissection (LND), whereas IIIB includes clinically or radiologically detected regional lymph node metastasis or in-transit metastasis. The new staging system acknowledges the improved prognostication for patients with clinically detected MCC lymph node metastases without a known primary tumor, who represent approximately 4% of all MCC cases. These individuals, now included in stage group IIIA, are consistently found to have survival rates similar to those with occult nodal metastases, rather than individuals with clinically detected nodal metastases and concurrent primary tumor (stage IIIB) [7]. The most common location of metastasis is the draining lymph node basin (27–60%), followed by distant skin (28–30%), lung (10–23%), central nervous system (18%), bone (15%), and liver (13%) [6, 33]. Stage IV signifies distant metastatic disease.

Imaging

For individuals with localized MCC without clinical evidence of metastasis based on thorough history or physical examination, there is no indication for cross-sectional imaging. SLNB is the most sensitive and specific staging test. While generally unnecessary with appropriate immunohistochemical staining of the primary tumor, appropriate imaging may be considered if a cutaneous metastasis from a primary visceral neuroendocrine carcinoma (e.g. SCLC) cannot be ruled out. Appropriate staging imaging studies are recommended for individuals diagnosed with high-risk MCC, including those presenting with clinically detectable lymph node metastases [3]. Retrospective studies and meta-analyses support use of fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT), citing high specificity and sensitivity due to high metabolic activity of MCC (2a, 2b) [34, 35]. CT alone has varying sensitivity and may be inadequate for bone and bone marrow metastases [35].

There are no prospective studies to evaluate the need for or the frequency of cross-sectional imaging following treatment of MCC. The need for routine follow-up imaging will greatly depend on the stage of presentation, the risk of recurrence, and patient-specific factors such as underlying

co-morbidities. The potential benefit of early detection of metastatic disease should be weighed against the cost and risk to the patient of repeated scans, including false positive results.

Treatment

Localized Disease

Treatment of primary MCC is generally by wide excision with 1–2-cm margins to fascia with the goal to achieve clear surgical margins. However, no prospective data are available to correlate margin size with recurrence risk. Historically, wide excision was performed with at least 2–3-cm margins. Existing evidence suggests that 1-cm margins may be adequate for smaller tumors, whereas 2-cm margins, when possible, may be preferable for larger tumors (stage II). In a study by Allen et al., relatively low local recurrence rates (8%) were obtained with a mean surgical margin of 1.1 cm. In this study, margins >1 cm were not superior in preventing recurrence compared to margins <1 cm (9 vs. 10%, $p = 0.83$ respectively) [26]. In a different study in which Mohs micrographic surgery (MMS) was performed for primary MCC, a mean margin of 1.7 cm with a median of 1 cm achieved negative margins in a group of tumors with a mean diameter of 1.6 cm. A margin recurrence of 4–8% and overall local recurrence of 16% were reported in this group (4) [36]. MMS may be considered as treatment for primary MCC when a tissue-sparing technique is deemed critical, provided it does not interfere with SLNB when indicated. Following excision of MCC in cases where primary closure is not possible, definitive reconstruction should be delayed until margins are pathologically verified as negative [3].

MCC tumors are known to be radiosensitive, and radiation therapy (RT) can therefore be a useful adjunct [37]. It is currently uncertain whether, or under which circumstances, adjuvant RT to the tumor bed provides a more favorable outcome. Most published studies are not standardized in their methods, which makes interpretation of the results problematic and the ability to draw meaningful conclusions difficult. Studies on the adjuvant use of RT for MCC are invariably retrospective with missing or mixed lymph node status, generally lack criteria for selection of adjuvant RT, and often group local and regional recurrences together. Furthermore, much evidence supporting the general use of regional RT in MCC antedates the routine use of SLNB. Representative studies that showed no benefit or benefit with adjuvant RT are listed in the references section for interest (2b, 4) [6, 24, 26, 31, 36, 38–45]. Clinically valuable recommendations regarding this issue come from the NCCN Practice Guidelines in Oncology. In these guidelines it is suggested that following wide excision with clear margins of a primary tumor <1 cm in diameter, without adverse histologic parameters such as lymphovascular invasion, in an immunocompetent patient, adjuvant RT may likely be omitted. Of note, single-institution studies suggest a similar approach for tumors <2 cm (2b) [31, 39]. Following wide excision of a primary MCC under all other circumstances (e.g. larger tumors, adverse histologic parameters such as lymphovascular invasion), or when sufficiently clear surgical margins cannot be obtained, strong consideration should be given to adjuvant RT to the primary tumor bed (2b) [31, 46]. 5-cm RT field margins are recommended with a minimum of 2 cm when anatomy is constraining (4) [3, 47]. Finally, if a patient is deemed inoperable for wide excision of a primary tumor due to comorbidities or based on tumor characteristics, RT monotherapy as primary treatment for MCC may be considered (4) [48–50]. Decisions regarding RT should be made based on multidisciplinary consultation, if possible [39].

Available retrospective studies do not suggest a prolonged survival benefit for adjuvant chemotherapy, which therefore has no established role in the treatment of localized MCC.

Regional Disease

For individuals with primary MCC without clinical evidence of nodal metastasis, SLNB is recommended at time of surgery, for staging and early detection of occult nodal disease [3, 29].

The recommendation relates to primary MCC in all locations, including the head and neck, where successful lymphatic mapping and SLNB can be achieved by experienced surgeons with similar false negative rates as in non-head and neck locations (2b) [51]. Sentinel lymph node biopsy should preferably be performed before excision of the primary tumor to obtain the most accurate lymphatic mapping and lowest risk of a false negative result [3].

A positive SLN confirms the presence of nodal metastasis, which is associated with a poorer prognosis compared to an individual with a pathologically negative SLN [7]. To decrease the risk of nodal recurrence, additional treatment to the involved lymph node basin is indicated. Failure to treat occult nodal disease has been shown to result in higher recurrence rates (4) [24, 52, 53]. However, optimal treatment for occult nodal disease remains uncertain. Completion LND (CLND) has been the most commonly reported treatment in the setting of a positive SLNB and has shown low rates of recurrence in several small case series (4) [52, 54, 55]. For patients with extensive lymph node involvement and/or extracapsular extension, adjuvant RT following CLND should be considered [3]. Radiation therapy has also been reported to be effective as monotherapy for occult nodal disease and may be considered as an alternative therapy for individuals in whom CLND may be associated with unacceptable morbidity [29, 56].

Importantly, if SLNB is negative, patients can be spared the morbidity of additional surgery and/or RT to the regional nodal basin. Several retrospective studies show no recurrence or survival benefit from RT to the regional nodal basin, including the head and neck, following successful lymphatic mapping and a negative SLNB (2b) [24, 25, 57].

When a clinically suspicious lymph node is detected on physical exam or imaging study, fine needle aspirate or core biopsy with appropriate immunohistochemical analysis should be performed to confirm metastatic disease. If clinical suspicion remains following a negative result, open lymph node biopsy should be considered [3]. For clinically detected lymph node metastases, without evidence of distant disease, CLND is considered standard of care, with RT as an alternative treatment for those in whom the morbidity of surgery is deemed to be unacceptable. Adjuvant RT following CLND should be considered for those with extensive lymph node involvement and/or extracapsular extension [32]. However, the available evidence is limited to case reports, retrospective case series, or meta-analyses, and prospective studies are lacking.

While earlier studies suggested a potential benefit from adjuvant chemotherapy with or without RT for patients with high-risk regional MCC [58], subsequent evidence has not confirmed a benefit (2a) [59]. In a prospective study, patients with high-risk localized or regional MCC who received synchronous RT and adjuvant chemotherapy with carboplatin and etoposide did not experience a survival benefit compared to historical controls not treated with chemotherapy (2b) [60]. Given the lack of evidence regarding the benefit of adjuvant chemotherapy and associated morbidity (including immunosuppression, a poor prognostic indicator in MCC), the use of adjuvant chemotherapy following treatment of localized or regional disease with surgery and/or RT is generally not recommended. It should be noted that case series have shown successful palliative treatment of intransit metastases with hyperthermic isolated limb perfusion with tumor necrosis factor α, interferon γ, and/or melphalan (4) [61, 62].

Distant

Historically, the most common systemic chemotherapeutic regimens for metastatic MCC have been combination therapy with cisplatin or carboplatin plus etoposide or second- and third-line chemotherapy regimens (such as topotecan, cyclophosphamide, doxorubicin, epirubicin, or vincristine). MCC is generally very sensitive to chemotherapy, with response rates reported in case reports, retrospective series and reviews as high as 60–70% [63]. However, responses are not durable, generally resulting in tumor recurrences within 4–15 months (2b) [64]. Moreover, the associated toxicity, including chemotherapy-induced immunosuppression, may have an

additional negative impact on survival (2a) [59, 65]. Factors such as an individual's anticipated lifespan and performance status, the anticipated toxicity of the selected chemotherapy regimen, and potential survival benefit should all be considered when deciding upon chemotherapy.

Advances in immunotherapy have dramatically changed the treatment of patients with metastatic melanoma since the introduction of ipilimumab in 2011 [66]. Recent studies cautiously suggest a potentially equally significant impact of immunotherapy on the management of patients with metastatic MCC. Pembrolizumab is an anti-programmed death 1 (PD-1) antibody approved for treatment of melanoma and non-SCLC. A small single-arm phase II trial of pembrolizumab as first-line treatment for 26 patients with advanced MCC recently reported a 56% response rate (4 complete and 10 partial) and 6-month progression-free survival of 67% (2b) [67]. Drug-related grade 3 or 4 adverse events occurred in 15% of the patients.

The first US Food and Drug Administration-approved treatment for metastatic MCC was granted in March 2017 for avelumab, an anti-programmed death-ligand 1 (PD-L1) antibody. Approval was based on data from an open-label, single-arm, multi-center phase II trial of 88 patients with stage IV chemo-refractory MCC. After a median follow-up of 10.4 months, the objective response rate was 32%, including 8 complete and 22 partial responses, with ongoing responses at time of analysis. Serious treatment-related adverse events were reported in 6% of patients; there were no treatment-related deaths (2b) [68]. Of note, response rates to both pembrolizumab and avelumab were regardless of MCPyV status [67, 68].

Results of ongoing and future trials are needed to confirm these initial favorable results of immune checkpoint inhibitors for the treatment of patients with metastatic MCC. Moreover, despite promising results, immunotherapy is relatively contraindicated in solid organ transplant recipients, due to the risk of organ rejection. Ongoing research and the development of targeted therapy are needed to impact the management of MCC in this cohort of patients with a generally poor prognosis. Finally, trial development is currently in progress to determine the role of immunotherapy as an adjuvant treatment for patients with MCC.

Postoperative Care and Follow-Up

Overall recurrence rates for MCC in the literature are generally high, ranging from 40% to as high as 77% on the head and neck, although this may no longer be an accurate reflection of current practice [6, 69]. The median time to recurrence is consistently around 8 months with over 90% of recurrences occurring within 2 years of diagnosis [6, 38, 69]. Therefore, close clinical follow-up with complete total body skin exam, lymph node exam, and focused review of systems with symptom-directed imaging work-up is recommended to monitor for local, regional, and distant recurrence. While no prospective evidence exists, NCCN recommends follow-up every 3–6 months for 2 years and every 6–12 months thereafter [3]. For high-risk individuals, based on disease stage or underlying co-morbidities such as immunosuppression, routine cross-sectional imaging may be considered to monitor for recurrence. Recent studies suggest that determination of MCPyV T-antigen oncoprotein may assist in the management of patients diagnosed with MCC; when present, increasing titers may have a predictive value for recurrent disease [70].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: Quality of evidence
Histologic diagnosis	
Excisional biopsy with narrow margins is preferred to incisional biopsy	D
Appropriate immunohistochemical stains should include CK-20 and TTF-1 to differentiate between primary cutaneous Merkel cell carcinoma (MCC) and metastatic visceral neuroendocrine carcinoma	C
Appropriately experienced dermatopathologists should perform the histopathologic interpretation	D
Staging	
Initial work-up includes thorough history and physical exam with complete skin and lymph node exam	D
Imaging (CT, MRI, PET/CT) may be indicated to rule out distant metastatic disease based on clinical suspicion or in individuals diagnosed with high-risk disease such as clinically detected nodal disease	D
PET/CT has high specificity and sensitivity for metastatic MCC	B
Pathologic lymph node status is the most consistent predictor of survival	B
Sentinel lymph node biopsy should be performed antecedent or concurrent to wide excision for clinically node-negative patients	D
Treatment	
Localized disease (clinically node negative)	
Wide excision with 1–2-cm margins to investing fascia of muscle or pericranium with clear pathologic margins should be obtained whenever possible	C
Adjuvant radiation therapy (RT) to the tumor bed should be considered for larger tumors, adverse histologic parameters, or positive margins	B
Adjuvant RT may be omitted for smaller tumors (e.g. ≤1 cm) without adverse histologic parameters, in an immunocompetent individual	B
Sentinel lymph node positive: completion lymph node dissection (CLND) and/or RT to nodal basin	C
Sentinel lymph node negative: Observation of nodal basin	B
Regional disease (clinical nodal metastasis without distant disease)	
CLND	C
Adjuvant RT following CLND should be considered for those with extensive lymph node involvement and/or extracapsular extension	D
Distant disease	
Clinical trial preferred if available	D
Consider following therapies alone or combination: immunotherapy, chemotherapy, radiation therapy, and/or surgery, as clinically indicated	C
Follow-up	
Complete skin and lymph node exam every 3–6 months for year 1–2 and every 6–12 months thereafter	D
Imaging studies as clinically indicated	D

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Self-Assessment Questions

1. Given the gravity of a diagnosis of MCC, accurate initial diagnosis is critical to facilitate appropriate and timely treatment. Which of the following is FALSE?
   (a) Incisional biopsy is preferred to excisional biopsy with narrow margins.
   (b) MCC is histologically composed of small round blue cells and can resemble small cell lung cancer, melanoma, or lymphoma on standard hematoxylin and eosin (H&E) staining.
   (c) Cytokeratin-20 is a sensitive marker for MCC, but it may also stain positively in small cell lung cancer.
   (d) Thyroid transcription factor-1 is a sensitive marker for small cell lung cancer and is absent in MCC.
   (e) For the highest probability of accurate diagnosis, appropriately experienced dermatopathologists should perform the histopathologic interpretation.

2. Correct staging of MCC is important to help determine prognosis and proper treatment. Which of the following is FALSE?
   (a) The most consistent predictor of survival is lymph node status.
   (b) The incidence of sentinel lymph node positivity in patients with MCC without clinical evidence of nodal metastasis has consistently been reported in the 20–50% range regardless of primary tumor size.
   (c) For asymptomatic patients with clinically localized disease, imaging studies are indicated as part of staging work-up.
   (d) Patients with clinically detected MCC lymph node metastases without a known primary tumor have survival rates similar to those with occult nodal metastases.
   (e) There is no clear evidence that early detection and treatment of asymptomatic distant metastatic disease has a significant impact on survival.

3. MCC most commonly presents as localized disease. Which of the following statements is TRUE concerning the treatment of localized disease?
   (a) Wide excision with 2-cm margins and postoperative radiation therapy is indicated for all primary tumors.
   (b) Wide excision with 1–2-cm margins and antecedent or concurrent SLNB, with or without adjuvant radiation therapy, is indicated for most primary tumors.
   (c) SLNB can be performed either before or after wide excision with equal accuracy.
   (d) Postoperative radiation therapy has been definitively shown to be beneficial in the treatment of localized disease.
   (e) Adjuvant chemotherapy is associated with prolonged survival.

4. MCC may present as regional or distant disease. Which of the following statements is FALSE concerning the treatment of regional or distant disease?
   (a) For clinically detected lymph node disease, fine needle aspiration (FNA) or core biopsy is indicated, followed by appropriate imaging studies if positive.
   (b) When FNA or core biopsy of clinically concerning lymphadenopathy is negative, open lymph node biopsy is appropriate.
   (c) There is evidence definitively substantiating a benefit from chemotherapy in the treatment of regional or distant disease.
   (d) Avelumab, a PD-L1 antibody was FDA approved for stage IV chemo-refractory MCC.
   (e) Immunotherapies have shown up to 30% objective response rates regardless of MCPyV status.

5. All patients with MCC will require close follow-up due to the propensity for recurrence. Which of the following statements regarding follow-up for MCC is FALSE?
   (a) Follow-up schedules for MCC are determined by the fact that the median time to recurrence is 8 months with 90% of recurrences occurring in 24 months.
   (b) An appropriate follow-up schedule is every 3–6 months for the first 2 years and every 6–12 months thereafter.
   (c) At each follow-up visit, a complete skin exam and PET/CT scan should be performed.
   (d) MCPyV T-antigen oncoprotein titer may assist in the management of patients diagnosed with MCC; when present, increasing titers may have a predictive value for recurrent disease.
   (e) The NCCN practice guidelines are an excellent resource to stay current on the latest in consensus and evidence-based treatment recommendations regarding MCC.

Correct Answers

1. a: Incisional biopsy is preferred to excisional biopsy with narrow margins. This is false. Excisional biopsy is preferred for the most accurate diagnosis and microstaging information. All other statements are true.
2. c: For asymptomatic patients with clinically localized disease, imaging studies are indicated as part of staging work-up. This is false. There is no indication for cross-sectional imaging for individuals without clinical evidence of metastasis.
3. b: Wide excision with 1–2-cm margins and antecedent or concurrent SLNB, with or without adjuvant radiation therapy, is indicated for most primary tumors. This is true. A is false because SLNB, a standard of care for MCC staging, is not mentioned. Not all tumors require excision with 2-cm margin and adjuvant radiation therapy. C is false because SLNB should be performed before or concurrent to the wide excision for most accurate mapping. D is false because it is uncertain whether and under which circumstances adjuvant RT provides a more favorable outcome. E is false because available retrospective studies do not show prolonged survival benefit for adjuvant chemotherapy.
4. c: There is evidence definitively substantiating a benefit from chemotherapy in the treatment of regional or distant disease. This is false; MCC is generally very sensitive to chemotherapy; however, response rates are not durable, and treatment is associated with high toxicity. All other statements are true.
5. c: At each follow-up visit, a complete skin exam and PET/CT scan should be performed. C is false because the need for routine follow-up imaging will greatly depend on the stage of presentation, the risk of recurrence, and patient-specific factors such as underlying co-morbidities. All other statements are true.

Dermatofibrosarcoma Protuberans

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Jennifer Hau and Shang I. Brian Jiang

Abstract

Dermatofibrosarcoma protuberans (DFSP) is a rare, slow-growing sarcoma. DSFP has low metastatic potential but may be locally aggressive, exhibiting extensive subclinical extension and a high local recurrence rate. Treatment of disease centers on complete surgical resection with emphasis on negative histologic margins and maintaining good function and cosmesis. Treatment options include Mohs micrographic surgery (MMS), modified MMS, wide local excision (WLE), and WLE with circumferential and peripheral deep-margin pathologic assessment. MMS or modified MMS may allow lower recurrence rates than conventional WLE and may be considered first-line options. WLE with circumferential and peripheral deep-margin pathologic assessment may also enable lower recurrence rate with smaller margins. Postoperative adjuvant radiotherapy may be considered in unresectable disease. Imatinib mesylate may be used for unresectable, recurrent, and/or metastatic cases. Other targeted therapies may be beneficial. Treatment approach should take individual factors into account including patient comorbidities, tumor characteristics, and treatment availability.

Keywords

Dermatofibrosarcoma protuberans · Cutaneous sarcoma · Mohs micrographic surgery · Wide local excision · Imatinib mesylate

Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma. DFSP is typically locally aggressive, with high local recurrence but low metastatic potential.

Epidemiology

DFSP accounts for 0.1% of all malignancies with an annual incidence of approximately 4.1–4.5 cases per million person-years in the United States (2c) [1–3]. DFSP typically presents in the third to fifth decade of life but may present in infants or elderly patients as well [2]. While a slight male predominance has been reported (2c) [4, 5], other large population-based studies have found a slightly higher incidence rate in women [1, 2]. Hence, there seems to be an overall similar incidence of DFSP in men and women (2c) [2, 6]. The annual incidence of DFSP in African

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Americans in the United States is almost twice as high as in Caucasians and significantly higher than other racial groups [1, 2]. A pigmented variant, the Bednar tumor, accounts for approximately 5% of DFSP cases and is more common in black patients [1]. DFSP most commonly arises on the trunk in 42% of cases. Less often, it is found on the upper extremities (23% of cases), lower extremities (18%), and head and neck (16%) [2]. Rare sites of involvement include the breast, vulva, or penis (5) [7].

Risk factors for DFSP development have not yet been defined (5) [8]. Prior traumas have been suggested, though the significance of this association remains unclear. In a study of 12 African-American patients, 4 reported prior trauma (4) [9]. Associations with surgical scars, burn scars, and prior immunizations have also been reported (4) [10]. These studies suggest that approximately 10% of patients with DFSP reported prior trauma at site of the tumor. However, other studies have failed to find an association between DFSP and trauma (4) [11]. As such, the significance of trauma on DFSP development remains unclear [8].

Kurlander et al. reviewed the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) data for 3734 patients with DFSP and found a 25% increased risk of a subsequent primary malignancy. This increased risk was largely due to a 21-fold higher risk of other nonepithelial skin cancers, including a subsequent primary DFSP, and 5-fold increased risk of soft tissue malignancy. Also, women with DFSP had a higher risk of subsequent female hormone-related cancers including breast cancer, other soft tissue cancers, and melanoma (2b) [12]. DFSP onset and an accelerated growth phase have been noted during pregnancy (4) [13, 14]. This raises the possibility of a hormonal influence in tumor development and/or growth, but the association remains uncertain [14]. The increased risk of subsequent primary nonepithelial skin cancers and melanoma is specifically of note as localized tumors would likely require further treatment with cutaneous surgery.

Treatment Overview

Treatment of localized disease, primary or recurrent, is complete surgical resection with negative histologic margins, either by wide local excision (WLE), Mohs micrographic surgery (MMS), or modified Mohs surgery followed by surgical repair. DFSP is characteristically a locally infiltrative tumor that can have an irregular, tentacle-like growth pattern. The tumor may diffusely infiltrate the dermis and subcutaneous tissue, as well as deeply involve fascia or muscle. The extension of the tumor may be difficult to visually define, presenting a challenge for surgical excision and contributing to the propensity for local recurrence (4) [15]. Positive or close resection margin involvement is associated with increased risk of local recurrence [4]. Confirmation of negative margins is paramount, and it should precede reconstructions requiring extensive undermining or tissue movement if possible (5) [16].

Currently, there are no standard margins for WLE [8]. The National Comprehensive Cancer Network (NCCN) and European interdisciplinary group consensus guidelines recommend 2–4-cm margins to investing fascia or muscle or pericranium (5) [16, 17]. WLE using en face tangential sectioning to allow complete circumferential and peripheral deep-margin assessment in pathologic evaluation may lead to a lower recurrence rate (4) [18, 19].

Sometimes the recommended 2–4-cm margins can be difficult to obtain in tissue-limited areas such as the head and neck. Thus, Mohs micrographic surgery is increasing in use and may be preferable for the treatment of DFSP in younger patients or tumors involving the face or neck where tissue conservation is critical. However, there is some concern that residual or peripheral DFSP cells may resemble normal benign scattered spindle cells in dermal tissue, especially in frozen sections even with the use of rapid CD34 immunostaining (5, 4) [20, 21]. This potential difficulty in histologic interpretation prompted some surgeons to send an additional

final margin of tissue for permanent formalin-fixed, paraffin-embedded sectioning and histopathologic evaluation after tumor clearance using frozen section technique. Others prefer avoiding frozen sections altogether and adopt the modified Mohs surgery technique or "slow Mohs" in which all tissue specimens are sent for permanent sectioning at every stage (5) [22].

Regardless of approach for surgical removal, repair of the surgical defect, specifically reconstruction that involves extensive undermining or tissue movement, should be delayed until after negative histologic margins are confirmed. If concern for positive surgical margins exists, split-thickness skin grafting is recommended to allow monitoring for recurrence [16].

Due to the rarity of DFSP, there are no randomized trials comparing WLE with Mohs surgery. Individual tumor characteristics, as well as functional and cosmetic concerns, should be considered when determining surgical approach (2a) [8, 23]. SEER data from 1972 to 2012 demonstrated 3381 cases treated by excision (91.7%) and 305 (8.3%) treated by MMS (2c) [24].

DFSP is radiosensitive and radiotherapy may be used for unresectable tumors, recurrent tumors, or as adjuvant therapy for locally advanced large tumors with positive surgical margins (4) [25]. If negative surgical margins are achieved, adjuvant radiotherapy is not recommended [16]. Over 90% of DFSP tumors have a t(17;22) translocation. The resulting platelet-derived growth factor beta (PDGF-beta)/collagen Type 1A1 fusion gene mutation leads to upregulation of PDGF-beta receptor that can be targeted by the protein tyrosine kinase inhibitor imatinib [15]. Imatinib may be helpful in locally advanced, unresectable, or recurrent disease [22]. Currently, imatinib is recommended for patients with positive surgical margins after re-resection, recurrent disease in functional or cosmetically sensitive areas, or in metastatic disease [15].

A small percentage of DFSP demonstrate higher-grade fibrosarcomatous change with increased cellularity, cytologic atypia, and mitotic rate and a herringbone pattern on histologic exam. These tumors are categorized as a fibrosarcomatous variant of DFSP (DFSP-FS) and are potentially more aggressive [4]. While the prognostic significance of fibrosarcomatous change and/or high-risk features including high mitotic rate in DFSP remains unclear, tumors with these histologic features should be treated according to NCCN guidelines for soft tissue sarcoma. Treatment of these tumors may include surgical excision with appropriate margins, radiation therapy, chemotherapy, and/or observation and supportive care depending on staging (5) [26].

Effectiveness of Treatments

DFSP has the best overall prognosis of soft tissue sarcomas in the US [6]. Overall, 15-year survival is 97.2% and cause-specific 15-year survival is 99.7% [2]. However, morbidity relating to tumor extent can be significant, especially in cases of local recurrence [4].

Historically, in reports from the 1960s to 1980s, wide local excision recurrence rates ranged widely from 11% to 60%, depending on location and surgical margins [22]. Interpretation of past data has been difficult as wide local excision was not well defined and margins not standardized. An association between resection margin and prognosis was demonstrated in a study of 159 patients, 51 of which had involved resection margins and 15 of which had close involvement (<1 mm from margins). At a median 57-month follow-up, 34 recurrences were noted, 29 of which developed in patients with either positive or closely involved margins [4].

As such, recent studies of WLE of DFSP advocate for wider margins and are associated with much lower rates of local recurrence (2c) [27]. In 2006, Monnier et al. performed a retrospective review study of 66 patients from a population-based French cancer registry and found a local recurrence rate of 47% with margins less than 3 cm and 7% with margins from 3 to 5 cm [5]. In 2009, Huevel et al. examined 38 patients in The Netherlands treated with WLE

with 2–3-cm margins and found negative resection margins in 95% and a local recurrence rate of 7% at a median follow-up of 89 months (4) [28]. In a retrospective study of 24 patients with primary or recurrent tumors treated with 2.5–3.3-cm margins, Khatri et al. found a 100% local recurrence-free survival at a median 54-month follow-up (4) [29]. Cai et al. studied 260 patients treated in China and demonstrated that patients treated with margins ≥3 cm had a lower local recurrence rate of 5.7% compared with a 13.6% local recurrence rate in patients treated with 1.5–2.5-cm margins (4) [30]. In a study of 244 patients with DFSP, tumor depth was strongly associated with disease-free survival in primary tumors, underscoring the importance of excision of deep fascia. Margin status was strongly associated with disease-free survival in recurrent tumors (4) [31]. Accordingly, NCCN guidelines have since established margins for wide local excision of DFSP between 2- and 4- cm and down to investing fascia or muscle or pericranium (5) [16, 32]. Additional recent studies have further supported the use of WLE for DFSP (4,4) [33, 34]. Pooled data from the past 20 years demonstrates a local recurrence rate of 7.3% in 1443 patients treated with WLE [22]. However, head and neck lesions have higher reported recurrence rates than other sites treated with WLE, up to 50–75% [23]. Up to 80% of local recurrences occur in the first 3 years after WLE [27].

While it is now largely accepted that wider surgical margins lead to decreased local recurrence, modified surgical and histopathologic approaches with decreased margins have been proposed. In a study of 204 patients, Farma et al. reported only a 1% recurrence rate in patients with DFSP treated using a modified approach with narrower 1–2-cm margins and en face tangential sectioning at a 64-month follow-up period. Defects were not closed until negative complete histologic margins were confirmed. Approximately 20% of tumors treated required multiple excisions [19]. DuBay et al. reported a 0% recurrence rate in 44 patients treated with a multidisciplinary modified WLE approach emphasizing meticulous pathologic exam [18]. Woo et al. found that intraoperative frozen section analysis of wide local excision margins had an accuracy rate of 100% when compared with permanent sections (4) [35]. These studies demonstrate that a meticulous surgical and pathologic approach that allows complete circumferential and peripheral deep-margin assessment in pathologic evaluation enables a lower recurrence rate. In this way, this modified WLE approach shares similarities with the MMS technique [22, 23].

While wide local excision has long been the treatment of choice, MMS has emerged as another effective treatment. The asymmetric and infiltrative architecture of DFSP can make determination of optimal margins for WLE challenging. In a study of 58 patients with primary and recurrent DFSP treated with MMS, Ratner et al. found that microscopic disease was detected beyond 1 cm in 70.7% of patients (4) [36]. Serra-Guillén et al. studied 74 patients treated by MMS and found microscopic disease was detected beyond 1 cm in 46% of cases (4) [37]. These studies demonstrate that subclinical extension can be extensive and vary widely, thus DFSP tumors can benefit from treatment with the MMS technique. Given the size and extent of DFSP, some authors report performing an initial debulk of clinically visible tumor before taking a first layer with wider (0.5–1.0 cm) margin around and under the debulked lesion in order to decrease number of stages required for tumor clearance (5,4) [22, 38, 39]. MMS enables a higher rate of margin clearance at time of excision. Furthermore, MMS may afford smaller defects and subsequently require less complex repairs.

In 1997, Ratner et al. reported an overall recurrence rate of 2% (specifically 0% for primary tumors and 4.8% for recurrent tumors) in a study of 58 patients treated at three institutions from 1981 to 1994 [36]. Loghdey et al. found a recurrence rate of 1.5% in a study of 76 patients treated at one center in the United Kingdom from 1996 to 2013 (4) [40]. In recent years, several other studies have demonstrated similarly low rate of tumor recurrence for patients with DFSP treated with MMS, ranging from 0 to 8.3% [15]. A systematic review of 19 nonrandomized noncomparative trials by Foroozan et al. demonstrated a mean raw recurrence rate of 1.03%

(95% CI, 0.37–2.22%) after MMS with follow-up times of 26–127 months. The mean time to recurrence in these patients was 68 months, later than that seen with WLE. Furthermore, complete excision was achieved with median maximum lateral margins of 1–2 cm [23].

Of four nonrandomized comparative trials reviewed by Foroozan et al., two were performed using fresh frozen tissue sections for MMS, one utilized formalin-fixed tissue sections for modified "slow Mohs," and one study did not clearly specify. Foroozan et al. also examined 19 nonrandomized noncomparative studies. Seven of these studies used fresh frozen tissue sections, six used formalin-fixed tissue sections, and six studies did not clearly specify. Recurrences were reported in six studies using frozen section technique, one with formalin-fixed section and three studies that did not clearly specify. CD34 immunostaining was reported in eight of these studies, predominantly for suspicious cases. However, reports of CD34 immunostaining were unavailable in the majority of studies. Overall, data is lacking to determine whether conventional frozen-section MMS, modified "slow Mohs" using formalin-fixed tissue, and immunostaining enable better outcomes [23].

Interestingly, a study of 3686 patients with DFSP from SEER data revealed that treatment type (wide local excision or MMS) did not influence overall survival [24].

Comparative Effectiveness of Common Treatments

At present, studies comparing WLE and MMS for treatment of DFSP are limited, owing largely to the relative rarity of the condition. In a retrospective review of 48 patients, local recurrence rates were statistically similar even though positive margins were higher in patients treated with wide excision than with Mohs (3.6% for WLE vs. 0% for MMS) (2b) [16, 41]. It should be noted that four of six patients with positive excision margins were subsequently treated with MMS in this study introducing a potential bias (5) [41, 42].

In a nonrandomized comparative trial, Paradisi et al. reported a significantly lower local recurrence rate with modified "slow MMS" versus WLE (1.3 vs. 20.7%). The local recurrence rate difference was even greater in patients with DFSP involving the head and neck, at 1.9% with "slow MMS" versus 51.8% with WLE (2b) [43]. A systematic review performed by Foroozan et al. also demonstrated a lower recurrence of DFSP after MMS (1.11%, 95% CI, 0.02–6.03%) versus WLE (6.32%, 95% CI, 3.19–11.02%) [23]. As a result, many authors argue that MMS is indicated in the treatment of these locally aggressive tumors and is superior to excision for DFSP treatment (5) [24, 43, 44].

In recent years, there have been noteworthy reports of WLE enabling similarly low recurrence rates. These reports highlight a modified WLE approach with meticulous histopathologic exam via en face tangential sectioning. Farma et al. found a 1% recurrence rate with narrow 1–2-cm margins at 64-month follow-up, and DuBay et al. reported a 0% recurrence rate after WLE using a similar technique [18, 19]. The low recurrence rate in these reports emphasizes the value of complete circumferential and peripheral deep-margin analysis [16, 18, 19, 23]. The success seen with this modified WLE approach, as with MMS, centers on a meticulous pathologic examination that includes full margin evaluation.

Aside from the importance of complete margin control and minimizing recurrence rates, superior treatment of DFSP also centers on minimizing the morbidity associated with significant extent of disease and surgical excision that is often required. In a retrospective study of 79 DFSP cases treated from 1990 to 2005, Paradisi et al. found that lesions treated with "slow MMS" were slightly larger clinically (56% of MMS cases were >2 cm versus 44% for WLE), but the postoperative defects were greater in cases treated by WLE (60% of defects from WLE were >10 cm versus 40% for MMS). Though the findings were not statistically significant, the differences suggest that WLE defects were larger as a result of the technique rather than tumor size, in keeping with the tissue-conserving property of the MMS technique [43]. In another study of 62

patients, DFSP tumors treated by MMS were smaller compared with those treated with WLE (5.3 cm^2 versus 14.8 cm^2, respectively). Consequently, the resulting defect was smaller for the lesions treated with MMS compared with WLE (21.7 cm^2 and 63.4 cm^2, respectively) [18].

DuBay et al. found that there was no significant difference in repair with skin grafts or tissue advancement flaps between patients treated with WLE and MMS [18]. In contrast, Meguerditchian et al. noted that in 48 cases of DFSP treated by WLE or MMS, the defect size was similar (10 cm when treated with WLE versus 9.4 cm for MMS), but primary closure was performed more often in cases treated with WLE [41]. The significance of this finding, however, has come into question, as decision for closure is largely determined by surgeon preference [42].

Serra-Guillen et al. performed a prospective study of 74 tumors treated with modified "slow MMS" using paraffin-embedded tissue in which they calculated the minimum margin that would have been needed to achieve complete clearance by conventional surgery and the percentage of healthy tissue preserved by MMS versus wide local excision with 2- and 3-cm margins. They found the mean minimum margin for clearance was 1.34 cm. The tissue conservation afforded by MMS was significant, with 49.4% and 67.9% of healthy tissue preserved when treated with MMS compared with wide local excision with 2- and 3-cm margins, respectively. The authors reported a local recurrence rate of 3% with no lymph node or distant metastasis at a median follow-up time of 59.3 months. A smaller surgical defect typically allows for reconstruction that is less complex and therefore may correlate with fewer postoperative complications and smaller scars. Given the significant percentage of tissue spared with modified MMS, nearly 70% when compared with WLE with 3-cm margins, the authors concluded that MMS likely enables enhanced functional and cosmetic results with less surgical complexity, fewer postoperative complications, and greater potential for monitoring for recurrence [37]. As a result, MMS has the potential to significantly reduce morbidity associated with the locally aggressive nature of DFSP [42].

The majority of local recurrence after WLE, up to 80% of cases, occur in the first 3 years after treatment [27]. The mean time to recurrence in patients treated with MMS was 68 months on average [23].

Decision to treat with MMS or WLE is typically mutually exclusive. However, in some cases a positive margin in WLE has been subsequently treated with MMS [41, 42] or a positive MMS margin has been cleared histologically with WLE [18]. There was no statistically significant difference in recurrence for these cases (4) [45]. Furthermore, a multidisciplinary approach to treatment has also been described in which MMS was performed to establish peripheral margin clearance using paraffin-embedded tissue sections analyzed by a dermatologic surgeon and a dermatopathologist. Deep margin clearance was then obtained in a second stage by wide local excision with a surgical oncologist in a controlled operating room with histologic confirmation by the dermatopathologist. A plastic and reconstructive surgeon then closed the resulting defect [15].

While a systematic review and several nonrandomized trials have demonstrated that MMS recurrence rates are lower and that the MMS procedure enables margin control with smaller resulting defects, it should be emphasized that data at this point is limited [23, 45]. Furthermore, recent reports demonstrate that a standardized WLE technique with meticulous, complete pathologic examination of margins may also enable similarly low recurrence rates [18, 19]. As such, the decision to treat with MMS or WLE should currently be made based on a case-by-case basis taking individual patient and tumor characteristics into account as well as availability and cost.

Preoperative Evaluation and Patient Selection

DFSP should be included in the differential for patients with a slow-growing, indurated plaque or nodule. Incisional biopsy is recommended to enable definitive histologic diagnosis. Immunohistochemical stains aid in histologic

examination; staining for CD34 is mostly positive and Factor XIIIa negative. Other tests, including nestin, apolipoprotein D, cathepsin K, and fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) analysis for t(17;22)(q22;q13), can be useful for diagnosis. NCCN guidelines recommend appropriate confirmatory immunostaining in all cases of suspected DFSP [32]. If clinical suspicion is high and initial biopsy does not confirm diagnosis, rebiopsy is recommended. Multiple biopsies may be required as misdiagnosis is common [16, 32]. A thorough history, review of systems, and physical examination including complete skin exam and palpation of area around tumor and regional lymph nodes should be performed [22].

Imaging is not required in every case and is not routinely performed [22]. However, imaging with magnetic resonance imaging (MRI) may contribute to evaluation of extent of local disease and may be helpful for preoperative planning especially in deeply infiltrative cases (5) [46]. MRI has higher sensitivity and specificity for detecting infiltration depth when compared with palpation (67% sensitivity and 100% specificity vs. 58% sensitivity and 90% specificity, respectively). It should be noted that determination of infiltrative depth via MRI was less precise for tumors located on the head, neck, and upper thorax. MRI was also useful in evaluating recurrent tumors but was not recommended for determining lateral extent of tumors or for detecting persistent tumor in cases of incompletely excised tumors (4) [47].

Lymphatic spread is rare; thus, physical exam of regional lymph node basin is sufficient, and there is not currently a role for sentinel lymph node biopsy. Distant metastasis is also rare, at approximately 1% [22], and is more likely in patients with positive surgical margins and multiple local recurrences (4) [4, 48]. The most common distant metastasis is hematogenous spread to the lung. In cases of extensive local disease or concerning history or physical exam findings, a plain chest radiograph and other imaging may be performed to evaluate for lung metastasis [22].

There have been contradictory reports regarding prognosis in patients with fibrosarcomatous variant of DFSP (DFSP-FS) compared with DFSP. In some reports, no association between DFSP-FS and worse prognosis was found (4) [25, 49]. However, in several other reports, DFSP-FS has been associated with more aggressive behavior and increased metastatic potential (4) [4, 30, 33, 50]. In 2014, a systematic review by Liang et al. demonstrated a higher risk of local recurrence, metastasis, and death in DFSP-FS when compared with DFSP. The study found local recurrence of 29.8% for DFSP-FS versus 13.7% for DFSP, metastasis in 14.4% of patients with DFSP-FS versus 1.1% with DFSP, and death from disease in 14.7% with DFSP-FS versus 0.8% with DFSP (3a) [51]. Therefore, NCCN consensus recommends treating DFSP-FS variant as a soft tissue sarcoma rather than according to guidelines for DFSP [16, 26, 32].

In their analysis of 3686 patients with DFSP from SEER data, Criscito et al. found that older age at diagnosis, male sex, and large tumor size were negative predictors of overall survival. Patients who were male or black were more likely to have large tumors. However, when controlled for tumor size and socioeconomic status, race itself was not associated with worse overall survival. Patients of older age, black race, and those with larger tumors or tumors affecting the head and neck were more likely to receive surgery and radiation compared with surgery alone [24]. Head and neck tumors may also be associated with poor prognosis (4,4,4) [52–54]. Tumors in these locations are also associated with higher rate of recurrence. One contributing factor may be the thinner subcutaneous layer in this location, so that the muscular plane lies closer to the cutaneous surface [47].

In addition to the size and extent of the tumor based on preoperative evaluation, tumor location may also play a role in treatment modality selection. Some authors recommend WLE for trunk and limb lesions, given the relative ease of excision adequate in these locations. The WLE procedure is typically shorter, and most resulting defects may be closed primarily. Head and neck tumors, which have had much higher reported recurrence rates when treated with WLE, may be better treated with MMS. In these sites, it is

difficult to obtain the 2–4-cm margins recommended for disease control, and there are greater functional and cosmetic concerns. The ability to achieve clear margins with smaller defect size afforded by MMS and the lower reported recurrence rates support growing recommendations for treatment of DFSP tumors on the head and neck with MMS [43].

Impact of Patient Preference

Based on data presented above, MMS is associated with low local recurrence rate and potentially smaller resulting defects when compared with WLE. WLE with meticulous pathologic exam of circumferential and peripheral deep-margin assessment seems to also enable low local recurrence rates with smaller surgical defect than conventional WLE. Thus, MMS and potentially WLE with circumferential and peripheral deep-margin assessment may be preferred by patients given the lower associated recurrence rates and by patients wishing to limit size of defect. A smaller surgical defect is also preferable as it likely decreases complexity of repair and subsequent extent of scarring (5) [37, 55].

In addition to modified WLE with circumferential and peripheral deep-margin assessment, MMS, and modified MMS, conventional WLE remains an appropriate treatment, especially as MMS may not be appropriate or available in all cases [37, 55]. MMS has limitations. Some report that MMS is costlier than WLE [40]. There are additional fees associated with WLE, however, including facility fees, cost of general anesthesia, and potential re-excision costs, which should be considered (4) [42, 56]. Furthermore, access to MMS is not widely available, as it requires intensive training and specialized staff [43]. In contrast, access to surgeons able to perform WLE is far greater [45]. Often, treatment with MMS for DFSP implies a staged procedure lasting multiple hours over several days. The average number of stages reported by Paradisi et al. was 1.8, with cases ranging from 1 to 5 stages [43]. Similarly, Serra- Guillen et al. found a mean number of stages of 1.66, with 54% of cases requiring a single stage, 31% two stages, 12% three stages, 1.4% four stages, and 1.4% six stages [37]. For MMS performed with frozen-section technique, processing of large tissue sections can be time and labor intensive. Even in cases where tumor removal and repair may be performed within the same day, the time the patient is in the office may be prolonged [40]. For MMS with permanent sections or "slow Mohs," the procedure may be extended over several days and require multiple office visits, which may cause considerable burden on patients. As MMS is typically performed under local anesthesia, safe dosing limitations and patient discomfort may be limiting factors for larger tumors or deep tumors, even when tumescent anesthesia is employed (4) [43, 57]. Additionally, MMS may not be sufficient for tumor-free margins, as in cases of cortical bone involvement [40].

Given these limitations, a comprehensive, thoughtful treatment plan should be developed on an individual basis with careful consideration of patient and tumor characteristics, cost, and accessibility. Patient counseling and education including risks, benefits, and expectations is integral to determining which treatment modality is preferable [57]. Multispecialty treatment should be considered, especially for deeply infiltrative tumors and large recurrent tumors or for those that may significantly affect cosmesis or vital structures [15, 40].

As noted previously, SEER data from 1972 to 2012 demonstrated 91.7% were treated by WLE and 8.3% treated by MMS. This study also found that patients who were white, female, and/or had higher median household income were more likely to receive MMS versus WLE. This may be related to aesthetic concerns in female patients, who typically presented with smaller tumors. Higher socioeconomic status is associated with increased use of specialized services, including MMS, and there are fewer Mohs surgery practices in lower income, rural areas [24].

Typical Treatment Plan

An otherwise healthy 45-year-old man presented to a dermatology clinic in an urban setting with a 2-year history of a slowly growing, asymptomatic, flesh-colored, indurated, irregular 4 × 3-cm plaque on the upper back. The tumor was largely mobile upon palpation, and no lymphadenopathy was palpated in draining lymph beds. The patient did not have a personal or family history of skin cancer. An incisional skin biopsy was performed and demonstrated dense spindle cells arranged in a storiform pattern extending throughout the dermis and forming a honeycomb pattern at the periphery. Immunohistochemical stains were performed, and the tumor cells stained positively for CD34 and negative for factor XIIIa, thus leading to a diagnosis of DFSP.

For this localized DFSP lesion, surgical excision is the first-line treatment. A thorough discussion regarding surgical options including Mohs surgery and WLE was had with the patient. Decision was made to treat with WLE. As the lesion was located on the trunk, WLE with 3-cm margins was effectively performed. Lesions on the trunk are able to support the wide margins recommended for WLE with less functional or cosmetic impact compared with those located on the head, neck, or distal extremities. For a lesion of this size, WLE performed under general anesthesia would help to minimize patient discomfort. This otherwise healthy patient was able to tolerate general anesthesia without adverse effects. The decision was also made to treat the patient with modified WLE in which frozen histopathologic analysis of en face tangential tissue sections was performed intraoperatively to confirm circumferential and peripheral deep-margin clearance. Although this meticulous pathologic approach is a bit more time and labor intensive, it affords a lower recurrence rate than conventional WLE. This multidisciplinary approach was possible in the urban setting in which the patient lived. After confirmation of clear margins, repair was performed with split-thickness skin grafting.

At follow-up 1 month postoperatively, the graft was intact and well-healing. The patient was instructed on routine self-exam for tumor recurrence. He continued to follow-up every 6–12 months for 3 years, at which time surgical site was evaluated for recurrence, full skin exam was performed to evaluate for subsequent primary cutaneous malignancy, and a detailed history and physical was performed. After 3 years, annual lifelong follow-up was recommended.

If there are novel, less commonly used, or soon to be available treatments for this condition that may also be effective, describe these and their effectiveness (250–500 words).

For treatments that already exist but are less commonly used, describe these treatments, explain why are these less frequently selected, and compare their overall effectiveness to that of more commonly used treatments. For treatments yet to be available, describe how they may work, and what their expected effectiveness is likely to be.

As previously mentioned, DFSP is radiosensitive. There are few and conflicting reports of radiotherapy as primary treatment for DFSP (4) [58–60], and treatment with radiation alone is not recommended (5) [22, 61]. Radiotherapy is recommended for unresectable tumors and considered as adjuvant therapy for locally advanced large tumors and recurrent tumors with positive surgical margins in which further resection is not possible [25]. As adjunctive therapy, radiation decreases the recurrence rate significantly (2b, 2b, 4) [62–64].

Imatinib mesylate, a tyrosine kinase inhibitor, has emerged as an effective treatment for advanced DFSP. Several studies have demonstrated a decrease in tumor burden in some cases of metastatic disease and decreased tumor size in locally advanced cases (4, 5, 5, 4) [20, 65–68]. A multicenter prospective phase II clinical trial was terminated early to poor accrual but demonstrated clinical response in 37.5% of patients with locally advanced or metastatic disease (4) [69]. Current NCCN guidelines recommend imatinib for patients with unresectable, recurrent, and/or metastatic disease [16, 32]. NCCN

guidelines recommend cytogenetic analysis prior to initiating therapy as some tumors lack t(17;22) mutations. However, data regarding the relationship between presence of mutation and lack of response is conflicting (4) [20, 68, 70, 71].

As tumors are often large, preoperative imatinib to decrease tumor size prior to surgery would significantly decrease morbidity from disease. However, the role of neoadjuvant imatinib in patients with locally advanced disease still remains unclear. In a French study of 25 patients with primary or recurrent DFSP, patients received imatinib for 2 months prior to WLE. Only 36% of patients responded, and long-term follow-up data is needed (4) [72]. A multicenter phase II trial in Germany evaluated 16 patients with locally advanced or recurrent disease who received imatinib prior to surgery. The median treatment duration was 3.1 months, and 7.1% of patients had complete response, 50% had partial response, 35.7% had stable disease, and 7.1% had progressive disease. Median tumor shrinkage was 31.5%. One patient developed resistance to imatinib and later died of distant metastasis, but no other patient had resistance, recurrence, or metastasis [71]. It is unclear whether neoadjuvant therapy enables smaller surgical margins. More evidence is needed to determine the efficacy of imatinib prior to surgery, including long-term follow-up data as well as further investigation into optimal dosing and duration of treatment (5) [22, 73].

Few case reports have suggested that DFSP may respond to other tyrosine kinase inhibitors that target the PDGF receptor, such as sorafenib and sunitinib (5,4) [74, 75]. These treatments may be useful in cases resistant to imatinib. In a study of 30 patients treated with sunitinib after imatinib failure, 6.7% had complete response, 33.3% had partial response, 40% had stable disease, and 6% had progressive disease [75].

Safety

A multicenter study of 20,821 tumors has demonstrated that MMS is a safe procedure with very low rate of adverse events (0.72%). These complications included bleeding and hematoma (15.4% of complications), surgical-site infection (61.1%), and full or partial necrosis and dehiscence (20.1%). Serious adverse events requiring hospitalizations are rare (0.02%), and rate of permanent disability and mortality undetectable (0%). It should be noted that only 0.6% of the 20,821 tumors treated in this study were rare nonmelanoma skin cancers other than basal cell carcinoma and squamous cell carcinoma (1b) [76]. DFSP lesions can be larger and more deeply infiltrative than other more common skin cancers treated with MMS and could therefore be associated with higher rates of adverse events.

MMS for DFSP treatment may be challenging, especially for large tumors. Adequate analgesia may not be attainable for large tumors. Even with tumescent anesthesia, safe dose amounts can be a limiting factor [43, 57]. Of 14 aborted MMS cases referred for reconstruction at a single private suburban plastic surgery practice from 2005 to 2008, 50% were halted due to intolerable pain. These defects had an average surface area of 34 cm^2. DFSP accounted for 33% of aborted cases, and the average surface area of these defects was 42 cm^2. Furthermore, high individual anxiety levels and lower pain thresholds can also play a role, and patients who may not tolerate a procedure under local sedation would benefit from sedation or general anesthesia (4) [77].

For soft tissue tumor resections, wound complications also include dehiscence, cellulitis, abscess, seromas, hematomas, and necrosis (4) [78]. Reports of complications specifically associated with WLE for DFSP are limited. Kim et al. evaluated 90 cases of DFSP treated with WLE. Mean lateral margin was 2.94 cm, and 64.4% of excisions included removal of deep fascia. Skin grafts were performed in 38.9%, primary repair in 27.8%, local flap in 23.3%, and free flap in 10%. There were no major complications. Minor complications were partial graft loss, local flap congestion, and wound dehiscence [34]. Cai et al. reported on 236 patients with DFSP who received wide excision. Again, there were no serious adverse effects. Soft tissue reconstructive procedures, principally split-thickness skin graft and/or pedicle flap, were performed in 92 patients. Complications were only seen in these patients

who received soft tissue reconstructive procedures and consisted of necrosis of skin graft in 22 cases, wound infection in 6 cases, and dehiscence and infection in 2 cases [30]. For 206 patients treated with narrow-margin (1–2-cm) WLE and en face sectioning for pathologic exam, 69% were repaired with primary closure, 25% with skin graft, and 4% with tissue flaps. Postoperative complications were observed in 11% of patients and included wound dehiscence (4%), infection (3%), failed skin graft (1%), and hematoma (1%) [19]. These studies demonstrate that WLE may be associated with minor wound complications, and no serious adverse effects were reported.

Comparative safety data is scant. In a nonrandomized study comparing MMS with WLE treatment for DFSP, Meguerditchian and colleagues reported no significant difference in the postoperative wound healing and infection rates between the two treatments [41].

For patients receiving adjuvant radiation therapy, moderate fibrosis or telangiectasia may result in the radiation field (3a) [63, 79]. In 53 patients treated with either preoperative or postoperative radiation therapy adjuvant to surgical resection between 1972 and 2010 at a single institution, complications were observed in 6 patients (11%) at a median time of 9.5 months. Four were classified as severe, including skin graft failure, and two had associated soft tissue necrosis. Three patients required subsequent surgical intervention [25]. However, in 2015, a systematic review of 12 studies including a total of 167 patients with DFSP receiving adjuvant radiation treatment demonstrated no other significant complications, and gradual advances have enabled an improved toxicity profile of radiotherapy over time [79].

Postoperative Care and Follow-Up

As DFSP has historically been associated with a high local recurrence rate, follow-up and clinical evaluation of the primary site should occur every 6–12 months and routine self-examination encouraged. At follow-up visits, a guided history and physical should be performed. Routine imaging or other testing is not recommended. Metastasis is rare, but if the history and physical above compel further work-up, additional imaging studies should be performed [16]. The majority of local recurrences after WLE occur within 3 years. However, in 25–30% of patients, local recurrence appears after 5 years (4) [4, 5, 80, 81]. According to a systematic review of the efficacy of MMS for the treatment of DFSP, average time to local recurrence was 68 months. Thus, an extended follow-up period well beyond 5 years is encouraged, and lifelong surveillance should be considered [1, 23, 38, 80, 81]. Many recommend patient follow-up every 6 months for at least 3 years and then annually thereafter [52, 61]. As patients with DFSP have an increased risk of subsequent primary malignancy, patients may also benefit from lifelong dermatologic surveillance for another primary DFSP, other nonepithelial skin cancers, and melanoma in addition to monitoring for local recurrence [12].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
DFSP most commonly affects both men and women in the third to fifth decade of life	B
Older age at diagnosis, male sex, and large tumor size are negative predictors of overall survival	B
Perform confirmatory immunostaining in cases of suspected DFSP	D
Extensive work-up including imaging is not routinely indicated, unless concerning history and physical findings or histologic features are present	D
For localized disease, treatment options include MMS, modified Mohs, WLE with circumferential and peripheral deep-margin pathologic assessment, and WLE	B
Perform WLE with 2–4-cm margins to investing fascia or muscle or pericranium	B
WLE with circumferential and peripheral deep-margin pathologic assessment may enable lower recurrence rate with smaller margins	C
MMS or modified Mohs can be used as first-line treatment of DFSP, especially for areas more prone to recurrence	B
MMS or modified Mohs enables a lower recurrence rate than conventional wide local excision	B
No significant difference in the postoperative wound healing and infection rates between WLE and MMS was found	C
Tumor depth of primary tumors and margin status of recurrent tumors are predictors of disease-free survival	C
Delay reconstruction with extensive undermining or tissue movement for reconstruction until negative margins confirmed	D
Postoperative radiotherapy may be used as adjuvant therapy for unresectable disease	B
Adjuvant radiotherapy is not recommended if negative surgical margins are achieved	B
Imatinib may be used for unresectable, recurrent, and/or metastatic cases	B
There is a 21-fold higher risk of other nonepithelial skin cancers, including subsequent primary DFSP	B
Follow-up and clinical evaluation of the primary site should occur every 6 to 12 months	D
Majority of local recurrences after WLE occur within 3 years	B
Average recurrence after Mohs was 68 months [23]	B
Follow-up should continue for many years or consider lifelong follow-up	D

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Self-Assessment Questions

1. What factor is associated with disease-free survival?
   (a) Patient age
   (b) Recurrent tumor
   (c) Tumor depth
   (d) Tumor size
   (e) Male sex

2. What factor is associated with decreased overall survival?
   (a) Treatment with MMS
   (b) Treatment with WLE
   (c) Black race
   (d) Male sex
   (e) Tumor location

3. After wide local excision, most local recurrences occur:
   (a) Within 10 years
   (b) Within 6 months
   (c) Within days
   (d) Within 3 years
   (e) Within 20 years

4. More aggressive tumor behavior is associated with:
   (a) Pigmented DFSP
   (b) Fibrosarcomatous change
   (c) Myxoid DFSP
   (d) Atrophic DFSP
   (e) Bednar tumor

5. Appropriate margins for WLE of DFSP would be:
   (a) 5 mm
   (b) 1 cm
   (c) 3 cm
   (d) 5 cm
   (e) WLE is not an appropriate treatment

Correct Answers

1. c: Tumor depth. Strong predictors of disease-free survival are tumor depth and margin status. However, tumor size, patient age, and gender were not significantly associated with disease-free survival [31].
2. d: Male sex. Older age at diagnosis, male sex, and larger tumor size may be negative predictors of overall survival. Male patients with DFSP had almost twice a risk of depth compared with female patients. Treatment modality (WLE and MMS) and anatomic site were not found to affect overall survival [24].
3. d: Within 3 years. After WLE, up to 80% of tumor recurrences occur within 3 years. However, 25–30% may develop after 5 years. Therefore, close monitoring is recommended for at least 3 years, and lifelong annual monitoring should be considered [4, 5, 80, 81].
4. b: Fibrosarcomatous change. Pigmented DFSP and Bednar tumor are the same entity. Histologic variants of DFSP include myxoid, atrophic, pigmented (Bednar tumor), and fibrosarcomatous [52]. A systematic review by Liang and colleagues reported a higher risk of local recurrence, metastasis, and death in DFSP-FS compared with DFSP [51].
5. c: 3 cm. WLE is a recommended first-line treatment of DFSP. NCCN guidelines recommend 2–4-cm margins to investing fascia or muscle or pericranium. Histologic confirmation of negative margins is important. Narrower margins (1–2 cm) may also enable lower recurrence rates if meticulous circumferential and peripheral deep-margin pathologic assessment via en face tangential sectioning is employed [16, 32].

Surgical Scars

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Shilpi Khetarpal, Jeffrey S. Dover, and Kenneth Arndt

Abstract

The realm of scar therapeutics is constantly changing. Several factors need to be considered when developing a comprehensive treatment plan for scar rehabilitation, including those related to the patient and the nature of the scar. Scar characteristics can be divided by color, scar type and thickness, and body location. Many agents including topical, intralesional, light and laser-based treatment modalities can be used to revitalize and restore damaged skin. The most commonly used lasers are the pulsed-dye laser (PDL) and either fractional ablative or fractional nonablative devices. Ideally, a combination approach using topical and intralesional medications along with PDL and a fractional laser should be considered in all patients wishing to undergo treatment of their scars.

Keywords

Scars · Hypertrophic scars · Keloids
Pulsed-dye laser · Fractional resurfacing
Microneedling

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Scars are formed as a reaction to dermal injury and are characterized by local fibroblast proliferation and production of new collagen. They are the final result of many common dermatologic and surgical procedures and are the final product of wound healing. Scars can affect patients of all ages and ethnicities. Wound healing is a complex process resulting in a scar. During the wound healing process, angiogenesis occurs that is apparent clinically as erythema, telangiectasia, and edema (1a) [1]. Collagen production and other extracellular matrix substances lead to the formation of a scar, which can lead to both functional and emotional difficulties and quality of life impairment. Surgical scars take approximately 1 year to fully mature. They continue to improve in appearance after 1 year (1a) [2]. The cosmetic appearance is problematic to patients who have surgical scars on their face or other visible areas. Scars are unpredictable and vary from person to person; they can present in different forms including keloidal, hypertrophic, or atrophic. They also vary based on body location and color. It is important to consider the tension, texture, and erythema of a surgical scar. There are numerous approaches when treating a scar. All the therapies aim to improve the appearance of a scar, as they are difficult to erase completely.

Current available treatment options for scars include a combination of topical and intralesional medications, surgical interventions, laser and light devices, and microneedling. Ultimately,

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depending on characteristics of the scar, some combination should be used to yield the best outcome. During the twentieth and early twenty-first century, the treatment of scars changed—the goal was no longer tissue replacement but rather tissue rehabilitation. Various modalities were used to improve the appearance of scars including topical, intralesional, and light and laser-based treatment modalities, all of which attempted to revitalize and restore damaged skin (1a) [3]. Topical medications include silicone gels and sprays, which decrease inflammation and thereby contribute to less scarring. While topical agents are convenient and non-invasive, few have shown the ability to significantly improve cosmetic and functional aspects of scars (1b) [4]. Intralesional medications that have shown efficacy include triamcinolone, 5-fluorouracil, mitomycin, bleomycin, interferon, and retinoic acid, which all target fibroblast growth and collagen production. The downside of intralesional agents is that they require serial injections over the course of weeks to months and take time to show an effect (2b) [5]. More aggressive therapies such as dermabrasion, radiation, and chemical peels have also shown to be effective. Dermabrasion is relatively quick and inexpensive; however, it requires local anesthesia and wound care for 7–10 days after treatment and can cause post-inflammatory hyperpigmentation (4) [6]. Prior to beginning therapy for scar rehabilitation, it is essential to gather information from the patient regarding time and mechanism of injury, comorbid conditions, current symptoms or functional limitations, psychological factors, and current or prior treatment and procedures (1b) [7]. It is also important to keep in mind other factors such as Fitzpatrick skin type, age, pain tolerance, symptom relief, and downtime when developing a treatment plan.

Surgical Intervention

If a surgical scar has significant tension or webbing, surgical revision is often warranted. [2] Fusiform excision is the most basic technique for surgical revision. It involves re-excision of the entire linear surgical scar with narrow margins. It can improve the appearance of the scar; however, it results in a longer incision line compared to the original scar. This technique is recommended for shorter scars.

A Z-plasty can be used if a fusiform excision is not possible. It breaks a linear scar down into a series of irregular lines, making the scar less apparent [2].

Lasers

In the late 1990s the advent of laser approaches changed the treatment of scars. These devices enabled treatment to bring about excellent results with minimal downtime with an overall low risk (3a) [8]. Lasers can improve various characteristics of scars including erythema, hyperpigmentation, atrophy, hypertrophy, and may decrease tension to increase functionality. These improvements lead to reduction in symptoms, improving functionality and cosmetic appearance (2a) [9]. They play a role in minimizing post-surgical scars as well as reducing the appearance of established scars. The most commonly used lasers are the pulsed-dye laser (PDL) and either fractional ablative or fractional non-ablative devices. These lasers improve vascularity, pigmentation, and scar thickness.

Vascular Lasers

Angiogenesis is an essential step in the development of scars, and lasers that target this proliferation of vessels are effective at improving many scar characteristics. The principle of selective photothermolysis described by Anderson and Parrish in 1983 supports the use of vascular lasers to treat surgical scars given that the target is hemoglobin (1b) [10]. By selecting the appropriate wavelength, pulse duration, and energy for a specific target, select thermal destruction of the target vessel occurs without damaging the surrounding tissue.

The pulsed-dye laser (PDL) is the gold standard for treatment of surgical scars, and there is a great deal of data which support its use and effectiveness (Ib) [11]. It is the most commonly

used laser to target vascular structures within a scar. Its effectiveness is attributed to its vascular specificity. It targets oxyhemoglobin within small blood vessels in the scar as well as telangiectasia in the surrounding skin, leading to decreased erythema and improved cosmetic appearance [2]. The PDL has been shown to stimulate collagen production and improve scar texture when used at sub-purpuric fluences. It can also provide long-term improvement in scar erythema, pliability, thickness, and pruritus [1]. It is recommended to treat the erythema of a scar prior to performing other procedures that might increase surrounding erythema and alter the optic absorption of vascular laser wavelengths. The potassium titanyl phosphate (KTP) laser is also vascular specific with a wavelength of 532 nm. A recent study done by Keaney et al. compared the PDL and KTP for the treatment of erythematous surgical scars [6]. Twenty patients with skin phototypes I to IV with matched bilateral erythematous surgical scars or a single linear erythematous scar > 5 cm less than 24 months old were included in the study. Scars were divided into equal halves with each half randomized to receive three successive treatments at 6-week intervals with either a 532 KTP laser (Excel V; Cutera) or a 595 nm PDL (Cynergy; Cynosure). Laser parameters were fixed for both devices; 532 nm laser settings were 4.6 J/cm^2, 3 ms, and a 7-mm spot while the 595 nm PDL settings were 4.5 J/cm^2, 2 ms, and a 7-mm spot size. Blinded physician assessment was done at baseline and 12 weeks after the third laser treatment using the Vancouver scar scale (VSS) including vascularity, pigmentation, pliability, and height were evaluated. The average scar age was 6.9 months and all scars were in nonfacial locations. Although improvement in scars was seen with both lasers, the KTP was found to be slightly more effective at reducing scar erythema, which was attributed to enhanced oxyhemoglobin absorption. The KTP treatments were found to be more painful and resulted in more erythema and edema when compared to the PDL. The KTP also has the potential for enhanced melanin absorption compared to the PDL, which can increase the risk for epidermal injury and pigment alteration.

There is debate as to how soon after a scar is formed laser treatment should be commenced. Several studies support the use of PDL shortly after suture removal (1b) [12]. Martinez et al. evaluated the improvement of scars, both clinically and histopathologically, resulting from dermatological surgery treated with PDL (1b) [13]. A split-scar study was performed with 30 patients, who were all Fitzpatrick skin types III or IV, where half of the scar was treated with a 595 nm PDL (Vbeam laser, Candela, Wayland, MA) settings of 7–8 J/cm^2, 1.5 ms pulse duration, and a 7 mm spot size for a total of three treatments. The other half of the scar was untreated and served as the control. Skin biopsies were obtained before and after laser treatment. Both the clinical evaluators of the scars and the pathologist examining the tissue were blinded. The histologic examination showed a presence of new collagen in seven out of ten PDL patients compared to three of ten in the placebo group, making it statistically significant. There was significant improvement on the Vancouver scar scale (VSS) in the treated half compared to the untreated half, including less erythema and improved texture. There was no difference in the inflammatory infiltrate. In summary, PDL has been proven to reduce scarring induration, swelling, erythema, and dysesthesia with minimal adverse events when treating surgical scars [1].

Fractional Lasers

Fractional lasers are the gold standard when treating the textural and structural abnormalities of scars. Both ablative and non-ablative fractional lasers have become the mainstay of scar treatment. Fractional lasers can be ablative (wavelengths of 2790–10,600 nm) or non-ablative (wavelengths 1320–1927 nm). Laser scar revision is based on the principle of controlled thermal injury to induce healing and remodeling in a specific area. The concept of fractional photothermolysis originated years ago but was formalized within the last decade and has revolutionized the management of scars. These lasers rely on bulk heating, which leads to significant thermal

injury (2b) [14]. They produce arrays of nonselective, microscopic thermal damage zones (MTZs) throughout the epidermis and dermis, to a specific fraction of the total area treated (2a) [15]. The MTZs lead to tissue contraction and induce tissue remodeling and production of new collagen, thereby improving the scar. Histological studies show tissue remodeling for up to 6 months after treatment leading to long-lasting results (2a) [16]. Laubach et al. described the histological changes induced by fractional photothermolysis in 2006 (1b) [17]. They showed the thermally damaged epidermal keratinocytes were replaced within 24 h and complete healing occurred after 7 days.

Fractional devices allow for islands of sparing in a treatment area that allow for rapid repair and stimulate collagen remodeling. Ablative fractional resurfacing (AFR) and non-ablative fractional resurfacing (NAFR) have similar mechanisms of action; however, AFR devices destroy the epidermis and dermis, while NAFR keeps the epidermis intact and forms MTZs in the dermis only. Because of this difference, AFR devices are more effective but also have more downtime and an increased risk of scarring when compared to NAFR devices (2a) [18]. Ablative devices produce a pattern of ablation and coagulation extending from the stratum corneum into the dermis with varying density and depth, separated by normal, undamaged skin. AFR devices penetrate the reticular dermis, allowing for more skin tightening when compared to traditional ablative devices [1]. Tightening is achieved by contraction of the collagen fibers in response to the denaturing laser-generated heat. As fluence increases, so does residual thermal damage, thereby causing more tightening. Fractional ablative devices include the 10,600 nm focused CO_2, the 2940 nm Er:YAG, and the 2790 nm erbium, chromium-doped yttrium scandium-gallium-garnet (Er, Cr-YSGG). Er:YAG has a higher affinity for absorption by water so its columns have a narrower rim of thermal coagulation when compared to CO_2. Fractional ablative devices have shown to improve scars by decreasing the vascularity, pigmentation, and scar thickness. AFR devices are preferred over fully ablative devices given improved safety profile and increased healing time.

Ozog and Moy demonstrated improved appearance and texture of Mohs surgical scars when treated with AFR at the time of surgery (1b) [19]. Their goal was scar prevention, rather than treatment. In addition, it was also more efficient given the laser treatment was done at the same time as surgical closure, avoiding the inconvenience of a repeat visit and anesthetic of an additional procedure. There is very little literature discussing the role of AFR at the time of surgery. It is hypothesized that compounding the laser thermal injury with surgical injury may lead to more scarring; however, preliminary studies show improvement in scar texture and color when done at the same time. A pilot porcine study by Baca et al. showed no difference in scar formation when treating surgical incisions with AFR [14]. This was based on histologic and photographic analysis. Future studies with larger sample sizes should be done to better elucidate if a true difference exists.

AFR has recently been used to help facilitate percutaneous drug delivery in the treatment of both hypertrophic and atrophic surgical scars. Microscopic ablative channels allow for drug delivery and even distribution within the tissue. Waibel et al. showed enhanced improvement in hypertrophic scars with laser-assisted drug delivery of topical corticosteroids (1a) [20]. Although the ablative channels remain open for several days, optimal absorption occurs when the medication is applied immediately following the laser procedure. It is recommended to use a Kenalog (triamcinolone acetonide) concentration of 20–40 mg/mL, depending on the thickness of a scar, applied topically until there is uniform coverage of the treated area. [2] Rkein et al. showed improvement of atrophic surgical scars treated with AFR followed by topical application of poly-L-lactic acid (each bottle diluted with 6 mL of sterile saline and 2 mL of 1% lidocaine) (2b) [21].

NAFR devices are helpful for atrophic scars; there is no bleeding because it creates a cylindrical zone of coagulation rather than a “hole.” By keeping the epidermis intact, NAFR has a lower risk of infection, pigment alteration, and further

scarring when compared to AFR. NAFR devices are the treatment of choice for flat, atrophic scars. They are also safer for darker skin types because they produce a number of narrow deeper wounds which maximize improvement in texture [2]. A significant advantage of NAFR compared to AFR is less downtime combined with an improved side-effect profile. As discussed previously, scars with erythema should be treated with a vascular laser prior to the use of fractional resurfacing. However, many clinicians have noted successful scar revision when combining PDL treatments followed by NAFR on the same visit. Several treatments are required, typically 4–6 weeks apart, and it is essential to lower the settings of each device to avoid complications [2]. Combination therapy can be considered as soon as 2 weeks after suture removal. In addition to PDL followed by NAFR, Intralesional Kenalog (ILK) and intralesional 5-FU can be performed after NAFR to avoid ulceration from bulk heating secondary to an increase in the aqueous target of NAFR (4) [22].

There is limited data comparing the final cosmetic scar of traditional fully ablative resurfacing versus ablative fractional resurfacing. Tidwell et al. looked at the difference in a split-scar study in 20 patients using the fully ablative Er:Yag compared to the fractional ablative Er:Yag (1b) [23]. The scars were treated at monthly intervals for 3 months and then followed up at 1 month and 2 months after the last treatment. Entities such as scar erythema, height, texture, and overall cosmetic appearance were examined, in addition to patient satisfaction and quality improvement. Both patients and physicians saw statistically significant improvement with the fractional ablative Er:Yag compared to the fully ablative device. One subject found improvement in scar thickness with the ablative Er:Yag. The downside of this study was the short follow-up of 5 months. Many argue that the final outcome of a scar cannot be assessed until after 12 months (3a) [24]. It is thought that ablative lasers in hypertrophic scars elicit a change in the expression of heat shock proteins, matrix metalloproteinases, tissue inhibitors of metalloproteinases, and transforming growth factor-beta that cause collagen remodeling (2a) [25]. In summary, AFR should be reserved for thicker scars and NAFR should be used for atrophic scars.

Non-ablative, Non-fractional Lasers

The role of fractional ablative, fractional non-ablative, and pulsed-dye lasers have been established in the literature. However, the role of the microsecond pulsed non-ablative 1064 nm neodymium yttrium-aluminum-garnet (Nd:YAG) laser is poorly defined. The Nd:YAG is a non-ablative, non-fractional laser that has less potential risk when compared to ablative lasers. Non-ablative lasers have a lower risk of infection, scarring, pigment alteration, and persistent erythema (2a) [26]. Tenzel et al. performed a split-face, prospective study that evaluated the use of 1064 Nd:YAG in the treatment of direct browplasty scars (1c) [27]. Scars that were less than 3 years old were treated at 2-week intervals for a total of six treatments. Laser parameters were pulse duration of 300 ms, energy of 14 J/cm^2, spot size of 5 mm, and pulse rate of 7–10 Hz for a total of 500 pulses per treatment (Xeo, Cutera, Brisbane, CA). Scar erythema, pigmentation, and height were evaluated in nine male subjects. Treatments were tolerated well with minor side effects of redness and swelling. All subjects reported improvement in the treated scars, even subjects whose scars were over 2 years old, while no subjects noted improvement on the control side. These data suggest that there may be benefit to delaying laser treatment after surgery until the inflammatory phase has subsided, however further studies are warranted.

Ezra et al. evaluated the microsecond 1064 nm Nd:YAG laser's ability to improve surgical scars after Mohs micrographic surgery (MMS) (2b) [28]. Ten patients underwent treatment for their surgical scars after MMS with treatment settings of 0.3 ms pulse duration, energy of 13–16 J/cm^2, 5 mm spot size, and repetition rate of 4–10 Hz (Laser Genesis, Cutera, Brisbane, CA). Most patients received their first laser treatment 5–8 weeks after surgery. Four patients had complete resolution of an ectropion or eclabium that

formed secondary to scar contracture as a result of MMS. For the 10 patients in this study, the Nd:YAG was found to help both the cosmetic and functional problems caused by surgical scars. The mechanism of action for scar improvement occurs by laser heating of the dermis, without damaging the epidermis, due to selective absorption of energy by oxyhemoglobin in the dermal capillaries [15]. The microsecond pulse duration allows for partial thermal relaxation of dermal capillaries, which causes gradual heating of the dermis and prevents collagen denaturation. The laser is thought to stimulate extracellular matrix and new collagen formation leading to scar improvement. The fibroblasts that produce new collagen are downregulated by the Nd:YAG laser, leading to less collagen production which decreases the appearance of a hypertrophic scar (1b) [29]. Decreased vascularity and heat shock protein stimulation are some of the alterations in dermal collagen architecture that can be seen after treatments with the 1064 nm Nd:YAG laser. The improvement in contractures is thought to occur by redistribution of collagen. In addition, since the epidermis is protected, the risk of infection and need for post-treatment care is eliminated, which can be beneficial in certain situations. It is recommended that laser treatments begin 6 weeks after surgery and subsequently at 4–8-week intervals. Although an endpoint is not defined for this device, it is important to be guided by patients' sensation of heat, which typically occurs between 43 °C and 46 °C.

Intralesional Medications

Intralesional Kenalog (ILK) (triamcinolone acetonide) and 5-fluorouracil (5-FU) can be used as first-line therapy for hypertrophic or keloidal scars, after erythema has been addressed. [2] Monthly ILK injections can be done until there is flattening of the scar. Several treatments are typically required using small aliquots of 20–40 mg/mL. The volume injected should not exceed 0.1 mL per 1 cm of scar. Skin blanching should occur when the appropriate amount is injected. If steroid is injected too frequently, at high concentrations or into the subcutaneous fat, epidermal atrophy can occur. An advantage of intralesional 5-FU is that it can be used in thickened scars without the risk of atrophy. Davison et al. showed the combination of 75% 5-FU and 25% triamcinolone (40 mg/mL) was superior to ILK alone when 0.1 mL was injected into 1 cm of scar (2a) [30]. It is important for the clinician to keep in mind that 5-FU is pregnancy category X.

There are a variety of soft tissue fillers that can be injected into atrophic surgical scars to provide additional volume. This can be done in conjunction with other therapies to achieve an enhanced effect. Goldman et al. showed that fillers are not affected by non-ablative laser/light and superficial ablative treatments (1a) [31]. Dermal fillers consisting of hyaluronic acid or calcium hydroxylapatite can be beneficial to fill and blend post-surgical depressed scars after reconstruction of skin cancer defects (2b) [32]. Hyaluronic acid fillers with a lower G prime can be injected superficially into the dermis with a lower risk of Tyndall effect.

Massaki et al. showed repigmentation of hypopigmented, atrophic surgical scars using a 1,550 nm NAFR combined with topical bimatoprost and tretinoin (2a) [33]. Fourteen subjects were treated with an average of 4–5 sessions at 4–8-week intervals, with 12 subjects having >50% improvement.

Microneedling

Microneedling, also called percutaneous collagen induction, is an alternative therapy that can be used to improve the appearance of surgical scars. It was initially used for skin rejuvenation, and it is now being used for a wide variety of indications. It is a minimally invasive procedure involving superficial and controlled puncturing of the skin by rolling with fine needles (3a) [34]. It is done in the office, using topical anesthetic, and the endpoint is uniform pinpoint bleeding. The microinjuries cause a wound healing cascade with release of various growth factors including platelet derived growth factor (PGF), transforming growth factor alpha and beta (TGF-α and

TGF-β), connective tissue growth factor, and fibroblast growth factor (FGF). This process helps break down old hardened scar tissue and allows it to revascularize. Neovascularization and neocollagenesis are initiated by migration and growth of fibroblasts. After 5 days of injury, a fibronectin matrix forms that determines the deposition of collagen. Histological examination of skin treated with four microneedling sessions 4 weeks apart shows up to 400% increase in collagen and elastin 6 months after the last treatment. Additionally, collagen bundles have a normal lattice pattern rather than the parallel pattern seen in scar tissue (2b) [35]. Results after each treatment are not seen immediately, because new collagen continues to be produced for 3–6 months after each treatment. It is recommended that 4–6 sessions are done for a significant improvement when treating all types of surgical scars [35].

Microneedling can be combined with other techniques to yield better results. There are various commercially available devices that have small microneedles (0.5–3 mm long and 0.1–0.25 mm in diameter) that break collagen bundles in the superficial layer of the dermis that contribute to scars. This leads to induction of more collagen beneath the epidermis (2a) [36]. The microneedles create small wounds in the epidermis, which enhances the delivery of drugs across the skin barrier since it bypasses the stratum corneum and delivers the drug directly in the vascularized dermis. However, laser-assisted drug delivery seems to be more effective. An advantage of microneedling over laser is a lower risk of post-inflammatory hyperpigmentation (PIH). Other techniques that damage the epidermis have a high risk of PIH, but microneedling is an exception. Microneedling has recently gained popularity given it is simple, inexpensive, safe and effective technique.

Summary

The realm of scar therapeutics is constantly changing. Many factors need to be considered when developing a comprehensive treatment plan, including those related to the patient and the nature of the scar. Scar characteristics can be divided by color, scar type, and body location. Many agents including topical, intralesional, light, and laser-based treatment modalities can be used to revitalize and restore damaged skin. The most commonly used lasers are the pulsed-dye laser (PDL) and either fractional ablative or fractional non-ablative devices. Ideally, a combination approach using topical and intralesional medications along with laser and light devices should be considered in patients of all ages wishing to undergo treatment of their scars.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
Scar rehabilitation with lasers can be safely started as soon as suture removal	A
A combination approach should be used when treating scars. The erythematous component of the scar should be treated first with a vascular laser	A
After the erythema of a scar has been addressed, fractional ablative devices can improve texture. NAFR devices have a safer side-effective profile and can have similar outcomes to AFR; however, more treatments may be required	B
Microneedling is a newer technique that is safe, effective, and minimally invasive. It can improve scar texture and color and assist with transdermal drug delivery	B

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Self-Assessment Questions: Surgical Scars

1. During the wound healing process, angiogenesis occurs and presents clinically as:
   (a) Edema
   (b) Erythema
   (c) Telangiectasia
   (d) All of the above

2. Several intralesional medications have shown to improve scars including triamcinolone, bleomycin, 5-fluorouracil, mitomycin, and retinoic acid. What is their mechanism of action for improving scars?
   (a) Increased angiogenesis
   (b) Decreased fibroblast growth and collagen formation
   (c) Increased epidermal turnover
   (d) Dermal injury
   (e) Neutrophil production and activation

3. When using vascular lasers (PDL, KTP) to treat surgical scars, what is the laser target?
   (a) Hemoglobin
   (b) Melanin
   (c) Water
   (d) Collagen
   (e) Keratinocytes

4. Which of the following is false regarding fractional non-ablative lasers?
   (a) They produce microscopic thermal damage zones (MTZs) throughout the epidermis and dermis
   (b) Their wavelengths are between 1320 and 1927 nm
   (c) They allow for controlled thermal injury to induce healing and remodeling in a specific area
   (d) Are helpful when treating atrophic scars
   (e) Can be used safely in all skin types

5. Microneedling causes an increase in which of the following:
   (a) Platelet derived growth factor (PGF)
   (b) Transforming growth factor alpha and beta (TGF-α and TGF-β)
   (c) Connective tissue growth factor
   (d) Fibroblast growth factor (FGF)
   (e) All of the above

Correct Answers

1. d: All of the above. Explanation: During the wound healing process, angiogenesis occurs that presents clinically as erythema, telangiectasia, and edema.
2. b: Decreased fibroblast growth and collagen formation. Intralesional medications that have shown efficacy include triamcinolone, 5-fluorouracil, mitomycin, bleomycin, interferon, and retinoic acid, which all target fibroblast growth and collagen production.
3. a: Hemoglobin. The principle of selective photothermolysis described by Anderson and Parrish in 1983 supports the use of vascular lasers when treating surgical scars given their target of hemoglobin. By selecting the appropriate wavelength, pulse duration, and energy for a specific target, select thermal destruction of the target vessel occurs without damaging the surrounding tissue.
4. a: They produce microscopic thermal damage zones (MTZs) throughout the epidermis and dermis. Ablative fractional devices destroy the epidermis and dermis, while non-ablative fractional devices keep the epidermis intact and forms MTZs in the dermis only.
5. e: All of the above. The microinjuries caused by microneedling create a wound healing cascade with release of various growth factors including platelet derived growth factor (PGF), transforming growth factor alpha and beta (TGF-α and TGF-β), connective tissue growth factor, and fibroblast growth factor (FGF). This process helps break down old hardened scar tissue and allows it to revascularize.

Post-acne Scarring

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Greg J. Goodman

Abstract

Acne is a very common inflammatory disease with superimposed opportunistic infection, which, if left untreated, will often lead to lifelong scarring. The resultant scarring is graded for the purposes of classification and communication, but the scarring is a very individual issue with even minor scarring a great issue for patients.

The treatment of scarring is usually incomplete with surface and volumetric treatments being the mainstay. Hence, grading revolves around these issues. The milder grades 1 and 2 scarring usually require multiple surface treatments with energy-based (fractionated and non-fractionated) and other surface treatments. For more severe grades where volume is a greater issue, fractionated devices appear to be the best form of energy- and nonenergy-based devices, but often, volume restoration (fillers and surgical techniques) or volume depletion (intralesional steroids and cytotoxics) is also required. The choice of the variety of fractional delivery is made on the basis of the scar and patient characteristics. Rarely, botulinum toxin may also be needed especially in hypertrophic scarring.

In all grades, it would appear that combining treatments either concurrently or sequentially is superior to employing a single modality. Combining fractionation and non-fractional therapies may be particularly efficacious (e.g. low-strength peels and needling or fractionated lasers). Otherwise combination therapy may involve fractional devices to be used to allow deeper ingress of agents by transdermal delivery (e.g. steroids, cytotoxics, bimatoprost).

Keywords

Scar · Atrophic scar · Keloid · Hypertrophic scar · Scar grade · Scar treatment

Epidemiology

Acne is so common in adolescence that it would be considered a normal stage in human development were it not for its devastating effect on the aesthetic appearance and the psychological distress it wreaks upon its sufferers (2c) [1]. Its prevalence has been estimated at 95–100% in 16– to 17-year-old boys and 83–85% in 16– to 17-year-old girls (1c) [2], (1c) [3], (1c) [4], (1c) [5]. Acne shows its polymorphous nature during its evolution as it begins with non-inflammatory comedones, evolving to the

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mildly inflammatory papular pustular acne before proceeding to the more inflammatory nodulocystic lesions. Each stage appears to be separated by some 2–3 years (2c) [6], (2c) [7]. It becomes more common and severe reaching its peak between ages 14 and 17 in females and 16 and 19 in males.

Acne may also present at an atypical age. Neonatal and infantile acne usually occurs in males in their first 12 months of life and lasts for 3–4 years on average (2c) [8],(2c) [9]. Often, a family history of acne is present in these patients. Early age development of comedonal acne, in females at least, appears predictive of later, more severe disease (2c) [10].

Acne will mostly resolve by the age of 23–25 years of age, but at 40 years of age, 1% of males and 5% of females exhibit acne lesions (2c) [11]. There is also a definite group of older females who develop acne for the first time or redevelop acne in their mid to late 20s (2c) [12].

There are very few prevalence studies looking at acne scarring in the population; however, the literature suggests that it is generally correlated to the severity of acne, its site and its duration. If left untreated for a period of 3 years or longer, acne has a high incidence of residual scarring (in up to 95% of patients) (2c) [13],(2c) [14]. In a study of 2133 volunteers aged 18–70 from the general population, nearly 1% of people had acne scars, although only one in seven of them was considered to have 'disfiguring scars' (2c) [11]. Severe scarring caused by acne is associated with substantial physical and psychological distress, particularly in adolescents.

The severity of inflammation in acne has been linked to an antibody titre to *Propionibacterium acnes* [15, 16]. Those unfortunate patients with severe inflammatory acne appear to have elevated indices of lymphocyte transformation to *P. acnes* antigens (1b) [17], abnormal neutrophil chemotaxis and phagocytosis (1b) [18] and excess activation of macrophages. There is considerable evidence against *P. acnes* causing actual dermal infection, as they tend to perish rapidly in human tissue. It also seems to be unimportant whether the organisms are alive or dead in terms of their ability to incite an inflammatory response (5) [19]. Thus, the role of *P. acnes* is to incite the breach in the follicular wall and to be part of the chemotactic and pro-inflammatory cascade that follows.

The Evolution of Inflammatory Lesion to Scar Formation

The end result of follicular rupture is a perifollicular abscess. Small abscesses incorporating the horny core will point and be discharged through the skin. This will be repaired without scarring in about 7–10 days. The epidermis is always attempting repair, and cells grow from the epidermis and appendageal structures to encapsulate the inflammatory reaction. If this is complete, there is resolution of the lesion without incident. Sometimes, however, this encapsulation is incomplete and further rupture occurs, and the end result may be the appearance of multichannelled fistulous tracts (5) [20].

Other types of outcomes depend on the extent and the depth of the inflammation. If the dermal inflammation is severe, total necrosis of the follicle may ensue and sloughing will produce a focal scar [12].

If the inflammation is severe and especially if the rupture occurs deeply in the follicle, the inflammation will extend well beyond the environment of the hair follicle into the subcutis, along vascular channels and around sweat glands. This wreaks havoc in these deep tissuesinducing deep scarring and destruction of subcutaneous fat [12].

When inflammation is very deep, transepidermal discharge is often not available as a method of resolving the abscess. As healing occurs and attempts at encapsulation of this deep inflammation ensue, this may form into papules, nodules or cysts. Cysts are, in effect, giant closed comedones.

Why one patient is able to heal without scarring whilst another with apparently similar severity goes on to scar has always been vexing. One study examined this by utilising patients known to be acne scar-prone and compared them to those who did not tend to scar. The study found that there were noticeable differences in their inflammatory profiles whilst healing (3a) [21]. In particular, they found that the cellular infiltrate was large and active (CD4+ T cells, macrophages and

Langerhans cells). There was a rather non-specific response with few T memory cells, significant early angiogenesis and vascular adhesion molecule expression in lesions of patients not prone to scarring. This response is typical of a healthy, robust, type 4 hypersensitivity response with effective and rapid clearing of the offending antigen. The relative poverty of a highly specific immune response is felt to suggest that the population of patients who do not readily scar are not highly sensitised to antigens responsible for acne. A relatively large number of the CD4+ T cells could not be classified as memory/effector cells or naïve T cells, suggestive of effective removal of the causal antigens and satisfactory resolution of the inflammatory response by mechanisms straddling both the innate and adaptive immune systems [20]. In contrast, patients prone to scarring tended to show fewer Langerhans cells, lower HLA-DR expression and fewer CD4+ T cells (although with a higher proportion of T memory cells): all in all, a relatively more specific but ineffectual early response. Macrophages, blood vessels and adhesion molecules were high. Angiogenesis remains high in resolving lesions with a further stage of inflammation comprising macrophages, skin-honing memory cells and increased HLA-DR expression. They suggest that based on the poorly resolving inflammation, scarring would be a more likely outcome and suggest a role for anti-inflammatory medications.

If prolonged angiogenesis is seen in those who go on to scar, then how may this relate to the atrophic scarring seen most commonly in the post-acne scenario? One scenario could be as follows. For blood vessels to flourish and invade into an injured area, there is a required increase in metalloproteinases to cut a path for this vascular advance. Metalloproteinases are important as enzymes able to remodel the extracellular matrix (3a) [22],(2b) [23]. Three main types of metalloproteinases in the dermis appear to be particularly important:

2. MMP 1—Type 1 collagenase
3. MMP 2—Type 4 collagenase (72 kDa gelatinase)
4. MMP 3—Stromelysin-1 (Transin)

It seems that *P. acnes* triggers inflammatory cytokine responses in acne by the activation of toll-like receptors (TLR2) (2a) [24], transmembrane proteins that are able, through activation of nuclear factor (NF)-kappa B (NFkB) and downstream cytokine production, to eventually lead to activation of AP-1-regulated metalloproteinase genes. Four inhibitors of the excessive activity of these enzymes have been described: so-called tissue inhibitors of metalloproteinases (TIMP). If collagenases and other metalloproteinases are overactive or active for a longer time than required to support prolonged angiogenesis, the dissolution of dermal support may occur. It may be that the interplay of metalloproteinases and their inhibitors may be involved in the eventual scarring whether atrophic or hypertrophic, as both appear to be a breakdown of the normal balance of collagen production.

Preoperative Evaluation and Patient Selection

Objectively, we can generally divide patients according to the severity of their scarring process.

There are mitigating patient factors that will sway therapy choices; these should be assessed along with scar severity and burden of disease at the initial consultation (Table 48.1).

Treatment Overview of Single Therapy Techniques

In the following analysis, most of the techniques will highlight either studies that are not comparison studies, are opinion or consensus, or not strong enough studies to be considered for later analysis under the example comparison studies. However, they still have pertinent points to make and are worth taking on board, even if the evidence for these views may be relatively weak. There is also a bias against older techniques or those that have no obvious corporate champion; some of these such as chemical peeling, dermabrasion, punch techniques and subcision will be discussed despite their mostly anecdotal studies.

Table 48.1 Key points to be gleaned from the patient's history and examination before proceeding to plan the patient's therapy

Parameter	What needs to be considered
Activity of associated acne or skin disease	Treat this before beginning treatment for scarring
Fitzpatrick skin type	In types III and V, one should be concerned about post-inflammatory hyperpigmentation with resurfacing procedures. In type VI (black skin), there is usually only a short-term problem with pigment. For darker-skinned patients, procedures with better safety margins are usually chosen
Sex	When considering the possibilities for treatment, keep in mind that most men do not regularly wear make-up and women do not have beards to hide demarcation lines
Age	Be concerned about treating the very young and the very old (possibilities for concomitant illness and motivation)
Psychological and physical health	Make sure it is appropriate to proceed with suggested course of action. Ensure that the patient has adequate understanding of the limitations of the selected treatment
Social constraints	Ensure that adequate care is available in the postoperative period and that the patient is able to attend follow-up appointments A patient's willingness to accept varying amounts of downtime associated with individual procedures may influence choice of therapy Payment needs to be discussed, especially if there is to be a long process or if expensive equipment is to be used
Burden of disease	The treatment required will vary according to how great a disease load is present Severe scarring may require a number of procedures and even hospitalisation, whereas this is less likely with milder disease. Even with milder disease, skin condition is not guaranteed to reach patient expectations, and the individual may still need multiple (if less morbid) procedures
Type of scarring	Certain types of scarring (e.g. ice-pick, gross atrophy and erythematous macular marks) may require their own specific treatments
Site of scarring	Treatment of certain scarring sites (neck, chest and back) has a higher risk of pigmentation and hypertrophic scarring

Objectively, we can generally divide patients according to the severity of their scarring process. Within each of the grades of scarring, it is useful to construct an approach where we look for reconstructive options similar to those currently in vogue for assessing the ageing patient or cosmetic enhancement as well as other reconstructive situations. This concentrates on surface-, volume- and movement-related changes, although movement-related changes are not usually a problem in the more minor grades of scarring. The paradigm is similar off the face and in any age range with some caveats. Surface issues are best dealt with by fractionated rather than full-field treatment as healing is not as simple with off face treatments and movement issues are not usually in play. Age only makes a difference with respect to loss of tone amplifying the appearance and the decreased healing capabilities of older skin.

In essence, surface treatment revolves around the skin's texture, altering the colour of the scar and inducing or reducing collagen in the underlying tissue. Volume requires augmentation or filling to correct volume deficits or sometimes decreasing volume in terms of hypertrophic scarring.

Grade 1 Scarring

Abnormally coloured, macular disease: erythematous, hyperpigmented or hypopigmented flat marks visible to patient or observer at any distance

Vascular Lasers

This form of scarring is often actually a phase in wound healing, and erythematous scars are likely to resolve if the inflammation is removed and the mark allowed to heal.

It may occur anywhere where recent activity has occurred and will usually last longer on the body than the face where healing is slower. Intervention is required if this process is not occurring in a timely fashion or where the patient is impatient for recovery. Resolving hypertrophic scars exhibit more prolonged erythema. This is most often seen in younger patients and may occur in facial or off face scarring. More than one treatment is required in most cases of erythematous acne scars.

A number of treatments, at one to two month intervals, are required with a relatively short pulse duration in the millisecond range (5) [25] using either intense pulsed light (IPL) or pulsed dye lasers (2b) [26].

In 1995, it was reported that the flashlamp-pumped pulsed dye tunable laser was useful in the treatment of keloid sternotomy scars, with improvement in scar height, skin texture, erythema and pruritus (1b) [27] with confirmation in other studies (1b) [28] (1b) [29]. The flashlamp-pumped pulsed dye laser has also been used for erythematous scars (2a) [30] and has been compared with the long-pulsed 1064-nm neodymium–yttrium–aluminium garnet (Nd:YAG) laser on acne scars in a split-face study. Unfortunately, scar colour was not specifically addressed in the article as a parameter, although looking at the clinical photographic examples, it appeared that colour was an important part of the improvement seen in these patients (1b) [31].

Other scar types judged according to the ECCA scar classification system (1b) [32] appeared to have modest scar improvement scores. It is probably better to consider vascular lasers in a patient where the predominant scar type is erythematous, although it is worthwhile knowing that it may have a positive effect on other atrophic and hypertrophic scar types if they are also present (3a) [33].

Comments and Recommendations

(a) Vascular lasers are useful for erythematous scars (B).
(b) Multiple treatments are necessary (A).
(c) Vascular lasers may be useful in other scar types (C).

Fractionated Lasers and Devices, Pigment Lasers and Intense Pulsed Light (IPL)

Fractionated lasers may sometimes be used for hypopigmented marks and scars on or off the face with significant improvements of 51–75% in hypopigmentation in six of seven patients cited in a pilot study by Glaich et al. (4) [34]. Fractionated 1550-nm laser may have particular efficacy in treating these scars (5) [38].

A mid-infrared-wavelength, thulium (1927 nm) laser is a superficial, non-ablative, fractional device that has been anecdotally noted to be effective for the treatment of post-inflammatory hyperpigmentation and melasma that commonly highlight hypopigmented scarring.

Intense pulsed light has its advocates for treatment of post-acne scarring both alone (5) [35] and in combination with other therapies (4) [36] for atrophic and hypertrophic disease; however, at this time, conclusive evidence for its efficacy is insufficient for its recommendation here (1a) [37]. These may be useful for erythematous scars, especially non-ablative 1550-nm fractional devices, although specific references are lacking at this time.

Another new mid-infrared-wavelength, thulium (1927-nm) laser is a superficial, non-ablative, fractional device that has been anecdotally noted to be effective for the treatment of post-inflammatory hyperpigmentation and melasma (1b) [39] that commonly highlight hypopigmented scarring. In this circumstance, it would be used to treat the hyperpigmented areas, decreasing the contrast between these areas and the hypopigmented scars.

Comments and Recommendations

(a) Fractionated lasers (especially 1550-nm lasers) are useful for hypopigmented scars (B).
(b) Fractionated thulium lasers may be useful for hyperpigmented scars (C).
(c) Intense pulsed light may be useful in several scar types (C).

Repigmentation Procedural Techniques

Hypopigmented scars may be additionally helped by repigmentation procedures. These may be added to resurfacing procedures such as topical latanoprost or bimatoprost (4) [40], (1b) [41]. ReCell automated cell transfer system may also add to a successful outcome for certain types of hypopigmented scars and may have a place in 'off face' hypopigmented scarring.

Hypopigmented scarring has been reasonably refractory to treatment. There have been scattered reports of repigmentation after manual dermabrasion (4) [42] and needling (5) [43]. Some pigment transfer procedures have been attempted. A number of techniques used to treat vitiligo may also be useful in treating certain types of superficial hypopigmented scarring. Cultured and immediate noncultured epidermal suspensions may also be somewhat useful (2c) [44]. ReCell (C3, Perth, WA, Australia) is an automated commercial kit for trypsin dermal–epidermal separation that has become available, allowing immediate autologous noncultured epidermal suspension. This may improve the ease of the technique considerably over current methods (4) [45], (4) [46].

Comments and Recommendations

(a) Bimatoprost and latanoprost may be useful for hypopigmented scars (C).
(b) Pigment transfer procedures such as automated trypsin-digested epidermal cells may be useful adjuncts to the treatment of scarring (C).

Grade 2 Scarring

Grade 2 scarring is a mild, atrophic or hypertrophic disease that may not be obvious at a social distance (e.g. talking to someone conversationally in normal lighting) and is easily covered with make-up.

Manual Skin Needling or Rolling

Manual skin needling comes in many forms from a rolling apparatus with embedded pins to motorised pen-shaped instruments that vibrate needles in and out of the skin through stamping fixed pin designs. They all injure the skin engendering a wound repair cascade that, over a number of sessions, usually five to six, will improve the quality of grade 2–3 atrophic skin scars (2a) [47] (1a) [48]. This is a very useful procedure in terms of low downtime for the patient with a low incidence of complications (1c) [49]. A small but well-performed study examined the efficacy of skin needling as a treatment with clinical end points and microrelief silicon impression (1b) [49] and found it to be useful.

Comments and Recommendations

(a) Manual skin needling appears to be a useful treatment for atrophic scars (A)
(b) Multiple treatments are necessary (A)
(c) Vascular lasers may be useful in other scar types (C)

Non-ablative Non-fractional Resurfacing

This category of treatment usually describes the use of lasers and radiofrequency (RF) to bulk heat the dermis whilst simultaneously cooling or otherwise protecting the dermis (4) [50]. This set of procedures has largely given way to fractional devices due to a number of factors. These treatments have really been the forerunners to a similar technology given in a safer and more efficacious manner by fractionation (1b) [51].

It has been of some use in milder forms of atrophic acne scarring but is limited because of safety concerns when higher energies are used due to transference of energy to and wounding of the skin surface. It is not limited to the face, but if epidermal injury is sustained, it will take longer to heal and may result in complications.

These lasers use conducted heat from the chromophore to produce a diffuse dermal injury, heating to >50 °C and inducing collagen remodelling. Repeated treatments are required, and longevity of the results remains largely unknown.

This technology seems safe [49], (2c) [52] with patient satisfaction and perception of efficiency appearing reasonable, although post-inflammatory hyperpigmentation may result, especially if blistering occurs.

Comments and Recommendations

(a) Non-ablative resurfacing may be useful for atrophic scarring (C).
(b) Multiple treatments are necessary (A).
(c) Efficacy and safety may not be equivalent to fractional laser delivery (A).

Microdermabrasion

Usually microdermabrasion is only useful for the mildest forms of scarring, often in the context of comedonal disease. It is often used in early pubertal acne or in grade 2 mildly atrophic disease.

It has been suggested that microdermabrasion using aluminium oxide crystals or sodium chloride is useful in the treatment of facial scarring (4) [53], (2c) [54]. Small crystals of aluminium oxide or other agents are expelled from one nozzle towards the skin, abrading it with a series of small lacerations, with the used crystals aspirated back from the skin surface and discarded (2c) [55]. Multiple treatments are required, and results usually only see mild improvement. However, this is a safe treatment on or off the face with limited downtime which is well tolerated and comparatively inexpensive.

Its efficacy for the treatment of scarring remains uncertain (5) [56]. It may owe its efficacy to changes in skin barrier function with its consequent transepidermal water loss (1b) [57]. A number of articles attest to its efficacy, and improvement is likely to be mild, making it useful in this grade of scarring (5) [58].

Comments and Recommendations

(a) Microdermabrasion is possibly useful in milder forms of atrophic post-acne scarring (B).
(b) Multiple treatments are necessary (A).

Volume Treatments

Volume treatments may be used for grade 2 scarring, usually lower prime agents amongst the hyaluronic fillers or an approach that ignores the individual scars but concentrating instead on the areas of scars flooding this to improve the underlying skin structure (1b) [59] (5) [60].

There are permanent fillers for the treatment of post-acne atrophic scars (2a) [61] although not everybody is comfortable with this approach.

One can also use dermal fillers if the individual scars are deep enough, and flooding the dermis with superficial dermal fillers is also a possibility. Although superficial dermal fillers are unproven in scarring, they have a rejuvenating effect on skin elasticity and dermal thickness (4) [62].

Comments and Recommendations

(a) Fillers probably have a limited role in the treatment of these milder forms of atrophic acne scarring (C)

Grade 3 Scarring

Moderately abnormally contoured disease, atrophic or hypertrophic scarring obvious at conversational distance incorporating rolling and superficial boxcar-type scarring

Ablative Non-fractional Laser Skin Resurfacing

Although not conclusively shown to be effective in a Cochrane report that was later withdrawn(1a) [63, 64], ablative full-face laser skin resurfacing has for nearly two decades been considered the criterion standard for the treatment of post-acne and other types of scarring but may be giving way to fractional devices (5) [65], (5) [66].

Comments and Recommendations

(a) Ablative non-fractional resurfacing was considered in the past the best form of therapy in post-acne scarring (A).
(b) Morbidity is significant (A).
(c) Fractionated delivery may have replaced this technology in terms of efficacy and safety (B).

Dermabrasion

Dermabrasion was the first major advance in the treatment of atrophic and traumatic scarring. It is probably at its best in treating grade 3 rolling scarring and will tighten the skin somewhat in an older patient with scarring (4) [67].

Comments and Recommendations

(a) Similar comments to ablative non-fractional resurfacing

Chemical Peeling

For patients with more-severe scarring, deeper peels are usually employed if peeling agents are employed. A number of case series have been presented on the use of medium and deep chemical peeling in the treatment of atrophic scarring (4) [68]. As with any resurfacing procedure, a proportion of patients will develop post-inflammatory hyperpigmentation, but even in darker skinned patients, as in this study, they have been useful.

Comments and Recommendations

(a) As for full-field treatments generally, medium and deep peels have been largely superseded by fractionated devices or methods that limit their morbidity such as combining lower strengths with other procedures or focal delivery such as CROSS (B).

Dermal Fillers

Considering how commonplace it is to use dermal fillers, there are few references as to the use of fillers in indented scars (4) [69], (4) [70], but these are either case reports or case series. Fillers that are not often used or not used at all have been the subject of studies, but more studies need to be undertaken with hyaluronic acid as this is very widely used. A permanent filler, polymethylmethacrylate, has been investigated in a large controlled study of 147 patients with a short 6-month follow-up period. Using a validated scar scale, they achieved success in 64% of treated patients versus 33% of control subjects. Only reversible adverse reactions were seen, but one must stress the short-term study time frame (1b) [71].

Comments and Recommendations

(a) Fillers are useful in atrophic scarring (C).
(b) Morbidity is mild (A).
(c) They are useful in combination with other modalities (B).

Botulinum Toxin

Botulinum toxin may be combined with fillers, although the fillers are usually administered at a later session, once the effect of the botulinum is established. The use of dermal fillers and botulinum appears to be synergistic in many cases (4) [72]. However, more exciting is the effect that botulinum toxin may have on hypertrophic varieties of post-acne scarring and keloids. In a randomised study of 24 female patients (1b) [73],

botulinum toxin injections (5 IU/cc keloid) at three 8-weekly sessions were compared to three 4-weekly intralesional steroids (10 mg/cc), and results showed that objective parameters such as hardness, elevation, redness and subjective complaints such as itching, pain and tenderness all decreased significantly ($p < 0.01$). The volume reduction was 82.7% for the intralesional steroid group and 79.2% for the botulinum toxin group. There was a significant decrease in the height of lesions and redness score compared with baseline ($P < 0.01$) with no significant difference between both groups. All patients mentioned a significant reduction of their subjective complaints ($P < 0.01$) which was more significant in group B. Skin atrophy and telangiectasia were evident in three patients of group A. Patient satisfaction was high in both groups. Very satisfied was 50% in the steroid group versus 75% in the botulinum toxin group. Only one patient in the intralesional steroid group was unsatisfied, all others being satisfied or very satisfied.

It may be because botulinum toxin becomes a drug to consider prophylactically in at-risk patients or resolving acne lesions that are likely to become hyperplastic (4) [74].

Comments and Recommendations

(a) Botulinum toxin may have a role in prevention and treatment of hypertrophic scarring (B)
(b) Morbidity is not significant (A)
(c) This may be combined with other modalities (B)

Subcision

Subcision works by breaking up the attachments of atrophic acne scars, releasing the surface from the deeper structures, with successive treatments producing further improvement (4) [75], (4) [76]. Intradermal insertion is suitable for small superficial scars, whereas deeper dermal undermining is performed for more severely bound down scars.

Some comparative and combination studies have been performed, and multiple papers have discussed variation in the initial subcision technique. One study of 20 patients compared one to three sessions of 100% trichloroacetic acid (TCA; CROSS) to scars on the left side of the face with subcision to scars on the right side (1b) [77]. The study showed more improvement in rolling scars and less adverse reactions (pigmentation) on the subcision side ($p < 0.001$), although one wonders whether the number of TCA sessions was sufficient in this study and maybe TCA is at its best for ice-pick scars (1b) [78].

In another study (within individual, split face and single blinded, $N = 10$, 20 sides) looking at comparing subcision against another modality (porcine collagen), subcision appeared marginally superior to the filler at 3 months ($p < 0.03$) according to patients, whilst there was no significant difference in objective measure at any other time points by patients. Nine patients completed the study, and follow-up was for 6 months post-treatment. Blinded observers and patients rated improvement on a five-point scale, and both techniques performed well with patient global satisfaction rates being 3.9 for subcision and 3.5 at 6 months versus lower rates by blinded observers (2.95 for subcision and 3.05 for porcine collagen).

There is an interesting combination study looking at 50 patients receiving topical treatment, subcision, 15% trichloroacetic acid (TCA) and needling in an alternating sequence (2b) [79]. Specifically, retinoic acid 0.05% was used to prime the patient for 2 weeks prior to a single subcision session using a 24# (gauge) needle. One day later, needling with a Dermaroller was performed and retinoic acid immediately used for 30 min after the procedure. Two weeks later, 15% TCA was used until speckled frosting occurred. The sequence of fortnightly needling and TCA peeling was continued up to six cycles.

A qualitative scale was used to assess improvement (1b) [80] which categorises patients into four grades of severity of scarring (grade 4 being the most severe and grade 1 the least). This grading system has been used in this manuscript.

Out of 16 patients with grade 4 scars, ten (62.5%) patients improved to grade 2 scars and

six (37.5%) patients improved to grade 3 scars. Out of 22 patients with grade 3 scars, five (22.7%) patients were left with no scars, two (9.1%) patients improved to grade 1 scars and 15 (68.2%) patients improved to grade 2 scars. All 11 (100%) patients with grade 2 scars were left with no scars. There was a high level of patient satisfaction.

Comments and Recommendations

(a) Subcision is a useful treatment in atrophic post-acne scarring (A).
(b) Morbidity is mild (A).
(c) It is readily combined with other therapies (B).

Intralesional Corticosteroids or Fluorouracil, Combined with Silicon Sheeting

High-strength intralesional corticosteroids are commonly used in the treatment of hypertrophic and keloidal scars. Over the last decade or more, reports have appeared of intralesional cytotoxics, including fluorouracil (5 FU) (5) [81], bleomycin (4) [82] and mitomycin (4) [83], as treatments for hypertrophic and keloid scars.

A meta-analysis was performed in 2016 (1a) [84], comparing intralesional steroids as the control group (TAC) and the combination of intralesional 5-fluorouracil and steroids (TAC) as the experimental group.

A pooled analysis of patient self-assessed effectiveness showed that the experimental group achieved better results than the control group (OR = 2.92, 95% CI = 1.63–5.22, P = 0.0003). Similarly, a pooled observer assessment produced similar conclusions (OR = 4.03, 95% CI = 1.40–11.61, P = 0.010). Scar height after treatment showed that the experimental group performed better than the control group (MD = −0.14, 95% CI = −0.23–0.05, P = 0.002). The erythema score of the experimental group after treatment was superior (MD = −0.20, 95% CI = −0.34–0.06, P = 0.004). So it would appear that TAC combined with 5-FU is superior in the treatment and prevention of hypertrophic scars and keloids, with greater improvement in scar height and patient satisfaction.

Comments and Recommendations

(a) Intralesional steroids are considered a front-line agent in the treatment of hypertrophic scarring (A).
(b) Adverse reactions of atrophy and telangiectases are possible sequelae of intralesional steroids (A).
(c) Intralesional cytotoxics combined with steroids especially 5-fluorouracil may be superior to steroids (A).

Grade 4 Scarring

This grade describes severely abnormally contoured disease, usually non-distensible, and includes severe atrophic or hypertrophic scarring obvious at conversational distance and not able to be flattened by manual stretching of the skin.

Trichloroacetic Acid (CROSS Technique)

A variation of chemical peeling involving the use of 60–100% trichloroacetic acid [77], termed the CROSS technique, has raised interest in the treatment of smaller ice-pick- and poral-type scars, which have always proved a challenge.

Comments and Recommendations

(a) Focal trichloroacetic acid (CROSS) is a very useful technique for ice-pick scarring (A).
(b) Adverse reactions of erythema and post-inflammatory hyperpigmentation are possible sequelae of CROSS (A).

Punch Techniques (Excision, Grafting or Elevation)

Punch excision removes a pitted scar using a straight-walled disposable or hair transplant

punch that is slightly larger than the scar. Sutures are then placed to oppose the wound, as per a normal excision (4) [85]. Punch replacement grafting, which has been used for several decades in dermatology (5) [86], is probably best used to treat sharp-walled or deep ice-pick scars with dystrophic or white bases. Resurfacing may be performed 4–8 weeks later to flatten the grafts and further blur the margins.

Punch elevation is a variation of other punch techniques, except that the scar is not discarded. The tissue cylinder is incised down to the level of the subcutaneous fat, and the scar is allowed to float up until it reaches the same level as the surrounding skin.

One study examining the combination of fractionated CO_2 laser in two sessions with punch elevations versus just the laser alone found greater improvement when punch elevations were used ($p = 0.02$) 4 months after surgery (1b) [87]. Both sides showed excellent improvement subjectively (61.9% noted good to excellent improvement), and objectively, all scar types improved, and there was no difference in their degree of improvement.

Comments and Recommendations

(a) Punch techniques including punch grafting, punch excision and closure and punch elevation are valid techniques for deep boxcar scars (C).
(b) These techniques may be synergistic with resurfacing procedures (B).

Fat Transfer

For severely atrophic disease in which there is destruction of the deeper tissues, fat remains the optimal replacement agent. Fat is easy to work with, cheap, and readily available. It will not be rejected or result in an allergic reaction; and is without risk of communicable disease. It is making a resurgence especially with the advent of plasma-rich protein, stromal vascular fraction and stem cell technologies (2a) [88] (1b) [89].

An interesting comparison trial looked at fat transfer versus fractional CO_2 laser (1b) [90] with 20 patients divided into two equal groups and their outcomes assessed with digital photographs taken by a committee of three physicians, by a single-blinded physician and by reports of patient satisfaction.

In the fractional CO_2 laser treatment group, less than 20% of patients were graded as having excellent scar improvement, 0 as having excellent and marked scar improvement, almost 70% as having moderate scar improvement and less than 10% as having mild scar improvement. In the fat-grafting group, the scar and overall improvement were graded as 30% excellent, 30% marked, 20% moderate and 20% mild. The authors concluded that fat transfer gave superior results in the treatment of post-acne scarring versus fractional CO_2 laser.

Comments and Recommendations

(a) Fat transfer is a valid method for severe atrophy associated with acne scarring (B).
(b) Longevity and reproducibility of issues have led to interest in the addition of platelet-rich plasma and stem cells (B).

Comparative Effectiveness of Common Treatments

We will compare some of the treatments most commonly used in post-acne scarring, utilising but varying the framework from a recent Cochrane review on evidence-based acne scarring interventions (1a) [48].

1. Non-fractional non-ablative laser versus
   (a) Placebo or no treatment
   (b) Other non-fractional non-ablative laser
   (c) Fractional laser
2. Fractional laser versus
   (a) Placebo
   (b) Radiofrequency
   (c) Needling

3. Chemical peeling versus
   (a) Placebo or no treatment
   (b) Combined chemical peeling plus any active intervention
   (c) Needling
   (d) Fractional resurfacing
4. Needling versus
   (a) Placebo or no treatment
5. Non-fractional non-ablative laser versus
   (a) Placebo or no treatment

   The majority of lasers for this purpose have been the mid-infrared lasers at wavelengths of 1320 nm, 1450 nm and 1540 nm, although many wavelengths have been used. Most of the infrared studies appropriately cooled to protect the epidermis whilst targeting dermal water. Non-ablative lasers appear to have a role in the treatment of minor atrophic scarring.
   (b) Other non-fractional non-ablative laser

   Comparative studies of laser systems have been performed. In one study conducted in 2004, (1b) [91] a series of 20 patients with mild to moderate atrophic facial acne scars randomly received three successive monthly treatments with a long-pulsed 1320-nm Nd:YAG laser on one facial half and a long-pulsed 1450-nm diode laser on the contralateral facial half.

   Digital photography, microtopography measurements and cutaneous biopsies taken before and at a number of time points after the final treatment along with clinical assessment scores served as objective measurements.

   Subjective patient satisfaction surveys were obtained at the end of the study.

   Mild to moderate clinical improvement was observed after the series of three treatments in the majority of patients studied. Side effects of the treatments were mild.

   It was suggested by the authors that each system was useful, and subjective and objective parameters were aligned in the noted improvement and may indicate utility in those seeking low morbidity treatment.

Some studies have looked at treating different conditions with the same technology.

In a study from 2001 (1b) [92], a split-face, within-patient design, a 532-nm long-pulsed laser was compared to a placebo where 11 patients had either one cheek (scars) or half their upper lip (wrinkles) randomised to receive an average of three treatments with the other cheek or upper lip kept untreated. Assessment was by the blinded observer and subjective assessment. Efficacy assessment was of an average of 53.6% improvement versus just over 51% for wrinkles. The blinded observer was asked to suggest which side was treated. Adverse events were mild and transient.

In another study conducted in 2004, (1b) [50] the role of 1320 Nd:YAG in non-ablative skin rejuvenation in Asians was explored for wrinkle reduction and atrophic acne scarring. Twenty-seven female patients were included, 7 for acne scarring and 20 for wrinkle reduction. A 1320-nm Nd:YAG laser was used to treat both the cheeks and forehead for patients with wrinkles and only both cheeks for those with atrophic acne scarring. All patients received treatment in the postauricular areas. A 10-mm spot size and three passes were used in six patient treatments over 6 months.

Subjective assessment was made using a structured questionnaire before the first treatment and after their last treatment session.

Objective assessment was by the use of clinical photographs for independent observers, a cutometer to assess viscoelasticity, and biopsies were taken in the postauricular site for assessment of pathology.

Subjective assessment showed an overall satisfaction rate of 4.9 (range 0–9.8) for wrinkle reduction and 4 (range 0–10) for acne scarring. Objective assessment by independent observers rated the

degree of improvement as mild or no change in most cases. The independent pathologist who assessed increase in collagen production detected no change in 8 patients, mild improvement in 9, moderate improvement in 10 and epidermal thickening in 13. Cutometer assessment of viscoelasticity indicated improvement in most patients in both groups.

Adverse reactions of blistering ($N = 5$) occurred in all in the central facial areas, and post-inflammatory hyperpigmentation occurred infrequently and responded to treatment ($N = 3$).

The authors concluded it was an effective treatment for both conditions although on their data it seemed a very mild effect with a significant adverse event profile.

(c) Fractional laser

A randomised comparative study between Q-switched 1064-nm and fractional CO_2 laser included 64 participants with atrophic acne scars who received four sessions of either fractional CO_2 laser or Q-switched 1064-nm Nd:YAG laser (non-fractional non-ablative) at 4-week intervals (1b) [93].

Results showed that in the fractional CO_2 group, participant-reported scar improvement at 6 months post-treatment in 12 out of 32 subjects was more than 50% compared to that of 3 out of 32 in the non-fractional non-ablative group. According to subjective satisfaction ($p = 0.01$) and physicians' assessment ($p < 0.001$), fractional CO_2 laser was significantly more effective than a Q-switched 1064-nm Nd:YAG laser. All patients completed the study, and side effects were stated to be mild and transient in both groups.

Comments and Recommendations

1. The effect of non-ablative resurfacing on atrophic acne scars is mild improvement (A).
2. The different visible and infrared wavelengths used are likely to produce similar effects (A).
3. The adverse reaction profile is manageable but is not ideal (B).
4. The fractional lasers may be more efficacious than non-ablative non-fractional lasers (B).

It would appear that this type of technology was reported more frequently 10–15 years ago and new studies are not frequent, maybe suggesting this has given way to newer technologies such as fractional delivery.

2. Fractional laser versus
   (a) Placebo

A within patient trial (1b) [94] with 13 participants in which similar sized areas on each side of the face was randomised to receive 3 × monthly treatments of fractional CO_2 laser and the area on the contralateral site received no treatment (placebo).

Objectively, patients were assessed by three blinded physicians on a ten-point scale showing significantly improved skin texture and scar atrophy in all 12 participants with atrophic acne scars, from a baseline mean of 6.15 to a post-treatment mean of 3.89 for skin texture and 5.72 for scar atrophy to 3.56 at 6 months ($P < 0.0001$). One patient was excluded from this data.

Subjectively, participant satisfaction was recorded. All 13 participants reported a median satisfaction score of 4.5 at 6 months based on a numerical scale from 0 (unsatisfied) to 10 (maximal satisfaction). No untreated side data was reported.

Adverse reactions appeared frequent (such as pain) on the treated side but mild and transient.

In another trial, (1b) [95] 30 Chinese patients with atrophic acne scars on both cheeks received a split-face treatment. One side underwent four sessions with fractional 1550-nm Er:Glass laser at 20-day intervals and the other with a control cream application three times daily. Clinical response and side effects were evaluated by a dermatologist 3 weeks after each treatment and again 12 weeks after the last laser treatment. In addition, self-evaluation of satisfaction by the patients was done at the end of treatment.

Mean scores for the acne scars decreased 5.65 ± 4.34 after treatment for the treated side and 1.23 ± 3.41 for the control side. The improve-

ment in acne scars after the fractional 1550-nm Er:Glass laser treatment was more significant than the control side ($p = 0.0001$). The side effects were mild and transient.

Similar findings of efficacy over baseline using different parameters of Erbium:Glass 1550-nm lasers as their controls rather than non-treatment were found in other studies (1b) [96] 1(b) [97] with both these studies commenting on hyperpigmentation as an adverse reaction.

Comments and Recommendations

1. Fractional laser resurfacing is efficacious as against placebo or nontreatment (A).
2. The adverse reaction profile is manageable with most being mild or transient (B).
3. Hyperpigmentation amongst these adverse reactions appears the most troublesome in those of darker skin (B).

Fractionated lasers seem effective and useful for atrophic post-acne scarring.

2. Fractional laser versus
   (b) Radiofrequency

A parallel-group trial design (1b) [98] randomly divided 40 participants into two equal groups (each $N = 20$) to receive either 1550-nm Er:Glass fractional laser (Group A) or a fractional radiofrequency device (Group B) over three sessions at 4-week intervals. Subjective assessment showed in both groups that 15/20 patients sustained average to excellent improvement in the appearance of acne scars. No statistically significant difference was reported.

All 40 participants completed the trial as planned, and no severe side effects were noted. Ten percent of patients in group A (fractional laser) ($N = 2$) had post-inflammatory hyperpigmentation versus none in group B (radiofrequency). There was shorter downtime and lesser pain in group B (radiofrequency).

In group A (fractional laser), the mean ECCA grading scale was reduced from 74.25 to 55.5, a 25.0% decrease from baseline ($P < 0.001$). In group B (radiofrequency), the mean ECCA grading scale decreased from 68.75 to 56.0 ($P < 0.01$), an 18.6% reduction. There was no statistical difference noted between the two arms of treatment.

Very similar results were seen in a within-subject comparison of fractional Erbium and fractional bipolar radiofrequency in 20 Thai patients (1b) [99] being delivered in a randomised fashion to one side of the face with the alternative technology to the other. After three treatments, 4 weeks apart, subjective analysis was similar with all patients (except one withdrawal) rating both treatments as being moderately (two out of four), very (three out of four) or most (four out of four) satisfied on a four-point scale.

Quantitatively, after treatment, subjective improvement was 2.89 (SD 0.57) for the fractional Er:Glass and 2.74 (SD 0.73) for the fractional bipolar RF devices, respectively.

Objective scar improvement showed mean improvement after treatment of 2.86 (SD 0.42) and 2.70 (SD 0.37) for the fractional Er:Glass and the fractional bipolar RF ($n = 19$) devices, respectively.

Adverse events such as pain, transitory facial erythema, facial dryness and scabbing were reported for both treatments with pain being statistically less significant with the RF device (mean difference = 1.85 (SD 1.30), $P < 0.001$), whilst the opposite was true for the scab separation with the length of scab-shedding treatment being longer with the fractional RF than with the fractional laser.

Comments and Recommendations

1. Fractional laser resurfacing is efficacious as is bipolar fractional radiofrequency (A).
2. There is little likelihood that one is superior to the other (B).
3. The adverse reaction profile is manageable with both technologies (B).
4. Hyperpigmentation may be more likely in fractional laser resurfacing than radiofrequency (B).
5. Fractional radiofrequency may take more time for scab shedding (C).
6. Both technologies seem very adequate treatment for atrophic scarring (C).

Fractionated lasers and fractional bipolar radiofrequency seem effective and useful for atrophic post-acne scarring with a satisfactory and similar adverse reaction rate.

2. Fractional laser versus
   (c) Needling

In 2015 a study of 46 participants were randomised to receive either fractionated 1340nm laser or microneedling over 3 sessions, conducted monthly (1b) [100]. Of the 46 assigned patients, 42 completed treatment, 22 in the laser group and 20 in the microneedling group. Subjectively, 65% of microneedling patients and 86.4% of the laser patients perceived an improvement after the first treatment session, and 100% of participants in both groups noted improvement after the second session. Both groups improved according to objective quantitative grading, the laser group from a mean of 15.82 to 12.41 and the microneedling group 14.9 to 10.85, both showing $p < 0.001$. Boxcar scars seemed to improve more than rolling scars, and both showed better improvement than ice-pick scars. There was no statistical difference between the two interventions in terms of efficacy, whilst adverse reactions showed a longer erythema and higher incidence of post-inflammatory pigmentation in the laser group.

Comments and Recommendations

1. Needling may be a promising treatment (B).
2. Needling may be a viable alternative to other fractional resurfacing techniques (C).
3. Hyperpigmentation may not be problematic with needling as compared to other fractional technologies in skin of colour (C).

Fractionated lasers and needling are both useful treatments, and needling probably needs to be further explored as it may provide a cheap alternative to other technologies.

3. Chemical peeling versus
   (a) Placebo or no treatment

One parallel-group study from 2000 (1b) [101] addressed this comparison in which 58 women with atrophic acne scarring were randomised into three groups: one group ($n = 23$) received serial biweekly (2-week intervals) glycolic acid peels with different concentrations in gradually increasing concentration and application times; another group ($n = 20$) received 15% glycolic acid cream daily for 24 weeks; and the remaining group ($n = 15$) received a placebo cream daily. Ice-pick and fibrotic scar patients were excluded from the study. Ten patients could not complete the study, mostly in the peel group where seven were unable to tolerate higher percentages of the peels and two were lost to follow-up. All arms showed improvement in the scars on the scale used (>60% grade change, 30–60% grade change and < 30% grade change), even the placebo arm; however, according to the authors, only patients in group A (peel patients) achieved significant decrease in their scarring. In the cream group B, eight patients were only able to use the cream daily rather than twice daily, and three developed pigmentation with the use of the cream, whilst in the placebo group, one participant was lost to follow-up, although no adverse reactions were noted in this group.

3. Chemical peeling versus
   (b) Combined chemical peeling plus any active intervention

An article published in 2014 addressed a 24-patient parallel-group trial [102] and compared a single deep chemical peel versus four sessions (6-week intervals) of chemical peeling with TCA 20% combined with skin needling.

The deep peel was a non-hydro-alcoholic solution of oil phenol in 60% concentration formula. Twenty participants (ten in each group) completed the study and were included in the consequent results. Two of 12 participants in each group did not go on to their allocated treatment after study enrolment and did not take part in the analysis.

Eight months after treatment, subjective patient-reported scar improvement was 50% in all ten patients in the deep peel group and eight of

ten patients in the light chemical peeling plus needling group using a weighted scale and then a quartile grading scale (0 = minimal improvement <25%; 1 = mild improvement 25–50%; 2 = moderate improvement 51–75%; 3 = significant improvement >75%). No statistically significant difference was noted between groups in efficacy.

Scar severity scores improved by a mean of 75.12% ($p < 0.001$) in group 1 and a mean of 69.43% ($p < 0.001$) in group 2. Compared to other scar types, within the individual groups, rolling scars in group 2 improved most significantly ($p = 0.005$).

The deep peel group was a significantly morbid procedure with all participants in the chemical peeling group showing erythema for 3–4 months and pigmentation for 6 months. Two of ten participants in this group had persistent erythema for 6 months. None of the participants in the chemical peeling plus needling group showed any adverse events 1 month after the procedure.

Another study looked at the combination of peels with other technologies (1b) [103]. Three matched groups of 13 patients were assigned to receive either six sessions of needling combined with simultaneous trichloroacetic acid 20%, six sessions of 1540-nm fractional laser or alternating sessions of the two previous treatments. One patient was lost to follow-up but was included in analysis in group 1.

Prior to treatment, scar type was established (rolling, boxcar and ice-pick), and the total severity in each patient was assessed according to the following weighted scale: three points for deep, two points for shallow and one point for superficial scars.

Both patients and a blinded dermatologist rated the scar improvement on a quartile scale (0, minimal improvement <25%; (1) mild improvement 25–50%; (2) moderate improvement 51–75%; (3) significant improvement >75%).

All groups improved well on objective analysis with a mean of 59.79% (95% CI, 47.38–72.21) ($p < 0.001$) in group 1, 61.83% (95% CI, 54.09–69.56) ($p < 0.001$) in group 2 and 78.27% (95% CI, 74.39–82.15) ($p < 0.001$) in group 3. The degree of improvement was significantly higher in group 3 when compared with both groups 1 and 2 ($p = 0.007$, $p = 0.019$).

Different scars improved differently in the different groups, possibly a key finding to the synergy shown here. Rolling-type scars showed a significantly higher improvement in group 1 ($p < 0.001$), the boxcar type showed a significantly higher improvement in group 2 ($p < 0.001$) and in group 3 the highest improvement was documented for both rolling and boxcar types ($p < 0.001$). Improvement in ice-pick scars only achieved significance in group 3 ($p = 0.05$).

The degree of improvement on the global response measures was significant, objectively in 11 patients (28.2%), moderate in 22 patients (56.4%) and mild in 5 patients (12.8%).

Subjectively, 28 of 39 patients reported improvement of their acne scars, ranging from 50% to 75%. This broadly matched their improvement in scar severity score.

Comments and Recommendations

1. Deep chemical peels are efficacious but have prolonged recovery (A).
2. Light peeling (GA) may impact milder scarring (C).
3. Lighter peels enhanced by needling may reduce atrophic scars significantly (B).
4. Synergy between procedures incorporating peeling appears promising (B).

Chemical peels especially light augmented peeling like 20% TCA and needling probably needs to be further explored as it may provide a synergistic, cheap and effective alternative to or work in with other technologies.

4. Needling versus
   (a) Placebo or no treatment

One within-individual single-centre, rater-blinded, balanced (1:1), placebo-controlled, parallel-group, randomised clinical trial was carried out initially with 20 participants (15 actually entered the study and were analysed) (1b) [104]. For each participant, one side of the face was randomised for needling. Three needling treatments were per-

formed at 2-week intervals, whilst on the other side, topical anaesthetic cream only was massaged onto the control area at three treatment visits.

Two blinded dermatologists separately rated participants' acne scars based on standard digital photographs obtained at baseline and at 3-month and 6-month follow-up visits using the Goodman and Baron quantitative global scarring grading system.

Subjective improvement in scars was reported at 41% mean improvement in acne scars on the treated side with high satisfaction ratings. No adverse events were reported during the study. Pain was minimal (1.08 of 10) and expected erythema and oedema seen in all patients. No other adverse reactions were seen.

Objectively, blinded investigators assessed improvement from photographs in the needling group with a mean scar score change of 3.4 from baseline ($P = 0.03$), whilst in the untreated control group, mean scar scores did not vary significantly from baseline at 6 months with a change of only 0.4 ($P > 0.99$), using the Goodman and Baron global scarring grading system (2b) [105].

Novel and Possible Future Acne Scarring Treatments

Two treatments may be worthy of discussion here.

First, advancements in laser technologies have led to some unusual options that may allow improvements in acne scarring to be separated from morbidity. Pico laser technology has been recently described for a number of texture issues including post-acne scarring (4) [106]. A specific study (1b) [107] has looked at post-acne scarring in a single-centre, 20 patient, prospective study. Patients received six treatments with a 755-nm picosecond laser with a spot size of 6 mm, fluence of 0.71 J/cm^2, repetition rate of 5 Hz and pulse width of 750 picoseconds using a diffractive lens array. Fitzpatrick skin types I–V were enrolled.

Subjectively, mean pain score was 2.83 of 10. Patients were satisfied to extremely satisfied with improvement in appearance and texture at their final treatment and follow-up visits. Objectively, blinded assessment scores of 17 patients were 1.5 of 3 and 1.4 of 3 at 1 and 3 months, respectively (a score of 0 indicates 0–25% improvement and a score of 3 indicates >75% improvement). A three-dimensional analysis revealed a mean 24.3% improvement in scar volume, maintained at 1 (24.0%) and 3 (27.2%) months after treatment. Histologic analysis revealed elongation and increased density of elastic fibres, with an increase in dermal collagen and mucin.

The other interesting technology is the application of substances topically utilising the micro thermal zones, needle marks or ablated holes made by temporary fractionated technology or needling breaches in the epidermis. In this chapter we have seen this applied with needling and low concentration of TCA peeling (20%) acting similarly to more aggressive peels [102] and the application of bimatoprost after fractional laser for hypopigmentation [40]. An article that may be useful for atrophic scarring utilising similar concepts of percutaneous access provided by fractionated delivery has been published (2b) [108]. Although this study is uncontrolled, it offers interesting observations. Four blinded dermatologists evaluated a total of 20 photographs taken at baseline and 3 months after fractional CO_2 laser and PLLA treatments using the Modified Manchester Scar Scale.

All four blinded observers accurately identified 76 of the 80 'before' and 'after' photographs agreeing that at the 3-month follow-up visit, 95% of the scars had improved. Four criteria were evaluated: (1) overall improvement, (2) improvement in scar atrophy, (3) improvement in scar colour/dyschromia mismatch and (4) improvement in scar contour. Each of these criteria demonstrated an average improvement of at least 33%.

Typical Treatment Plans for Acne Scarring Cases

Patients with post-acne scarring are a protean group. Let us discuss a number of case examples and follow them through their experience of available and suitable treatments.

A 23-year-old female with skin phototype 2 presented with type 2 atrophic acne scarring,

somewhat visible in tangential lighting but not readily at conversational distance. She was concerned because it was visible to her in the mirror each morning and evening when cleansing her face and applying make-up and skin care. She felt that make-up did not hide but rather accentuated the appearance of her scars. She had no real barriers to treatment and was available to have a series of treatments if required and could take leave from her job if downtime in terms of healing was needed. She had no illnesses and allergies and was on no regular medications aside from vitamins and was neither pregnant nor breastfeeding. However, she was still suffering some active acne. There were no financial or lifestyle issues that would interfere with treatment planning.

A treatment plan was created, and on the basis of best evidence and limiting morbidity, a series of five to six sessions at monthly intervals of fractionated radiofrequency was suggested. However, before this was undertaken, two suggestions were made: control of her acne was considered essential before proceeding to active scarring treatment, and long-pulsed 532-nm laser is suggested for the erythema in her marks and scars [92].

The patient would be expected to experience mild to moderate discomfort from her procedures with post-treatment erythema and swelling lasting 1–2 days and treatments delivered at 4-weekly intervals.

A 40-year-old male with skin type 3 presented with more severe atrophic (grade 3–4) ice pick, deep boxcar and plentiful rolling scaring visible at conversational distance on his temples and upper cheeks. This patient's acne was inactive and the scarring stable although he felt it was getting a little worse with ageing. Financial issues and work responsibilities could interfere with treatment.

In this patient, subcision and punch techniques were suggested initially and then an alternating series of needling along with a number of low-strength (15%) trichloroacetic acid peels. Consideration needs to be given to the position of the scarring as his temples would require care with subcision to avoid the temporal branch of the facial nerve. Although the punch techniques would require dressings, they would not prohibit the patient from working for a prolonged period and could be performed in one session. They could be combined with subcision as long as the scars treated by each technique are different. Needling and 15% TCA peels were chosen for their relative inexpensiveness and low morbidity.

The patient's first procedure would be the most major one and would involve the best part of a week's recovery incorporating the punch and subcision modalities. Thereafter, alternating light TCA peels and needling either at fortnightly intervals as described by Garg and Baveja [79] or as the patient can fit into his work schedule for six cycles.

A third patient, a 17-year-old female, with skin type III has hypertrophic post-acne scarring on the jawline, chin and chest after nodulocystic acne which has now abated. The scars were quite severe and symptomatic with pruritus and tenderness. This patient was still at school and shy but impatient for a result and with a self-confessed low pain threshold.

Treatment planning is difficult with this patient as the ideal may be intralesional fluorouracil and steroids as described by Ren et al. [84]; however, mitigating circumstances here may issue challenges. If fluorouracil is considered, pregnancy prevention is required and injection is relatively frequent and painful. Here, it was decided that intralesional botulinum toxin at 8-weekly intervals as described by Shaarawy et al. [73] would be utilised in conjunction with silicon gels and sheeting finally finishing with vascular laser when erythema remained as the main unresolved issue.

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Self-Assessment Questions

1. With regard to hypopigmented macular scarring
   (a) It is untreatable
   (b) It is treatable with vascular laser
   (c) It is treated by a single treatment of fractional lasers or needling
   (d) It can be treated with fractional lasers and topical agents
   (e) It is likely to settle spontaneously

2. Fractional lasers
   (a) Are not adequate replacements for non-ablative non-fractional technologies
   (b) Are more morbid with more severe adverse reactions than fully ablative procedures such as dermabrasion and full-field ablative lasers
   (c) Are mainly useful in grossly atrophic scarring as the only required treatment but needs several sessions
   (d) Are useful for both atrophic and hypertrophic disease
   (e) Are not synergistic or able to be combined with other therapies

3. Needling
   (a) Is useful for atrophic disease
   (b) Is a form of fractional technology
   (c) Is a treatment that requires several sessions
   (d) Is a treatment of limited morbidity and may be used in higher skin phototypes
   (e) All of the above

4. Intralesional cytotoxic therapy
   (a) Is mainly used for atrophic acne scarring
   (b) Is limited to bleomycin
   (c) Maybe combined with intralesional steroids
   (d) Is completely safe no matter what dose is used
   (e) Only requires one or two treatment sessions of fluorouracil in keloid therapy

5. Regarding chemical peels
   (a) Deep peels remain a mainstay of treatment especially in those of darker skin colour
   (b) Trichloroacetic acid (TCA) is used across the full face in a popular procedure termed CROSS
   (c) May be modified to treat ice-pick scars
   (d) Must not be used in combination with other treatments
   (e) Glycolic acid peels are useful in gross atrophic disease

Correct Answers

1. d: Whilst difficult to treat, hypopigmented scarring is unlikely to respond to the passage of time, vascular lasers or a single session of fractional treatments (requires a number of treatment sessions). It may be responsive to fractional lasers and topical latanoprost or bimatoprost.
2. d: Fractional technologies are superior to non-ablative technologies and less morbid than fully ablative technologies. Gross acne scarring probably requires some sort of filling agent or subcision as well as lasers to achieve success no matter how many sessions are used. Fractional lasers may be used in both atrophic and hypertrophic disease and is the correct answer. Fractional lasers are very much able to be combined successfully with other treatments.
3. e: Needling is a form of fractional technology, although it produces a more limited wound. It requires several sessions (usually about six). It produces very low-risk adverse reactions even in darker skinned patients and is useful in atrophic disease.
4. c: Intralesional cytotoxic drugs, especially 5-fluorouracil and also mitomycin and bleomycin, have been used successfully in the treatment of keloids. Multiple sessions are required, and consideration of their potential toxicity need to be kept in mind (pregnancy and immune suppression), especially if delivered with fractional lasers or needling. Since the original article in 1999, it has been common to mix 5-fluorouracil with steroids.
5. c: Deep chemical peels have become somewhat outdated because of their morbidity, prolonged recovery times and risk of adverse reactions. They are particularly problematic in darker skin types. TCA 100% may be used but is only used as CROSS to individual ice-pick scars; hence, b is wrong and c is correct. Lower strength peels may be augmented safely using needling or similar devices and are readily able to be combined with other therapies. Glycolic acid is a superficial peel only with little utility in deeper forms of scarring.

Traumatic and Burn Scars

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J. Thomas Landers, Kent Saunders, and Peter R. Shumaker

Abstract

The addition of a chapter on "Traumatic and Burn Scars" in the second edition of this text is an acknowledgment of the interval emergence of minimally invasive technologies and techniques in traumatic scar management (e.g., ablative fractional laser resurfacing) and perhaps even a nascent niche in "trauma dermatology." Traumatic scars are inherently heterogeneous and derived from a wide variety of etiologies such as thermal burns, friction injuries, acid burns, lacerations, and blunt force. The final presentation also includes the sequelae of any related reconstructive procedures such as full- and partial-thickness skin grafting. These scars may occur in an unlimited number of locations and may have associated underlying injuries such as tissue loss and injury to bones, tendons, and nerves. Traumatic scars can cause profound disability, deformity, and chronic pain and itch, all of which may lead to significant psychosocial issues that can negatively impact treatment.

Keywords

Traumatic scars · Burns · Botulinum Toxin
Autologous Fat Grafting · Dermabrasion
Microneedling · Laser treatment
Radiofrequency

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Epidemiology

The addition of a chapter on "Traumatic and Burn Scars" in the second edition of this text is an acknowledgment of the interval emergence of minimally invasive technologies and techniques in traumatic scar management (e.g., ablative fractional laser resurfacing (AFR)) and perhaps even a nascent niche in "trauma dermatology." Traumatic scars are inherently heterogeneous and derived from a wide variety of etiologies such as thermal burns, friction injuries, acid burns, lacerations, and blunt force. The final presentation also includes the sequelae of any

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related reconstructive procedures such as full- and partial-thickness skin grafting. These scars may occur in an unlimited number of locations and may have associated underlying injuries such as tissue loss and injury to bones, tendons, and nerves. Traumatic scars can cause profound disability, deformity, and chronic pain and itch, all of which may lead to significant psychosocial issues that can negatively impact treatment.

The global burden of traumatic scarring remains poorly characterized and likely underestimated, as data is generally limited to higher-income countries in limited subsets (e.g., burns). Furthermore, initial posttrauma management may differ widely between high- and low-income countries. For example, standard post-burn care in higher-income countries includes early excision of devitalized tissue with grafting, followed by comprehensive hospital and posthospital management that includes ongoing physical therapy and other support. However, burn care in lower-income countries may more frequently be associated with delayed treatment with prolonged periods of inflammation and limited posthospital care that predisposes to higher rates of pathological scarring [1]. It is estimated that in the developed world, approximately 100 million people acquire scars each year related to surgical procedures, burns, and other injuries. Approximately 25 million of these are derived from trauma and related surgeries [2]. A frequently cited retrospective study by Bombaro et al. reported a prevalence of 67% of hypertrophic scarring in burn patients [3]. Mirastchijski et al. reviewed the costs of burn care in both the acute (immediately after injury) and longer-term (reconstruction and rehabilitation) periods [4]. When their regional data was extrapolated globally, the cost of rehabilitative care (physical therapy, splints, prescriptions, etc.) was estimated to be approximately 240 billion Euros ($297 billion) using 2006 data. This was approximately 4.4 times the estimated cost of acute care and notably did not include perhaps even much larger societal costs such as lost productivity.

Range of Dermatologic Surgery Procedures for Traumatic Scarring

This chapter will focus on minimally invasive adjunctive procedures performed frequently by dermatologic surgeons in the outpatient setting. Commonly accepted treatments for traumatic scars such as surgical intervention (i.e., "cold steel"), pressure, silicone, and physical therapy will not be discussed in detail, although they remain foundational to current paradigms in traumatic scar management. Injectables such as triamcinolone acetonide and 5-fluorouracil are well-established treatments that have been central to hypertrophic scar management for many years, whether or not the scar is traumatic in origin. However, for the purposes of this chapter, such treatments will be considered medical therapies that may be applied in conjunction with other procedures, such as laser-assisted delivery after ablative fractional laser treatment. Overall, the body of literature supporting the efficacy of various procedures for traumatic scars is limited relative to surgical and acne scars. The reasons are multifactorial, but the difficulty in performing controlled studies in the heterogeneous environment after trauma and reinvigorated interest in applications in traumatic scarring in the community are likely contributors. Furthermore, many studies do not necessarily distinguish among the various scar types when reporting their data.

The major categories of procedures selected for discussion in this chapter include "mechanical" techniques (dermabrasion and skin needling), injectables (limited to botulinum toxin and autologous fat here), and energy-based devices (radiofrequency and a variety of lasers and light devices). The largest group, laser and light devices, primarily includes platforms that target water and hemoglobin. Those that target tissue water include full-field ("thermal dermabrasion") and fractional ablative devices, including the 10,600-nm carbon dioxide (CO_2) and 2940-nm erbium–yttrium–aluminum–garnet (Er:YAG) lasers and fractional nonablative (e.g., 1540- and 1550-nm) devices. Devices that target hemoglobin include the 595-nm

pulsed dye laser (PDL) and intense pulsed light (IPL). Other laser devices that target melanin and hemoglobin, such as the 755-nm alexandrite and 1064-nm neodymium-doped–YAG (Nd:YAG), have been reported infrequently for traumatic scar treatment but may also serve as adjuncts in the setting of traumatic scarring to remove problematic hair and traumatic tattoos.

Full-field ablative lasers, such as the 10,600-nm CO_2, and vascular lasers including the 585- and 595-nm PDL have been available for decades. Full-field ablative procedures have been described sparingly for use in traumatic scars, likely due to a limited penetration depth and the extensive associated thermal injury that has rendered the technique useful mainly for focal superficial contouring. In the view of the authors, the advent of fractionation of nonablative and ablative laser platforms around 2004 and 2007, respectively, has been primarily responsible for stimulating increased interest in minimally invasive procedures for traumatic scars [5, 6]. While the 585- and 595-nm PDL has also been available for decades and is supported by multiple studies both in and out of the burn literature, relatively modest efficacy has seemed to relegate it to a subordinate role in the setting of large traumatic scars [7, 8]. Offering tunable depths of penetration and relatively low treatment densities, fractional lasers can be applied for most clinical situations with little regard for skin type and in the absence of erythema, since ubiquitous tissue water is the target chromophore.

Injectables: Botulinum Toxin and Autologous Fat Grafting

Botulinum Toxin

Reports supportive of the use of botulinum toxin to mitigate the formation of scars after trauma began to emerge around 2002. Sherris and Gassner published a case involving revisional excision of a 20-year-old traumatic scar of the forehead, followed with immediate postoperative botulinum injection into the underlying musculature to minimize tension underlying the wound (4) [9]. They later described the concept of "chemoimmobilization" in a series detailing the postoperative injection of botulinum toxin following the repair of traumatic lacerations of the forehead and central face (4) [10]. A study from Egypt in 2006 reported similar findings with the use of botulinum toxin to prevent widening of facial scars. Forty patients had unsightly facial scars excised followed by local botulinum toxin injections. In all but four cases, flatter, narrower scars were reported (3) [11]. Following these promising reports, Gassner et al. published a blinded, placebo-controlled prospective study evaluating the effects of botulinum toxin on wound healing in forehead surgeries and lacerations in 31 patients (2) [12]. A statistically significant difference in the treatment group was noted by two blinded observers using a visual analogue scale (VAS). Ziade et al. published a similar placebo-controlled study of 30 patients treated for traumatic wounds of the face in the emergency department (2) [13]. This study demonstrated statistically significant improvement in the botulinum toxin group using a ten-point VAS but did not show a significant difference using other validated scar evaluation scales including the Patient and Observer Scar Assessment Scale (POSAS) and the Vancouver Scar Scale (VSS).

In addition to efficacy through immobilization of the underlying musculature, botulinum toxin may have direct effects on scar formation through mechanisms including inhibition of transforming growth factor (TGF)-β1 and fibroblast migration and differentiation [14, 15]. A 2009 prospective case series demonstrated statistically significant improvement in erythema, itch, and pliability in 19 existing hypertrophic scars of at least 2 years of duration treated monthly for 3 months with intralesional botulinum toxin (3) [16]. A literature review and report of personal experience published by Goodman in 2010 supported the prophylactic use of botulinum toxin (5) [17]. In his assessment, limitation of dynamic movement and skin tension in the vicinity of a recent injury may prevent the undesirable effects on the

healing wound, as well as help to improve the appearance of existing scars. However, a commentary by Freshwater in 2013 argued that the comparison between the cost of botulinum toxin and the relatively modest improvement documented in existing studies did not justify the use of botulinum toxin in this manner (5) [18]. This viewpoint was supported in a recent systematic review of the literature by Prodromidou et al. in 2015 evaluating botulinum toxin for the prevention and treatment of scars (2) [19]. The conclusion of the authors was that the current evidence does not support the use of botulinum toxin for the treatment or prevention of hypertrophic scars but that additional study is warranted. However, Zhang et al. published a meta-analysis of randomized controlled trials evaluating the efficacy of botulinum toxin type A in the prevention of hypertrophic maxillofacial and neck scars (1) [20]. The authors concluded that botulinum toxin was safe and effective in improving cosmetic outcomes for scars of mixed origin but also noted that the analysis was limited by a paucity of high-quality trials.

Autologous Fat Grafting

Although the history of autologous fat grafting (AFG) for volume correction spans over 100 years, it was not fully recognized until the 1990s that grafted fat might induce active tissue remodeling in addition to providing simple volume replacement. This remodeling process appears to be driven primarily by adipose-derived stem cells present within the graft (5) [21, 22]. In 2007, Sardesai and Moore conducted a prospective cohort study including 14 patients with facial scars of various etiologies (3) [23]. They noted statistically significant improvements in dermal elasticity, scar thickness, and perceptions of stiffness despite the subdermal placement of the graft. Klinger et al. followed 20 patients for 1 year after fat grafting and found statistically significant improvements in scar elasticity as measured by durometer, as well as improvements in appearance and patient perception of pain as measured by the POSAS (3) [24].

Burns are the most studied etiology with respect to a potential role for AFG in traumatic scar management. In 2010, Caviggioli et al. published a case series including 24 patients utilizing AFG for reconstruction of the nipple–areola complex following burns, a technique that they called "nipple resuscitation." At 2-year follow-up, patient satisfaction was good or excellent for all patients, and improvements in skin texture, softness, and elasticity of the nipple–areola complex were also noted (3) [25]. Bruno et al. conducted a split-scar clinical and immunohistochemical study including 93 burn scars that showed a relative normalization in examined specimens at 6 months, accompanied by corresponding functional and aesthetic improvements (2) [26]. A retrospective evaluation of a single session of fat grafting as an adjunct to secondary burn reconstruction of the hand by Byrne et al. demonstrated statistically significant improvements in range of motion, scar quality, and hand outcome scores in 13 patients followed for an average of 9.1 months (3) [27].

Jaspers et al. utilized a comprehensive scar evaluation protocol including the Cutometer to measure scar pliability and POSAS and DSM II ColorMeter to evaluate scar quality to study the effects of single-session AFG on adherent scars. At 3-month follow-up, statistically significant improvements in pliability and POSAS scores were noted (3) [28]. In a long-term follow-up study, these effects were sustained for 1 year after a single session of AFG (3) [29]. Fredman et al. published a small cohort study in 2016 that demonstrated improvement in refractory neuropathic pain following severe burns in six of seven patients treated with AFG. Assessments were performed using the Patient-Reported Outcomes Measurement Information System (PROMIS), an 11-item questionnaire funded by the NIH that measures pain and quantifies the effects on daily life. Additionally, improvements in pruritus and scar pliability, texture, and color were reported (3) [30]. In contradistinction, a recent, randomized, prospective, controlled, split-scar pilot study evaluated the efficacy of AFG compared to saline infiltration in mature burn scars in pediatric patients. Six to 12 months after treatment, no significant differences were noted in the treatment and control arms using the Vancouver Scar Scale (VSS) (2) [31].

Two systematic reviews of the literature addressing the role of AFG in scar rehabilitation were published in 2015 (3,2) [32, 33]. Both detailed the overall promising results seen with AFG, noting improvements in both the appearance and the quality of the treated skin. These observations have been supported by consistent changes on histopathological evaluation of the treated tissue. However, they concluded that the level of evidence supporting the efficacy of the technique is relatively low, and additional studies are warranted.

"Mechanical" Methods

Despite recent advances in energy-based treatments for the cosmetic and functional sequelae of traumatic scarring, established "mechanical" techniques are associated with varying degrees of experience and evidence. Although the volume of data is limited with regard to the treatment of traumatic scars, dermabrasion and needling (percutaneous collagen induction, PCI) will be introduced here.

Dermabrasion

Conceptually, dermabrasion is one of the most intuitive forms of procedural scar revision. This technique has been traced back as far as ancient Egypt, when sandpaper was used to revise scars [34]. The limited available literature regarding this technique for traumatic and burn scars reflects use primarily for cosmetic (i.e., textural irregularities) rather than functional sequelae, as mechanical dermabrasion is associated with significant potential for worsening scarring when performed over large areas in compromised scar tissue. In 1998 Yarborough compared 97 traumatic and surgical scars treated with dermabrasion within 4–8 weeks of injury to 64 mature, traumatic facial scars of at least 3 months duration (3) [35]. Assessments were unblinded and performed by the author. He reported that immediately after re-epithelialization in the early intervention group, the outlines of the scars were essentially unchanged but the contours were improved. Over the next 3–6 months, he reported near resolution of the scar in 89% of these patients and significant improvement in all cases. He reported only modest improvement at best in the mature scar group.

Emsen published two case series evaluating manual dermabrasion with sandpaper for the treatment of traumatic and surgical scars. The first included six patients with facial burns and nine patients with postsurgical or posttraumatic scars (4) [36]. The burn patients were treated in the very early phases of recovery, essentially to remove the damaged tissue. The non-burn traumatic scars were more mature. Photographs were evaluated by three physicians to assess the degree of improvement. The author concluded that the best results were seen in patients with superficial and partial-thickness burn injuries. In the non-burn scars, the results were mixed with a trend toward a better response in younger scars; this raised questions about how early intervention may or may not have affected the trajectory of scar development. The second was a larger series of 41 patients; 23 of these patients had scars resulting from burns or trauma. (4) [37]. Each patient was treated with a single session of manual dermabrasion and evaluated after an average of 29 months. Patient satisfaction was rated on a four-point scale (not good, good, very good, excellent). One patient graded the cosmetic outcome as good, and the rest of the traumatic and burn scars were rated as very good to excellent at the end of the study period. These series only addressed cosmetic concerns and did not assess changes in scar thickness, pliability, or other functional characteristics.

A handful of case reports and series are also present in the literature. In 2011, Surowitz and Shockley reported the effective use of a rotary dermabrader to resurface traumatic facial scars 6–24 months after injury (4) [34]. All three patients were injured in motor vehicle accidents, resulting in superficial and deep soft tissue injuries. Following removal of foreign material and surgical repair, dermabrasion was utilized primarily to address contour and textural irregularities of the resultant scars. The authors concluded, upon comparison of before and after photographs, that the dermabrasion had improved the

appearance of the scars. Kirschbaum reported an excellent cosmetic outcome in a traumatic facial scar due to a motor vehicle accident treated with manual dermabrasion performed approximately 2.5 months after injury (4) [38].

Microneedling

Skin needling is another technique that has been practiced for many decades but has evolved since the concept of microneedling was introduced in 1995. It is a minimally invasive procedure that involves superficial puncturing of the skin by a roller or other device affixed with very fine needles. Although radiofrequency and other light- and energy-based variations are available, the original technique has gained popularity due to the associated safety, simplicity, and low cost [39]. Similar to dermabrasion, there is some evidence for efficacy in the treatment of the cosmetic sequelae of traumatic scarring but little to address the functional sequelae.

A cohort study was published in 2010 evaluating PCI using the Medical Roll-CIT (Vivida, Cape Town, South Africa) in post-burn scarring (3) [40]. This study evaluated 16 patients with mature burn scars treated with one to four sessions of microneedling. Patients and two independent observers rated the scars prior to treatment and 1 year after treatment utilizing the VAS, VSS, and POSAS, with statistically significant improvement documented with each. Furthermore, histological comparison demonstrated considerable normalization of the collagen/elastin matrix, a thickened and normal-appearing epidermis, and return of rete ridges. Similar findings were published by the same group in a 2008 prospective study which included 72 burn and acne scars (3) [41]. Improvements in the histologic architecture and upon clinical evaluation with the same scar scales were reported.

A study including 25 patients with symptomatic burns scars treated with a series of microneedling treatments was published in the Korean literature in 2010. Statistically significant improvements in itch induration, pain, and restriction were noted within an average of five treatments, but the study failed to demonstrate statistically significant improvement in joint deformity or the shape of the scar (4) [42]. The age of the burn scars and the specific assessment tools utilized were not presented, which limits the conclusions that can be drawn.

Laser and Light Therapy

Vascular (Target Hemoglobin)

Erythema is a normal finding within the initial weeks of injury and initial scar formation, but prolonged erythema can be a sign of persistent inflammation and pathological scar formation. Laser and light wavelengths absorbed by hemoglobin may therefore have a potential role in traumatic scar management whenever significant erythema is observed. Since shorter wavelength devices in the visible spectrum also demonstrate significant melanin absorption, caution is warranted for darker skin types. While vascular laser treatment has long been shown to be efficacious in the management of surgical and acne scars, the available data is more limited for traumatic scars. Among vascular-specific devices, the 585/595-nm pulsed dye laser (PDL) is the most studied. Although early studies yielded encouraging results, more recent studies with longer follow-up periods have demonstrated more mixed results. Other common devices used to treat erythematous scars (whether early or pathological) include the 1064-nm neodymium–doped–yttrium–aluminum–garnet (Nd:YAG) laser, 532-nm potassium titanyl phosphate (KTP)/frequency-doubled Nd:YAG laser, and broadband intense pulsed light (IPL).

585/595-nm Pulsed Dye Laser

In 1994, Alster reported improvement in 14 patients with traumatic and surgical scars at least 2 years after injury treated with the 585-nm PDL. Scars were documented with clinical photographs evaluated by blinded observers and with rubber surface impressions at 6-month follow-up (3) [7]. She noted that the degree of clinical improvement was proportional to the number of laser treatments received, with 9 of 14 patients receiving 2 treatments 6 weeks apart and 5

patients receiving only a single treatment. No complications were observed. In 1998, Alster and Nanni evaluated 16 patients with 40 scars (including 16 burn scars) treated with the 585-nm PDL. Patients received an average of 2.75 treatment sessions at a minimum interval of 6 weeks. All patients demonstrated improvement in scar appearance based on photographic evaluation by two blinded physicians. Of note, 50% of patients reported pretreatment pruritus that decreased within one or two sessions (3) [43].

In 1997, Sheridan et al. reported no significant improvements as evaluated by the VSS in ten children with hypertrophic burn scars who received one treatment with the 585-nm PDL, despite each site having the expected clinical endpoint of mild post-treatment purpura. No significant side effects or complications were noted (3) [44]. An early treatment study (< 8 weeks after injury) by Liew et al. in 2002 demonstrated initial improvements after treatment with the 585-nm PDL in two separate sessions at 6-week intervals for five burn scar patients, but at follow-up 6 and 9 months after treatment, there was no significant difference between the treated and untreated sites (3) [45]. No side effects were seen in any patient. The authors concluded that early intervention with the PDL helped to hasten scar resolution. In 2003, Allison et al. reported a study in which 38 patients with burn scars of mixed ages received three treatments with the 585-nm PDL at monthly intervals (3) [46]. Patients were assessed at 6 and 12 months after treatment using the VSS and a pruritus scale. They found that there was no significant difference between treated and untreated sites using the VSS, regardless of the age of the scar, and that improvement was seen in both sites. There was, however, a statistically significant reduction in pruritus at 6- and 12-month follow-up. In 2005, Kono et al. reported the treatment of 15 Asian patients with 22 hypertrophic scars with the 595-nm PDL. Nine of the 15 patients had scars resulting from burns. All patients received two treatments at 4-week intervals, and evaluations were performed using photographic and clinical assessment 1 month after the last treatment. Blinded observers documented statistically significant improvements in the VSS, and additionally, there were reported improvements in symptoms such as pain, pruritus, and burning of the treated scars (3) [47]. Bailey et al. published a pilot study in 2012 comparing the effects of early PDL treatment plus standard compression therapy to compression therapy alone in patients undergoing burn scar reconstruction with skin grafts on the extremity. Two to three laser treatments were applied to one-half of the graft seam at 6-week intervals, and scars were evaluated using the VSS. Laser-treated areas demonstrated greater improvement in height, pliability, pigmentation, and vascularity than compression alone (3) [48].

Other Laser and Light Devices that Target Hemoglobin

1064-nm Nd:YAG

The 1064-nm Nd:YAG has been reported in both long- (ms) and short-pulsed (ns) modes for the treatment of hypertrophic scars. In 2010, Cho et al. reported improvements in keloids and hypertrophic scars associated with a series of treatments with the 1064-nm Q-switched (ns) Nd:YAG laser (3) [49]. Twelve patients with 21 scar sites, 3 of which resulted from trauma or burns, were treated with 5–10 sessions at 1- to 2-week intervals. Using the VSS, statistically significant improvements in pigmentation, vascularity, pliability, and height were all noted at the 3-month follow-up. Observed side effects were a mild prickling sensation during treatment and mild post-treatment erythema, both of which resolved within a few hours.

In 2012, AkaishI et al. reported the results of a study including 22 patients with hypertrophic and keloid scars treated with the long-pulsed (ms) 1064-nm Nd:YAG (3) [50]. Of the 22 patients, 5 had scars resulting from burns or other trauma. The number of treatments ranged from five to ten at 3- to 4-week intervals. Scars were evaluated using the Japan Scar Workshop score, based on a four-point scale (0–3) assessing the degree of associated erythema, hypertrophy, hardness, itching, and pain (maximum of 15 points). The authors reported a significant

decrease in total scores with no reported complications. In 2015, Koike et al. reported the results of 102 patients with hypertrophic scars and keloids treated with a long-pulsed 1064-nm Nd:YAG laser at 3- to 4-week intervals over a 1-year span (3) [51]. Of the 102 patients, just over 10% developed their scars after trauma. The average Japan Scar Workshop score dropped significantly for both hypertrophic scars and keloids over the 1-year observation period, but the authors noted that hypertrophic scars responded better than keloids to the treatment course.

532 nm

In 2003 Cassuto and Emanuelli reported the results of a study involving 23 mature scars treated with a frequency doubled long-pulse 532-nm laser. Sixteen of the 23 scars resulted from burns or trauma. At the end of the study, an average improvement of 81% was reported after two to three treatments. Nineteen out of 22 patients developed microcrusting that resolved within 1 week, but all patients reported satisfaction with the treatment (4) [52].

Intense Pulsed Light

In 2014, Sarkar et al. published a prospective study evaluating the use of intense pulsed light in 19 patients with immature, nonhypertrophic burn scars. Study areas received four treatments at 21-day intervals using a 590-nm cutoff filter. Using the VSS, statistically significant improvements in vascularity, pliability, and height were observed at 1-year follow-up. Treatments were well tolerated, and most patients complained of only mild snapping sensation with treatments (3) [53]. In 2008, Erol et al. published a prospective study including 109 patients with hypertrophic scars of varying etiologies; 43 of the 109 had scars resulting from burns and other trauma. After a minimum of six sessions at 2- to 4-week intervals, clinical improvements were noted in 92.5% of patients including appearance and reductions in height and hardness; 58.7% were rated as good or excellent on photographic evaluation. Side effects such as pain and darkening were noted but quantity was not reported (3) [54].

Ablative Lasers

Ablative lasers are comprised primarily of the 10,600-nm carbon dioxide (CO_2) and 2940-nm erbium–yttrium–aluminum–garnet (Er:YAG). Absorbed avidly by ubiquitous tissue water, these lasers vaporize tissue in a precise manner based on the properties of the delivery system and operator-determined parameters. Although ablative platforms have been available for decades, they had been used relatively sparingly for the treatment of traumatic scars until the advent of microfractional technology around 2007 [6]. The transition from relatively large superficial wounds (mm) up to hundreds of microns deep ("full field") to an array of narrow (μm) and widely spaced columns with penetration up to thousands of microns ("microfractional") has helped to revolutionize traumatic scar management. Initially limited largely to surface contouring of traumatic scars in what amounted to a controlled burn, ablative fractional lasers have advanced full-thickness scar remodeling with promising applications for treating both the cosmetic and functional sequelae of traumatic scars. With significantly higher water absorption, Er:YAG lasers are associated with less thermal "leakage" and a narrower rim of coagulation around the ablative columns than CO_2 lasers. This generally leads to a greater propensity for bleeding, but the relative impact of tissue coagulation on subsequent tissue remodeling remains not fully defined.

10,600-nm CO_2

In 1998, Bernstein et al. reported improvement in 30 patients after scar treatment with a full-field ablative CO_2 laser. All patients (two of these patients had traumatic scars) had greater than 50% improvement based on photographic evaluation by four independent observers graded on a quartile scale 4 months following a single treatment session (3) [55]. Before the development of fractional laser technology, Whang et al. reported improvements in scar texture, color, and relaxation in two patients with hypertrophic burn scars using a "pinhole" method, essentially drilling a series of individual holes in the scar tissue using a small spot size (4) [56]. Lee et al. conducted a

retrospective study including nine patients with hypertrophic scars treated with a combination of laser-cision and the pinhole method in 2014. The authors reported mild to moderate improvement in all patients on photographic assessment using a quartile scale (4) [57]. Waibel and Beer first reported the successful use of an ablative fractional CO_2 laser for the cosmetic improvement of a mature facial burn scar in 2009 (4) [58]. In 2010, Weiss et al. reported a series of 15 patients with non-acne atrophic scars (two of which were traumatic scars) that were treated with a course of three AFR treatments at 1- to 4-month intervals. At 6-month follow-up, patient and investigator scores documented improvements in texture, pigmentation, atrophy, and overall scar appearance. Furthermore, image analysis with a three-dimensional optical profiling system revealed a 38.0% mean reduction in scar volume and a 35.6% mean reduction in maximum scar depth (3) [59].

Kwan et al. addressed the use of ablative fractional CO_2 laser resurfacing (AFR) specifically for functional improvements in a patient with traumatic scar contractures associated with an improvised explosive device in 2011 (4) [60]. In 2012, Shumaker et al. reported the successful application of AFR for a range of functional sequelae associated with traumatic scarring (4) [61]. Overall evidence and a histopathological basis for the efficacy of AFR were bolstered by Ozog et al. in 2013. Ten patients with burn scars received a series of three AFR treatments. Evaluation included VSS and POSAS scores as well as biopsy specimens taken before and 2 months after the final treatment. The authors noted improvements in scar appearance accompanied by a relative normalization of scar architecture and a collagen subtype profile (type I and III) resembling that of non-wounded skin (3) [62]. Perry et al. documented objective improvements in range of motion and subjective reductions in pain, associated with a course of AFR for scar contractures of the upper extremities in a retrospective analysis from 2014 (3) [63]. Anderson et al. synthesized the results of an accumulating number of early reports and series documenting the successful use of AFR for traumatic scars in a consensus paper published in 2014. The authors noted the promising early results and safety of the technique and advocated for more widespread use guided by further research (5) [64].

Since the consensus report described above, the literature has been characterized by additional larger studies with increasing contributions from the burn community. The literature to date demonstrates notable consistent efficacy and safety. Khandelwal et al. published a retrospective study including 44 adult and pediatric patients with burn scars who received a course of AFR. Statistically significant improvements in VSS were documented without reported complications (4) [65]. El-Zawahry et al. performed a prospective split-scar study including 15 burn scars treated with a course of AFR. Three months after the third treatment session, statistically significant improvements in VSS, POSAS, and patient evaluation scores were noted. In addition, scar histopathology revealed concomitant decreases in collagen bundle thickness and density (3) [66]. Blome-Eberwein et al. published a prospective controlled study involving a series of 3 AFR treatments in mature burn scars (48 treated, 32 control). Subjective and objective measurements included VSS, POSAS, cutometer, spectrometer, ultrasound, and sensory evaluation at least 1 month after the final treatment. The authors noted statistically significant improvements in scar thickness, sensation, erythema, and pigmentation (3) [67]. In 2016, Levi et al. reported results from a retrospective study including 131 patients with symptomatic burn scars and skin grafts treated with a course of AFR. A questionnaire was administered that included patient-reported outcome measures. The overall patient satisfaction was 96.7%, with a very low rate of complications and reported reductions in neuropathic pain, tightness, and pruritus along with improvements in scar appearance and pliability (3) [68].

In 2016, Issler-Fisher et al. published results from a prospective study including 47 patients with 118 burn scars treated with at least a single session of AFR. Subjective and objective outcome measures included VSS, POSAS, ultrasound,

assessment of neuropathic pain and pruritus, and quality of life using the Burns Specific Health Scale. Patients with hypertrophic scars also received topical application of a corticosteroid suspension immediately after treatment. The authors reported improvement in thickness, texture, color, and scar symptoms, accompanied by improvements in quality of life in patients with both mature and immature scars (3) [69]. Lee et al. performed a prospective uncontrolled study including 11 patients with burn scars treated with a series of ten AFR treatments at approximately 5-week intervals. VSS assessments 6 months after the final treatment showed significant improvement from baseline. Histologic findings included changes in the upper dermis with newly formed dermal papilla that corresponded to clinical improvements in surface smoothness and tension. Post-inflammatory hyperpigmentation and itching sensation were the most common adverse effect reported, although the treatments in this study were relatively aggressive including multiple passes and a large number of treatments at relatively narrow intervals (4) [70].

Zadkowski et al. reported results from a study in which 47 pediatric patients underwent 57 AFR procedures for mature burn scars. Scar thickness was determined by ultrasound, and VSS assessments were completed independently by the surgeon and the parents of the patients at 1, 4, and 8 months following the procedure. The VSS improved in all treatment areas as evaluated by both the parents and physicians, accompanied by statistically significant improvements in scar thickness measured by ultrasound (3) [71]. In 2017, Poetschke et al. published a prospective study including ten patients treated with a single session of AFR. Each treatment followed a standard treatment paradigm involving multiple passes that included deep microfractional treatment as well as focal superficial ablation appropriate for the selected treatment area. Scar evaluation included pre-treatment and post-treatment assessment 6 months after AFR using POSAS, VSS, Dermatology Life Quality Index (DLQI), and an imaging system. The authors noted significant improvements in POSAS, VSS, and DLQI, as well as scar relief and firmness (3) [72].

2940-nm Er:YAG

In 2000, Kwon et al. published a study including 36 patients with various types of mature scars (including burn and other traumatic scars), treated with single-session resurfacing using a pulsed full-field (non-fractionated) 2940-nm Er:YAG laser. Nine of 12 hypertrophic scars, 17 of 20 depressed scars, and 2 of 4 burn scars improved by more than 50% as evaluated by 2 independent physicians and surgeon based on a quartile assessment scale 6–12 months after treatment. Postoperative erythema was observed in five patients (four with burn scars) 4 months after treatment, and one patient developed post-inflammatory hyperpigmentation 3 months after treatment (4) [73]. In 2005, Eberlein et al. published their experience treating burn scars using a full-field Er:YAG laser in the setting of a large burn center. Twenty-four patients with 96 scars received a single session of Er:YAG laser, and cosmetic improvements were noted consistently in a variety of body sites (4) [74]. Kim et al. published a study including 12 patients with 15 scars following facial lacerations with primary repair in 2012. Scars were treated with a 2940-nm fractionated Er:YAG laser over four sessions at 1-month intervals, beginning at least 4 weeks after injury. All treated scars demonstrated improvements on follow-up assessment 1 month after the final treatment using the VSS and an overall cosmetic scale (3) [75].

Nonablative Fractional Laser Resurfacing

Evidence supporting the use of nonablative fractional laser resurfacing (NAFR) for burn and other traumatic scars is limited primarily to case reports and series and a few small prospective trials. Despite this limited level of evidence, there are encouraging results that appear consistent with the results seen in other types of scarring and rejuvenation. The first report describing the concept of fractional photothermolysis was published by Manstein et al. in 2004. The authors assessed clinical effects including linear

shrinkage and a wrinkle score after facial treatments, as well as corresponding histology (3) [5]. In 2008, Waibel and Beer first described the successful use of NAFR for clinical improvements in a woman with hypertrophic burn scars of the face refractory to intralesional corticosteroids and PDL treatments (4) [76]. The report heralded the coming explosion in interest in the use of fractional photothermolysis for traumatic scars over the coming decade. Waibel et al. published a prospective uncontrolled pilot study including ten patients with burn scars who received a course of five monthly treatments with a 1550-nm nonablative fractional laser. Overall improvement was noted in 90% of subjects as documented by blinded investigators 3 months after the final treatment, with 60% rated as moderate to excellent. Ninety percent of subjects demonstrated improvements in skin texture, and 80% in dyschromia and atrophy or hypertrophy. Persistent erythema was present in one subject at the 3-month follow-up, but otherwise, no adverse events were reported (3) [77].

Vasily et al. performed a prospective clinical and histological study including 33 traumatic or postsurgical scars treated with a 1540-nm nonablative fractional laser. Treatment response was evaluated through blinded photographic assessments. The authors reported that following three to seven treatments, 73% of scars improved 50% or more. Histologic assessment of a surgical scar demonstrated rapid re-epithelialization within 72 h of treatment, and "renewal and reorganization" of collagen fibers within the dermis 2 weeks after treatment. Side effects including swelling and erythema were mild, and downtime was reported as minimal to none in all subjects (3) [78]. Haedersdal et al. conducted a prospective randomized controlled (side by side) trial including 17 patients with mature burn scars treated with a series of three monthly 1540-nm laser treatments in 2009. Blinded response evaluations were performed 4 and 12 weeks after the final treatment. At the end of the study, skin texture was significantly improved compared to controls, but no difference was noted in pigmentation. Patients evaluated scars to be moderately or significantly improved and were satisfied with the treatment. One patient developed minor scarring (2) [79]. Taudorf et al. conducted a similar prospective randomized controlled trial evaluating the efficacy of a series of three monthly 1540-nm NAFR treatments for mature burn scars in 17 patients up to 6 months after treatment. Outcomes including modified POSAS and patient-evaluated satisfaction and improvement were documented, in addition to histological assessment. Treated areas demonstrated statistically significant improvements in appearance, with corresponding remodeling noted on histology at 6 months. Of interest, at the 6-month follow-up, 11 of the 17 patients were noted to have discrete erythema, hyperpigmentation, or imprints from the laser grid pattern in the treatment area, although none were judged as inferior to baseline appearance. In the opinion of the authors, these findings were due to the use of standardized, rather than customized treatment settings (2) [80].

Other Modalities

Recent interest in the minimally invasive management of traumatic scars has resulted in newer approaches with as-yet limited associated evidence. While inclusion of every attempted modality is beyond the scope of this chapter, given their prevalence for other applications, radiofrequency treatments and low-level laser therapy (LLLT) will be discussed briefly here.

Radiofrequency

Wang et al. published a prospective study employing fractional microplasma radiofrequency technology for nonhypertrophic postburn scars in 95 Asian patients in 2017. Patients received three to five treatments at 8- to 16-week intervals. The authors reported an overall response rate of 86.3%, with statistically significant improvements in scar color, thickness, and pliability using the POSAS before and 6 months after the final treatment. Complications included prolonged post-inflammatory hyperpigmentation, acne eruption, herpes simplex eruption, and abnormal hair growth, without severe adverse events noted (3) [81]. Pinheiro et al. performed

monopolar radiofrequency treatment and histopathological evaluation in a 61-year-old woman with long-standing hypertrophic burn scars on her abdomen in an area that was to be removed by abdominoplasty. She received five sessions of monopolar radiofrequency with corresponding epidermal temperatures both above and below 40°C. Histology demonstrated favorable collagen remodeling at temperatures below 40°C but fibrosis at temperatures above 40°C (4) [82].

Low-Level Laser Therapy (LLLT)

Gaida et al. performed a prospective controlled study evaluating the use of LLLT with a 400-mW 670-nm laser twice weekly for 8 weeks in 19 patients with burn scars. Adjacent untreated scar tissue served as a control. Scar evaluation using the VSS and a VAS for pain and pruritus demonstrated improvements, if limited in some, in 17 of the 19 patients without negative effects (3) [83]. Vranova et al. published a comparative prospective controlled study evaluating the efficacy of LLLT at 670 nm alone, and LLLT plus treatment with the PDL. Forty-one children with facial scars were included in the study, and evaluation using the POSAS was performed at 4, 8, and 12 weeks. Statistically significant improvements were noted in both treatment groups at all time points, and enhancements in scar quality were noted for the combination group in all evaluations except for pigmentation and pliability (3) [84].

Early Intervention

An accumulating body of literature exists supporting early laser intervention to optimize surgical scars, but studies focusing on traumatic scars are much more limited at this time. Considering the tremendous worldwide morbidity resulting from traumatic scarring (especially burns) and the advent of very promising and minimally invasive technologies (e.g., fractional photothermolysis), early procedural intervention is mentioned briefly here despite a lack of "maturity" in the literature. In their 2010 article, LeClére and Mordon reviewed decades of experience in laser scar "prevention," the concept of minimizing scar formation in the early period after wounding with minimally invasive laser procedures (5) [85]. Indeed, at the end of the last millennium, McCraw et al. reported the successful use of the 585-nm PDL for prophylactic scar management in a combined group of patients with 171 elective and traumatic incisions. They noted that treatment within the first few weeks of injury resulted in faster resolution of scar stiffness and erythema and less frequent development of hypertrophic scarring (3) [86]. As noted above in the vascular laser section, Liew et al. [45], Allison et al. [46], and Bailey et al. [48] all noted at least some indication of improved outcomes associated with early intervention with the PDL after injury. The potential benefits of early intervention are certainly not limited to PDL. For example, Capon et al. reported significant improvement in burn and surgical scars as evaluated by a VAS after early intervention with an 810-nm diode laser (3) [87]. The potential benefits of techniques such as AFR to minimize hypertrophy and contracture formation after traumatic injury and associated reconstruction have been proposed previously, and in some centers, it is already standard practice to begin treatment with vascular and fractional lasers within weeks and months of major trauma (5,4) [64, 88]. Large, prospective, controlled studies are still needed to confirm the benefits of adjunctive laser and other procedures and to elucidate the optimal timing, settings, and combinations.

Comparative Effectiveness of Common Treatments

High-quality evidence is relatively limited for individual treatment modalities in the treatment of traumatic scars and in even shorter supply for comparative studies. Furthermore, given the relatively noninvasive nature of many of the procedures featured in this chapter and the inherently heterogeneous nature of traumatic scars, they are frequently used in combination to address distinct components of the presentation (e.g., contracture, textural irregularity, dyspigmentation,

etc.). This section will therefore include discussion of studies evaluating combined procedures for traumatic scarring in addition to available comparative studies.

The multimodal approach is exemplified by Hultman et al. who published short-term (3) [89] and long-term (3) [90] results from a prospective, before–after cohort study including 147 burn patients with hypertrophic scars treated with a combination of PDL for pruritus and erythema and CO_2 AFR for stiffness and abnormal texture. Laser treatments were initiated a minimum of 6 months after burn injury and continued every 4–6 weeks until a plateau was reached (average 2.8 sessions). Outcome measures included the VSS and the University of North Carolina "4P" Scar Scale (UNC4P), which rates pain, pruritus, paresthesias, and pliability. The authors noted rapid, significant, and durable improvements using both the VSS and UNC4P which continued during the 25-month follow-up period. In 1998, Alster et al. published a split-scar study examining the effect of full-field (non-fractionated) CO_2 laser ablation alone and in combination with 585-nm PDL for nonerythematous hypertrophic scars. Twenty scars were treated with ablation, and one half of each scar was also treated with the PDL. Global assessment and erythema spectrometry scores were improved after laser treatment in both groups, and the results were more significant in the combination group (3) [91].

Since the PDL is one of the most widely accepted energy-based interventions in the treatment of traumatic scars, it is also frequently included in combination treatments. Asilian et al. published a randomized prospective clinical trial including 69 patients with keloids and hypertrophic scars of various etiologies who were assigned to one of three treatment groups: intralesional triamcinolone acetonide (TAC) 10 mg/mL injected weekly for 8 weeks; TAC (40 mg/mL) mixed with 5-fluorouracil (5-FU, 50 mg/mL) in a 1:9 ratio injected intralesionally weekly for 8 weeks; and intralesional TAC and 5-FU plus 585-nm PDL at 1, 4, and 8 weeks. Based on patient assessments and evaluation of photographs by a blinded observer, the overall efficacy was similar between the TAC + 5-FU and TAC + 5-FU + PDL groups, but there was greater improvement and increased patient satisfaction in the group that included PDL (2) [92]. Bowes et al. published a prospective comparative study evaluating the efficacy of a 585-nm PDL compared to a 532-nm frequency-doubled Nd:YAG laser in both Q-switched (ns) and variable pulse (ms) modes for the treatment of pigmented hypertrophic scars. The scars of six patients were divided into four segments: three treatment segments and an untreated control. After an average of 3.3 treatments at 4- to 6-week intervals, scars were evaluated at 22 weeks using the VSS. Statistically significant improvement was noted after treatments with both the Q-switched 532-nm laser and the 585-nm PDL, without a significant difference between them. The sites treated with the variable pulse 532-nm laser did not differ significantly from controls. Interestingly five of six patients chose the Q-switched 532-nm laser site as the best overall (3) [93]. Lee et al. published a report including two cases of traumatic scarring of the chin successfully treated with a combination of intramuscular botulinum toxin and 595-nm PDL (4) [94]. Park et al. reported two cases of traumatic facial scars successfully treated with a course of PDL combined with 1550-nm NAFR. Following three and five sessions at intervals of 9–15 weeks, the authors reported dramatic cosmetic improvement documented in clinical photographs (4) [95].

In 2010, Cervelli et al. published a study comparing CO_2 AFR performed in both microfractional and macrofractional modes with "classic" dermabrasion in 60 skin type II and III patients with posttraumatic and pathological scars on the face. Photographs were evaluated 12–15 months after treatment using the Manchester Scar Scale. Greater improvements in skin tone, texture, and appearance were observed by both the investigators and patients in the scars treated with AFR. No major complications were observed in either group, and minor complications included transient erythema and edema. The authors concluded that AFR was a viable alternative for the treatment of moderate to severe scars (3) [96]. Ibrahim et al. published a case series in 2016 including 13 patients treated with a CO_2 laser using a

"pinpoint" technique followed by NAFR with a 1540-nm laser. Photographs were evaluated using the VSS and a five-point grading scale. Significant improvement was noted in vascularity, pigmentation, and height, but not pliability (3) [97]. Cho et al. published a case report involving the successful treatment of a burn scar with a combination of a CO_2 laser using the pinhole technique and collagen induction therapy (microneedling) (4) [98]. Another case report documented the successful treatment of a traumatic facial scar with a combination of a 1064-nm Nd:YAG and an ablative 2790-nm yttrium–scandium–gallium–garnet (YSGG) ablative laser (4) [99].

In 2011, Cervelli et al. conducted a prospective randomized comparative trial including 60 patients with traumatic scars. The patients were divided into three treatment groups and received regimen of fat grafts and platelet-rich plasma, 1540-nm NAFR, or both. At the end of the study, all three regimens were reported as effective on blinded physician assessment, but the most effective was the combination treatment followed by NAFR alone (2) [100]. Ohshiro et al. detailed an algorithmic approach to scar management based on clinical findings. Multimodal treatments including LLLT and PDL for erythema, Q-switched lasers for hyperpigmentation, NAFR for superficial scarring, and AFR for thicker scars were advocated (4) [101].

Fractional Laser and Radiofrequency-Assisted Delivery of Therapeutic Agents

Waibel et al. performed a prospective uncontrolled pilot study involving 15 patients with hypertrophic scars following surgery, burns, and other trauma that were treated with CO_2 AFR and immediate postoperative topical application of TAC suspension at a concentration of 10 or 20 mg/mL. Patients received three to five treatment sessions at 2- to 3-month intervals and were reevaluated 6 months after the final treatment. Scars were evaluated based on overall appearance, dyschromia, hypertrophy, and texture using a quartile scoring scale. Eleven of the 15 patients were noted to have over 75% improvement, and the remaining had 50–75% improvement with no adverse effects reported (3) [102]. Issa et al. published a case series in which four patients with hypertrophic scars were treated with ablative fractional radiofrequency followed by the application of topical triamcinolone acetonide suspension 20 mg/mL and acoustic pressure ultrasound to enhance drug delivery. "Complete resolution" was noted in scars of the nose and mandibular area after a single treatment; four treatments were required for a scar on the neck, and partial resolution was observed after four sessions on an extremity. Mild atrophy was noted after treatment of the neck scar (4) [103]. Rkein et al. published the results of a prospective uncontrolled pilot study including 19 patients with atrophic scars resulting from surgery, trauma, and acne treated with CO_2 AFR and immediate application of topically applied poly-L-lactic acid (PLLA; Sculptra®, Galderma Laboratories, L.P.) in 2014. Photographs were evaluated by blinded observers using the modified Manchester Scar Scale 3 months after treatment. Improvement was documented in 95% of the evaluated scars, and the authors noted there may be a synergistic effect between AFR and PLLA. However, the lack of control limited the ability to discriminate between the individual contributions of the laser and PLLA (3) [104]. Massaki et al. treated 14 patients with hypopigmented scars (two following trauma) with 1550-nm NAFR and topical bimatoprost 0.03%. Patients received a mean of 4.5 NAFR treatments at 4- to 8-week intervals, and an independent observer evaluated photographs taken 4 weeks after the final treatment using a quartile scale. Five patients had >75% improvement, while 12 of the 14 had >50% improvement. Side effects were limited to mild transitory post-treatment edema and erythema (3) [105].

Preoperative Evaluation

Traumatic scar evaluation begins like any condition—with the history and physical examination. Important amplifying information includes the mechanism and time since the injury, any

associated injuries, the presence and degree of symptoms such as pain and itch, functional limitations, previous evaluations and treatments, and any pending surgeries or other procedures. Physical examination findings will include considerations of scar location, area of involvement, color (erythema and dyspigmentation), texture and contour irregularities, pliability (stiffness) and range of motion, and the degree of disfigurement. For patients with severe traumatic scarring and existing or incipient functional limitations, physical and occupational therapists can be critical in ongoing contracture management and in properly documenting baseline deficits and treatment progress (e.g., degrees of range of motion, etc.). Additionally, surgical consultation should be considered for any patient with significant functional limitations or for refractory scars.

Periodic traumatic scar evaluation at initial presentation and at intervals is critical to determine the best initial treatment course and evaluate outcomes for both clinical treatment and research to determine the effectiveness of novel therapies. For primarily research purposes, there are a variety of tools and instruments available to assist in gathering both objective and subjective data. These fall into two main categories: (1) clinical scar assessment, facilitated with more than a dozen published and validated scar evaluation scales, and (2) instruments to objectively evaluate scars according to four key components (color, surface area, height/depth, pliability). Furthermore, specialists in physical and occupational therapy can assist with measurements delineating any functional deficits (i.e., degrees of range of motion) [106].

Scar evaluation scales vary considerably depending on their intended purpose but usually integrate to varying degrees: the visual characteristics of the scars, functional impairment, and impairment in quality of life. To date, there is not a single comprehensive scale that adequately incorporates all of these characteristics. In the treatment of traumatic scars, probably the most notable deficiency is the evaluation of function; this is likely because previous minimally invasive therapies have been rather ineffective in the context of severe functional impairment [107]. The most commonly used scales are the VSS and the POSAS. The VSS was developed in 1990 to evaluate burn scars and has provided a foundation for scar evaluation for decades [108]. It assigns numerical values to individual scar characteristics including pigmentation, vascularity, pliability, and height. The POSAS is probably the most common scar evaluation scale used currently to evaluate burn scars. Introduced by Draaijers et al. in 2004, it contains components to be completed by both the clinician and patient [109]. In addition to evaluating physical characteristics of the scar, notably it incorporates subjective information from the patient perspective.

Traditional and emerging imaging techniques can offer objective structural information to supplement physical examination findings, particularly for research purposes. Scar thickness can be determined readily and noninvasively with traditional techniques such as high-frequency ultrasound. Objective evaluations of color (a composite of both vascularization and pigmentation in the area of interest) are offered by instruments such as the Chroma Meter (Minolta, Osaka, Japan). Scar pliability can be determined by instruments such as the Cutometer (Courage and Khazaka Electronic GmbH, Cologne, Germany) [106]. Optical coherence tomography (OCT) is a light-based technology that can offer superficial structural information, such as collagen architecture and tissue vascularity, which otherwise might only be available through skin biopsy. A variety of new devices can construct three-dimensional models of the area of interest to provide information such as scar height, width, elevation, and volume at baseline and over time [110].

Little data exists to pair the relative efficacy of various treatments to patient characteristics such as gender, skin type, scar age, presence or absence of a contracture, etc. However, there are some relevant findings that can guide treatment. Since erythema is more common in younger scars and can be prolonged in pathological scars, it follows that vascular devices will be more useful in these subpopulations. Furthermore, a mature, hypopigmented scar lacks the hemoglobin chromophore. An important observation is the relative safety of fractional devices, both ablative and nonablative,

in a wide variety of skin types. Furthermore, there is mounting evidence that fractional devices offer significant efficacy in the correction of both hyperpigmentation and hypopigmentation. Fractional devices can also be used in mature as well as early scars since tissue water is the chromophore.

Impact of Patient Preference

By the time they present to the dermatologic surgeon, patients who have suffered significant traumatic injury have frequently endured multiple major procedures related to associated reconstruction. Procedure fatigue is a common issue, and the ability to offer management options with predictable efficacy and minimal morbidity in the outpatient setting is frequently well received. All of the procedures discussed above are generally well tolerated in the outpatient setting, and with the possible exception of the donor site after fat grafting, they require minimal postoperative care and downtime. All are also generally associated with a relatively minor risk of complications such as dyspigmentation, relative to the posttrauma baseline. Postoperative pain is also generally minimal and rarely rises above the level of any baseline pain issues. Safety data is limited in the setting of traumatic scars. When treated with appropriate parameters, the risk of worsening scarring also appears to be minimal; once improvements are realized, they tend to be cumulative with little tendency to return to baseline. Interestingly, judicious application of the above procedures seems to have a low tendency to induce new hypertrophic scars and keloids or to worsen existing ones.

Multiple treatment sessions at approximately 1- to 3-month intervals for cumulative improvements are needed. Dermatologic surgeons have assumed a relatively new but expanding role in the treatment of traumatic scars. At present, reimbursement has not caught up with advances in techniques, and it may be challenging in areas to find providers with expertise in traumatic scar management, and billing issues may not be straightforward. For this reason, the availability of traumatic scar treatment and/or insurance reimbursement for treatment may be uneven in the near term [111]. Despite this current reality, effective but minimally invasive treatments are now available that can lead to consistent improvements in cosmetic appearance and function for patients, and continued increases in availability are expected.

Typical Treatment Plan

As illustrated above, while multiple dermatologic surgery procedures demonstrate promise for managing traumatic scars on an individual basis, large high-quality studies to guide optimal timing, combinations, parameters, and treatment order are still generally lacking. Furthermore, there are as many presentations of traumatic scars as there are patients. For these reasons, a "typical" treatment plan must be considered with appropriate flexibility and is still based largely on the experience of the treating physician. Was the scarring the result of a linear laceration from a blade? A large body surface area burn? A dog bite? What is the skin type of the patient? For instance, vascular-specific lasers have less to offer a patient with Fitzpatrick skin types V and VI due to competing absorption from epidermal melanin. With the above in mind, let us consider a patient with a significant but relatively localized thermal burn. This example has been chosen because rehabilitation from this type of trauma has only recently been considered under the umbrella of dermatologic surgery, yet it is amenable to management in the outpatient setting. Additionally, the larger surface area and need for reconstructive procedures such as tissue substitutes and split-thickness skin grafts require considerations relatively removed from linear surgical and acne scars discussed elsewhere.

Case Example

A woman in her 20s presented approximately 4 months after suffering second- and third-degree thermal burns of the anterior neck and upper chest.

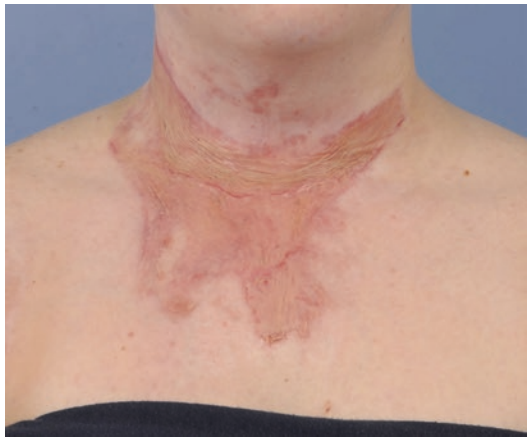

Fig. 49.1 A woman in her 20s approximately 4 months after a thermal burn of the anterior neck and upper chest reconstructed with cadaveric and autologous split-thickness skin grafts. She complained of decreased range of motion, pain, and itch. Moderate erythema and textural irregularity are noted

Treatment at the local burn center included debridement followed by cadaveric and autologous split-thickness skin grafts. Her posthospital care also included compression therapy with a customized molded plastic garment. On examination, the site was well healed, but erythematous mildly hypertrophic scars were noted (Fig. 49.1). Range of motion was limited with upward and side-by-side gaze. She had moderate textural irregularity including prominent horizontal corrugations near along the junction of the neck and chest, and she complained of moderate pain and itch.

In the experience of the authors, the timing of this presentation (approximately 6–16 weeks after injury) is fairly typical and is characterized by increasing clinical and social stability, as well as incipient scar hypertrophy and contractures. While the relative efficacy of early intervention has not yet been defined, this period appears to be a reasonable starting point for the dermatologic surgeon to consider procedural management. The treatment pathway selected will depend on multiple factors including the patient's dominant presenting complaint (e.g., restriction, itch, cosmetic appearance), age of the patient, age of the scar (including associated erythema), sensitivity, skin type, and patient preference at a particular point in time. Accumulating reports indicate that minimally invasive dermatologic procedures such as fractional lasers and vascular lasers may safely begin within a few months of injury, much earlier than the traditional standard of approximately 1 year for surgical revision. Traumatic scars are inherently heterogeneous, so naturally, a treatment plan may include various modalities concurrently or in serial sessions.

Scar Minimization

Prolonged healing time after injury has been associated with pathological scar formation. While this chapter is focused on the treatment of existing scars, procedures that expedite wound healing could minimize the ultimate impact of scars. The emergence of "tissue copying" provides an excellent example of the potential for advancements in dermatologic surgery procedures to reduce the burden of scarring. The concept is derived from the lessons of fractional photothermolysis. In tissue copying, an array of numerous narrow but full-thickness tissue columns containing remnants of all cutaneous adnexal structures can be harvested scarlessly from the donor site and be applied to the wound to attempt to push wound healing toward remodeling rather than scarring. Commercially available devices are the horizon [112]. Other procedural examples for early intervention include photobiomodulation (low-level light/laser therapy), a noninvasive procedure that shows promise in scar minimization when applied early in the wound healing process and may be applied painlessly over larger areas. Botulinum toxin injection may be considered for injection directly into the scarline or underlying musculature shortly after injury, particularly for more localized areas of trauma such as lacerations.

Procedural Considerations

Young scars are frequently erythematous, so vascular-specific devices such as the PDL have been a mainstay for decades. They may be

applied in concurrent or alternating sessions with other modalities. Nonablative fractional resurfacing is frequently considered by the authors for textural improvement and dyspigmentation, so it could be a good choice for integration here at some point. Focal areas of hypertrophy may be amenable to intralesional or laser-assisted delivery of corticosteroids and antimetabolites. The patient's primary complaint in this case was limited range of motion. Ablative fractional laser resurfacing appears to be more effective than other laser modalities for mild to moderate scar contractures and was selected as the initial treatment in this case. Since they generally heat tissue water, fractional devices can also be integrated readily for more mature scars without erythema and for patients of virtually any skin type. If lasers are unavailable, skin needling with or without laser-assisted delivery can be considered.

If vascular and fractional devices are combined in the same session, it makes sense to perform the vascular treatment first as the immediate skin changes after fractional lasers may interfere with the vascular treatment. If laser-assisted delivery is performed, it is prudent to treat the hypertrophic areas first and apply the agent within a few minutes of treatment. The interval between ablative fractional treatments should likely be a minimum of 1 month, but more commonly in the practice of the authors, it is approximately 6–12 weeks. After the "heavy lifting" is done with ablative fractional resurfacing (usually three to five treatments), NAFR may be integrated later in the treatment course. While fractional ablative resurfacing has largely supplanted fully ablative resurfacing for burn scars, it can still be useful when applied judiciously to improve focal textural or pigmentary abnormalities. Patients with tissue deficits and contour irregularities may be candidates for synthetic fillers or autologous fat grafting.

Mitigation of pain during treatment is an important consideration when employing ablative fractional resurfacing, though most traumatic scars of limited involvement can be treated in the clinic setting. Topical anesthetics applied under occlusion for an hour or more can be effective, especially when supplemented with forced cold air or cold packs. Infiltration of local anesthetic or regional blocks can also be considered in appropriate areas. Systemic medications such as opiates and/or benzodiazepines can be used in patients with sensitivity or extensive involvement. One effective combination used frequently by the authors for adults without contraindications is intramuscular ketorolac with oral diazepam or lorazepam about 30 min prior to treatment. Children or adults with extensive injuries may even require general anesthesia. Downtime after treatment is minimal, and generally, the only post-procedure care includes the application of petrolatum for 1–2 days after an ablative fractional laser treatment. The approximate interval between laser treatments is 1–3 months, with less invasive procedures such as vascular lasers, nonablative fractional lasers, and steroid injections toward the shorter end of the spectrum.

For this patient, a series of CO_2 AFR procedures was initiated, along with laser-assisted topical application of triamcinolone acetonide at a concentration of 10 mg/mL at approximately 6-week intervals. Microfractional treatments were performed beginning at a pulse energy of 40 mJ and 5% density (Lumenis UltraPulse, DeepFX™, Yokneam, Israel). Optimal treatment settings have not yet been elucidated in the literature, but in the experience of the authors, large traumatic scars should be treated at low densities with depth proportional to scar thickness and other factors such as tolerability. Focal non-fractional contouring of textural irregularities can be considered and was performed in this case (Active FX™, 125 mJ, density 5, small spot, high repetition rate with wiping) (Fig. 49.2). Large confluent areas of scar tissue should not be de-epithelialized to help avoid worsening scarring, since the relative lack of adnexal structures lowers the healing potential compared to unaffected skin. Excellent improvement in range of motion was noted within 2 weeks of her first treatment. After two treatments (approximately 4 months after her first treatment), significantly decreased erythema was observed along with much improved texture and pliability (Fig. 49.3). Furthermore, she reported substantially decreased pain and itch. Additional improvements in tex-

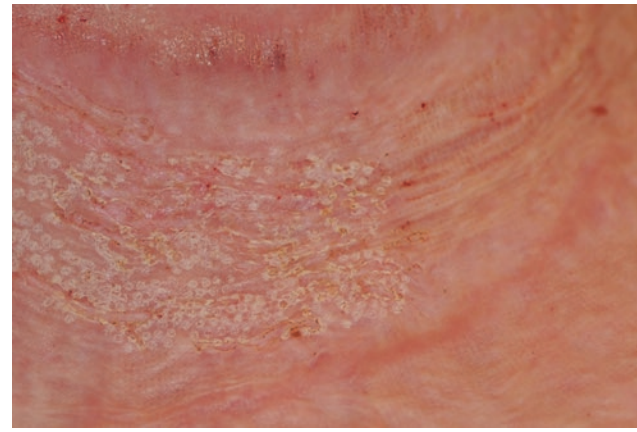

Fig. 49.2 Ablative fractional resurfacing in both microfractional and macrofractional modes was applied in this case. The entire scar sheet was first treated with microfractional resurfacing to a depth of approximately 1.5 mm at a low density. Within minutes of laser treatment, triamcinolone acetonide suspension at a concentration of 10 mg/mL was applied. Focal contouring was then performed using "full-field" laser ablation. Evidence of microfractional treatment appears as tiny dark dots in the background, while macrofractional treatment appears as white crusts

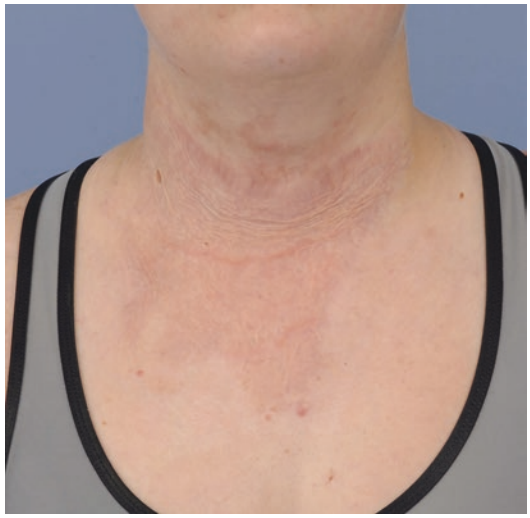

Fig. 49.3 Following two treatments, excellent improvements in erythema, texture, pliability, and range of motion were observed along with subjective improvements in pain and itch. Further improvement could likely be achieved with additional ablative fractional treatments, vascular laser treatments, and nonablative fractional laser treatments

ture and color could likely be achieved with additional ablative and nonablative fractional laser treatments and somewhat less invasive vascular and/or nonablative fractional laser treatments.

Safety

Fortunately, the entire range of procedures discussed in this chapter is associated with few reports of serious side effects or complications. In part, this is because these applications originated in experienced hands. As noted in the discussion on efficacy, there is also a paucity of safety data at present. In the future, as more experience is gained with procedures such as AFR, systematic evaluations of safety must follow. Autologous fat grafting is unique in this group since there is also a degree of associated donor site morbidity. It should also be noted that all of these devices and techniques have alternative aesthetic applications. In contrast to normal skin, scar tissue resulting from trauma and associated reconstruction is often devoid of adnexal structures and therefore underprivileged and underperforming with regard to healing. The therapeutic window for traditional rotary dermabrasion, for example, is relatively narrow in normal skin. The situation is even more perilous in the setting of large traumatic scars. Aggressive dosing and multiple concurrent procedures with cumulative injury should be approached with caution and humility.

Postoperative Care and Follow-Up

Scars are dynamic entities in a constant state of remodeling driven by various factors such as the time after injury, body location, tension, etc. Appropriate monitoring after treatment depends on the age of the scar, associated inflammation, presence of any pathological scarring (hypertrophic scars or keloids), and any associated injuries. In the first few weeks and months after injury and

reconstruction, traumatic scars proceed through a maturation process generally characterized by changes such as contraction and decreasing erythema. As noted above, mature scars that respond to treatment do not seem to have much of a tendency to revert back to the pretreatment state. However, early scars or pathological scars may need continued observation. Persistent erythema, symptoms such as pain and itch, and developing contractures are indications that additional treatment may be required. Surgical consultation may be required for symptomatic contractures to reduce tension, replace tissue deficiencies, and more favorably orient tissues. Appropriate wound care and physical therapy may also be required to achieve optimal results.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
A range of effective, safe, and minimally invasive procedures are currently available for the management of traumatic scarring, but the current quality of evidence in the supporting literature is still generally moderate at best. Additional large, prospective, controlled studies are required to confirm efficacy and elaborate appropriate treatment parameters	B
Procedures with GRADE B recommendations include *botulinum toxin* (considered both in the surrounding musculature and intralesionally), *autologous fat grafting*, *microneedling*, *pulsed dye laser*, *Nd:YAG laser*, *CO_2 ablative fractional laser resurfacing*, and *nonablative fractional laser resurfacing*.	B
Procedures with GRADE C recommendations include *dermabrasion*, *intense pulsed light*, *532-nm laser*, *full-field CO_2 and Er:YAG laser resurfacing*, and *low-level laser therapy*	C
Procedures with GRADE D recommendations include *microplasma radiofrequency*	D

Other Findings

1. **Among the procedures discussed in this chapter for traumatic scarring, ablative fractional resurfacing and autologous fat grafting stand out for their potential life-changing benefits.**
2. **Dermatologic surgery procedures can be an extremely helpful adjunct to traditional rehabilitative efforts for traumatic scar management.** For the benefit of our patients and practices, this skill set should become a part of the standard repertoire of any expert in cutaneous procedures.
3. **Early procedural intervention to mitigate scar and contracture formation is worthy of additional study and has the potential to revolutionize scar treatment paradigms.** Most investigations to date have focused (understandably, given their relatively small size and reproducible nature) on postsurgical scars, so a detailed discussion has not been included here. However, existing reports suggest there are promising potential benefits in anticipatory rather than strictly reactive scar management after trauma.
4. **Dermatologic surgery procedures such as laser hair reduction for amputees or patients with hair redistribution after trauma reconstruction, short-pulsed laser treatment for traumatic tattoos, and botulinum toxin for hyperhidrosis in amputees can be extremely helpful adjuncts in a comprehensive rehabilitative program.** A detailed discussion is beyond the scope of this chapter, but these issues frequently go hand-in-hand with traumatic scarring.

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Self-Assessment Questions

1. You are designing a prospective study on the management of hypertrophic scars. What is an appropriate assessment tool that can be used to evaluate the treatment response?
   (a) Vancouver Scar Scale
   (b) Toronto Scar Scale
   (c) Patient and Family Assessment Scale
   (d) Photographs only

2. True/False: The efficacy of most traumatic scar management procedures is supported by high-quality data derived from large, prospective, randomized controlled trials.

3. You are evaluating a 23-year old-female with dark macular hyperpigmentation adjacent to a scar resulting from a bicycle accident. Which adjunctive laser procedure might be most useful to treat the pigment?
   (a) Long-pulsed (ms) 1064-nm Nd:YAG
   (b) Q-switched (ns) 1064-nm Nd:YAG
   (c) 595-nm PDL
   (d) Intense Pulsed Light

4. A male with Fitzpatrick type V skin type has a hypertrophic traumatic scar on his back. Which laser may NOT be an appropriate choice for treatment?
   (a) Long pulse (ms) 1064 Nd:YAG
   (b) Q-switched (ns) 1064-nm Nd:YAG
   (c) 595-nm PDL
   (d) 10,600-nm fractional ablative CO_2

5. Which of the following laser modalities would likely be most appropriate just prior to topical application for laser-assisted delivery of topical corticosteroids in the treatment of a hypertrophic burn scar?
   (a) 595-nm PDL
   (b) 1064-nm Nd:YAG
   (c) Dermabrasion
   (d) Fractional CO_2

Correct Answers

1. a: The Vancouver Scar Scale (VSS) was developed in 1990 as the first validated scar scale to aid in the assessment of burn scars. It evaluates the scar according to four parameters including pigmentation, vascularity, pliability, and height to generate a score that ranges from 0 to 13, with higher scores indicating increased severity.
2. False: Although a range of dermatologic surgery procedures demonstrate promising results well worthy of continued study, the heterogeneity of traumatic scars and relatively nascent interest in minimally invasive procedural management have contributed to an overall moderate quality of evidence at the present time. Several of the most commonly recognized procedures are GRADE B as indicated above.
3. b: The history suggests a traumatic tattoo from dirt and asphalt. Lasers with a narrow pulse width (nanosecond and picosecond) can be useful adjuncts to treat traumatic tattooing, as well as having some demonstrated efficacy for various scar types.
4. c: The 595-nm wavelength demonstrates significant absorption by both hemoglobin and melanin. The constitutive pigment of this patient may increase the risk of complications such as dyspigmentation and worsening scarring. The longer-wavelength 1064-nm Nd:YAG can be a safer choice in patients with darker skin types.
5. d: Pretreatment with a variety of laser platforms can increase percutaneous absorption of topically applied substances to varying degrees. However, due to the uniformity of the wounding pattern, epidermal disruption, and available depth of penetration, fractional CO_2 laser treatment is the best choice in this group.

Excess Subcutaneous Fat

50

Lindsey Yeh and Sabrina Fabi

Abstract

Excess subcutaneous fat is one of the most common cosmetic concerns in the United States. Removal of excess subcutaneous fat has become an increasingly popular procedure in an outpatient setting. A large variety of devices with varying methods of fat removal or destruction are now available. The methods of treatment range greatly and include tumescent liposuction, injections with deoxycholic acid, cryolipolysis, and treatment with laser and ultrasound devices. The technology, effectiveness, and safety of these various treatments methods are reviewed in this chapter.

Keywords

Subcutaneous fat · Tumescent liposuction
Cryolipolysis · Body contouring
Fat-reduction

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Epidemiology

Over 2/3 of the adult population in the United States is overweight or obese [1]. According to the American Society for Dermatologic Surgery 2017 Consumer Survey on Cosmetic Dermatologic Procedures, the most common concern of those surveyed was excess fat, which is consistent with the data over the past few years. Eighty-five percent of the participants reported that they were bothered by excess weight and more specifically 74% had undesired fat under the chin [2]. Fifty-eight percent of the consumers were considering body sculpting [2]. Not surprisingly, there has been an increasing desire for new methods of excess fat removal and body contouring.

The accumulation of fat is influenced by genetic predisposition, lifestyle, diet, as well as aging. Even in those who are not clinically overweight, patients often desire treatment of areas with excess fat that persist despite adherence to a rigorous exercise routine and diet regimen. Others may be genetically predisposed to store fat in undesirable areas including hips, outer thighs, abdomen, waist, and inner thighs. Excess fat in selective areas, such as the submental region, can increase with age and can signify aging and be aesthetically undesirable. Lipomas can develop over time and most commonly present between the fourth and sixth decades of life with a slightly greater incidence in men than women. Lipomas are often solitary; however,

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multiple lipomas can be seen in lipomatosis. Other than surgical excision and liposuction for larger lesions, there are limited treatment options. Abnormal distribution of subcutaneous fat can also occur with medications such as highly active antiretroviral therapy and prolonged use of prednisone or systemic diseases such as Cushing's disease.

Which Dermatologic Procedures Address This Issue?

Given the pervasiveness and demand for treatment of fat in selective anatomical areas, there has been an advent of new non-invasive treatments. The destruction and reduction of subcutaneous fat is achieved through various mechanisms. There is the direct removal of adipose tissue through liposuction. Tumescent liposuction is a safe and effective method of treating excess subcutaneous fat; however, patients are often hesitant to undergo an invasive procedure. Minimally invasive treatments such as injections of deoxycholic acid are gaining popularity. Many non-invasive procedures are available that were designed to target specific areas of the body ranging from abdomen, flanks, arms, thighs and submental area. The non-invasive devices deliver laser energy, ultrasound, or radiofrequency to induce adipolysis, a reduction in adipocyte size, and/or neocollagenesis. There are also many devices that are FDA cleared for treatment of cellulite, but not specifically approved for treatment of excess fat. The devices approved for cellulite treatment often may have the additional benefit of some reduction in fat. None of these procedures are weight-loss alternatives and are all meant to be performed on patients that are within their ideal body weight and not those that have BMIs >30 (Table 50.1).

Invasive Body Contouring Techniques and Devices

Tumescent Liposuction

Liposuction has been a long-standing procedure for the surgical removal of unwanted subcutaneous fat through small incisions and thin cannulas. Tumescent liposuction was introduced by Jeffrey Klein, MD, in 1988 and has substantially decreased the recovery time, risk, and cost associated with liposuction. Tumescent liposuction is the gold standard for removal of adipose tissue on all parts of the body including submental fat, jowls, buffalo hump, back, arms, abdomen, suprapubic area, waist, hips, buttocks, thighs (inner, outer, and anterior), knees, calves, and ankles. The majority of patients can be treated with satisfactory results in a single session. There is a greater ability to contour areas to the satisfaction of the patient and physician. An additional advantage of tumescent liposuction is the ability to treat multiple areas in one session but still limited to a total of 5 liters of aspirate per session to avoid fluid shift. The cost of the procedure may seem prohibitive initially; however if the need for multiple treatments with non-invasive techniques is taken into account, it may be the most cost-effective treatment option with superior outcomes in just one treatment session.

Tumescent liposuction involves the use of large volumes of normal saline typically containing 500–1000 mg of lidocaine, 1 mg of epinephrine, and 12.5 mL of 8.4% sodium bicarbonate per liter of normal saline that is injected into the subcutaneous fat layer. This allows for safe administration of up to 55 mg/kg of lidocaine prior to liposuction, which is less than the standard recommended safety dose of lidocaine for analgesia in cases where liposuction will not be performed [3]. Epinephrine provides an added

Table 50.1 A summary of the number of treatments recommended, effectiveness and adverse events of available treatments for fat reduction

Device/ Technique	Mechanism of action	FDA approval	Number of publications	Number of treatments needed	Amount of reduction in abdominal circumference	Discomfort/side effects
Tumescent liposuction	Suction-assisted lipolysis	7 mg/kg of lidocaine dose limit	–	1	Variable based on patient and surgeon's preferences	Hematomas, bruising, hyper/ hypopigmentation at cannula entry site
SmartLipo	1064 nm, 1320 nm, and 1440 nm laser	Laser-assisted lipolysis	13	1	Variable based on patient and surgeon's preferences	Minor swelling, bruising, skin burns
Kybella	Injectable deoxycholic acid	Treatment of submental fat	15	2–6	Submental fat: 21.9% decrease in thickness (2 mg/cm^2 × ≤ 6 treatments)	Pain, swelling, edema, bruising, paresthesias at injection site
CoolSculpt	Cryolipolysis	Reduction of subcutaneous fat of the flank, abdomen, submental fat, and thighs	30	4–6	Abdomen: 10–28.5% or 1–4.5 cm after 1 treatment Submental fat: 20% or 2 mm after 2 treatments Thighs: 0.9 cm after 1 treatment	Numbness, tingling, bruising, transient erythema, dysesthesia
Liposonix	HIFU	Non-invasive abdominal circumference reduction	13	1	Abdomen: 2.5 cm after 1 treatment	Mild to moderate pain during procedure. Tenderness, hard lumps, ecchymosis, edema
UltraShape	Low-intensity focused ultrasound	Non-invasive abdominal circumference reduction	12	3 every 2 weeks	Abdomen: 3.58–3.95 cm after 3 treatments at 4 week intervals	Transient pain during treatment, erythema, and small blisters
Vanquish	Radiofrequency	Non-invasive abdominal circumference reduction	8	4–6 treatments weekly	Abdomen: 4.93 cm (range 1–13 cm) after 4 weekly treatments	Mild redness, swelling, temporary increased sensitivity to heat
VelaShape	Bi-polar radiofrequency, infrared light, pulsed vacuum, mechanical massage	Reduction of cellulite and temporary reduction of thigh and abdominal circumference	4	1–3 treatments every 2 weeks	Abdomen: 1.25 cm after 3 weekly treatments and 1.4 cm after 6 weekly treatments Buttocks: 0.5 cm after 6 weekly treatments Thighs: 1.2 cm after 6 weekly treatments Arm: 0.39 cm after 3 weekly treatments	Heat sensation during treatment, erythema, edema
SculpSure	1060 nm laser	Non-invasive treatment of adipose tissue in the abdomen and flank	4	1	Abdomen: 24% after one treatment	Mild to moderate tenderness, numbness, stinging

benefit of minimal blood loss through the vasoconstrictive effects of epinephrine. Sodium bicarbonate is needed to neutralize the acidic pH of lidocaine. The tumescent fluid is warmed to 27–40 °C to minimize the risk of hypothermia and slowly infiltrated (<100 mL/min) for patient comfort. Small incisions are strategically made in areas where scars can be hidden. A small cannula is inserted through the incision. Patients should be advised that there would be small scars remaining at the incision sites.

Patients do require at least 2 days of recovery and swelling in treatment areas can persist for a month. Vigorous exercise is prohibited immediately after treatment and compression garments should be worn for a minimum of 3–4 days postprocedure for optimal results. Patients are typically seen on postoperative day 1 to remove blood-tinged soaked pads from undergarments. Results continue to improve over a period of 3–6 months as the skin contracts.

Standards of care for monitoring and laboratory studies vary. Complete blood count with quantitative platelet count, prothrombin time, partial thromboplastin time, and β-human chorionic gonadotropin in women of childbearing age should be obtained. Additional studies should be ordered based on the patient's medical history, including hepatitis C panels and human immunodeficiency virus (HIV) testing. Tumescent liposuction is contraindicated in patients taking blood thinners, with a history of bleeding disorders, uncontrolled hypertension, hepatic insufficiency, immunosuppression, diabetes, pregnancy, and hernias at the site of desired liposuction. Due to the high use of epinephrine, the use of tumescent liposuction is contraindicated in those with a history of hyperthyroidism, cardiovascular disease, and pheochromocytosis.

In a review of over 4000 cases of patients undergoing tumescent liposuction by single surgeon, there were no reports of hospitalization, nerve damage, deep vein thrombosis, seromas, or permanent lymphedema. There were reports of three large hematomas that resolved over a few months with cold packs, anti-inflammatories, and pain control. One case of erysipelas was reported that rapidly resolved with antibiotics (2b) [4]. Data from a study of 15, 336 patients demonstrated a good safety profile for tumescent liposuction which has been found to be safer than traditional liposuction. There were no reports of death, hypovolemic shock, pulmonary embolism, seizures, or toxic reactions (2b) [5]. Tumescent liposuction performed in an outpatient setting under local anesthesia is safe and effective when performed by qualified physicians.

Laser-Assisted Lipolysis (LAL)

Despite the effectiveness and safety of tumescent liposuction, skin laxity or stretch marks can be a persistent issue after successful treatment with liposuction. To help address this issue, laser lipolysis was introduced. In 2006 the FDA-cleared SmartLipo (CynoSure, Inc., Westford, MA), a 1064 nm neodymium/yttrium aluminum garnet (Nd:YAG) laser system, for surgical incision, excision, vaporization, ablation, coagulation of all soft tissues and for laser-assisted lipolysis. Similar to tumescent liposuction, patients typically only require one treatment unless a significant amount of adipose tissue removal is desired or if additional contouring is needed. The length of the session may last anywhere from 45 min to 2 h for each area treated. Preoperative evaluation is identical to a patient to be treated with tumescent liposuction.

The device reduces adiposity with the added benefit of reducing blood loss, ecchymosis, and recovery times that simultaneously targets fat for destruction while tightening the skin (2b, 2b, 2b) [6–8]. Localized tumescent anesthesia is used after which laser energy is delivered through a 1 mm cannula to the subcutaneous tissue through the small incisions made in the treatment area. Ultra-short, high peak power laser pulses are delivered. Newer devices can fire multiple wavelengths to selectively target different types of tissues. The Smartlipo TriPlex (CynoSure Inc., Westford, MA) has three wavelengths (1064 nm, 1320 nm, and 1440 nm) that can be delivered individually or in various combinations. The 1064 nm and 1320 nm wavelengths are converted to heat after absorption by the adipose tissue,

which causes expansion and subsequent rupture of fat cells. The 1064 nm and 1329 nm wavelengths are also absorbed by oxyhemoglobin, which enhances coagulation of blood vessels in the fat tissue and hemostasis [6]. The 1320 nm energy also targets water and therefore has a greater effect on dermal collagen and skin tightening (5) [9]. Adipocyte membranes are lysed and fat tissue is ablated through thermolysis and later aspirated out. Simultaneously, there is coagulation of the tissue, which promotes collagen tightening and hemostasis [7, 8]. Histological examination of adipose tissue after exposure to the laser emitting cannula showed degenerated cell membranes, dispersed lipids, and heat-coagulated collagen fibers (2b) [10].

Investigators in a prospective, randomized, double-blind controlled trial comparing laser-assisted lipoplasty with suction-assisted lipoplasty treated comparable ipsilateral topographic areas of the body. There were no major clinical differences found between the two sides. Less pain was observed and higher triglycerides were detected in the LAL-treated side (1b) [11]. Badin et al. [8] reported improvement of skin flaccidity in areas that were already moderately flaccid or those with high potential for flaccidity if conventional liposuction were performed. A split abdomen study directly comparing LAL to liposuction alone showed greater reduction in surface area and skin tightening on the laser-treated side at 1 month and 3 months post-procedure. One side was treated with LAL followed by aspiration, and the contralateral side was treated with the laser cannula and fiber without delivery of laser energy followed by tumescent liposuction. In the same study, adverse events were limited to minor swelling and bruising in the treatment areas (1b) [12].

In a review of 537 laser-assisted liposuction cases, there was a low complication rate of 0.93%, which included infection and minor skin burns. Only 3.5% of the patients required a touch-up procedure. There were no reports of skin ulceration, dimpling, necrosis, permanent sensory nerve damage, persistent edema, or systemic complications (1c) [13]. LAL did not affect blood levels of hemoglobin, hematocrit, or triglycerides up to 1 month after treatment (1c) [14]. Although there has been some evidence of potential skin tightening, the procedure carries disadvantages of additional equipment cost, increased procedure time, and increased risk of thermal injury.

Deoxycholic Acid

Deoxycholic acid (Kybella, Kythera Biopharmaceuticals Inc., Westlake Village, California) was approved by the FDA in 2015 for the treatment of moderate to severe submental fat in men and women over 18 years of age. The FDA has not approved the safety and effectiveness of the treatment of subcutaneous fat outside the submental region, although there have been case reports of off-label uses for treatment of lipomas and HIV-associated lipohypertrophy [15, 16]. Deoxycholic acid is a bile acid produced in the body that emulsifies fat for absorption in the intestines. Kybella is a synthetically derived deoxycholic acid that is adipolytic when injected, disrupting adipocyte membranes and irreversible cell breakdown and adipocyte lysis, prompting mild inflammation and recruitment of macrophages for clearing of the cellular debris (1b) [17]. Histological evaluation of tissue after treatment with deoxycholic acid showed adipocyte lysis as early as the first day after treatment. After 7 days, lipid-laden macrophages and septal inflammation can be observed in the septal layer and by day 28, nearly all inflammation has resolved while fat lobule atrophy is visualized along with neovascularization and neocollagenesis (1c) [18].

Multiple phase III clinical trials in Europe, the United States, and Canada have demonstrated the effectiveness and safety of deoxycholic acid (1b, 1b) [19, 20]. European studies indicate that both 1 and 2 mg/cm^2 dosages are effective for reducing submental fat; however greater improvements were seen with the 2 mg/cm^2 dose (1a) [21]. The REFINE-1 trial, a multicenter, randomized, double-blind, placebo-controlled trial conducted in the United States and Canada, treated patients with 2 mg/cm^2, for a maximum of 10 mL (50 mg), five vials, per treatment session, at approximately 28-day intervals for up to six treatments. Improvement was graded by both the patient and

clinician with the Patient-Reported Submental Fat Rating Scales (PR-SMFRS) and the Clinician-Reported Submental Fat Rating Scales (CR-SMFRS), respectively. MRI before and after treatment demonstrated an 8 times greater reduction in submental volume in responders when compared to placebo-treated subjects. Seventy percent of the subjects treated were responders compared to 18.6% in the placebo group. Fifty-five percent responded in two treatments and 75% responded after four treatments [20]. Even with reduction of submental fat, skin laxity remained unchanged or even improved [21]. Patients who responded to treatment were followed for 1 year, and over 90% maintained a clinical improvement [21]. Long-term follow-up concluded that reductions in submental fat were sustained and maintained for up to 4 years in approximately 80% of patients [22].

Optimal patients are those with palpable fat located submentally in the preplatysmal plane. To ensure fat is not located behind the platysma, patients are asked to grimace on exam and submental fat is pinched to ensure it is still palpable. Patients with significant skin laxity and minimal to no fat are not ideal candidates for treatment with deoxycholic acid. Those that had more severe submental fullness required more deoxycholic acid, which may prove cost prohibitive, especially when considering off-label indications. A single treatment takes approximately 5 min to perform. In the trials patients were treated as early as 4 weeks from the last injection even when mild swelling was still present, but in clinical practice longer treatment intervals of 6–8 weeks are recommended to allow all swelling to subside and it can take up to 6–8 weeks for full results from a single treatment to be seen.

Adverse events related to deoxycholic acid injection are localized to the injection site and include pain, swelling/edema, hematoma/bruising, anesthesia, erythema, induration, paresthesia, and nodules. Most patients only experienced mild to moderate symptoms that resolved within 28 days of treatment, with swelling and paresthesias being the most common. Adverse events were typically most severe after the first treatment and improved with subsequent treatments. The more concerning adverse effects of marginal mandibular nerve paresis, ulceration, and dysphagia were rare and resolved without sequelae [20]. The sense of dysphagia is related to the injection volume and posttreatment swelling and edema. Marginal mandibular nerve paresis presents with an asymmetrical smile and is likely due to injection 1.0–1.5 cm above the inferior border of the mandible above which the marginal mandibular nerve runs medial to the facial artery. Superficial injections can cause skin ulcerations. To avoid ulceration, injections should be made midway into the preplatysmal fat. A single case report of alopecia in the beard area of a male after treatment with deoxycholic acid has been reported. The alopecia has persisted in the treated areas despite topical treatment with 0.03% bimatoprost (Latisse, Allergan, Irvine, CA) [23].

Non-invasive Body Contouring Techniques and Devices

Cryolipolysis

Cryolipolysis was introduced in 2007 based on observations that lipid-rich areas were more susceptible to injury from cold temperatures as observed in cold-induced panniculitis such as popsicle panniculitis in children or equestrian panniculitis seen in young women. The exposure to cold temperatures elicits a localized inflammation of the subcutaneous fat resulting in rupture of the adipose tissue cells and death of adipocytes. Inflammation is seen histologically 3 days after exposure and peaks at 14 days. After 14–30 days of treatment, phagocytosis of lipid by macrophages is seen. After the inflammatory response subsides, a lower volume of fat cells is left with no residual evidence of inflammation and no persistent damage to any tissues (1c, 1c, 1c) [24–26]. The FDA cleared a cryolipolytic device (CoolSculpting®, ZELTIQ Aesthetics, Pleasanton, CA) for reduction of subcutaneous fat in the flank, abdomen, thighs, submental area, bra fat, back fat, underneath the buttocks (also known as the banana roll), and upper arm. It was

also recently FDA cleared for the treatment of skin laxity in the submental area.

Typically, excess tissue is placed between two cooling plates through a vacuum suction with varying lengths of contact time. Optimally, the subcutaneous fat layer is cooled to 4 °C for a total of 35–75 min per applicator, depending on the applicator that is used. There is no downtime, no need for analgesics during the procedure, and patients are able to resume normal daily activities immediately. Multiple animal and clinical trials have proven the efficacy and safety of cryolipolysis through histological, caliper, visual comparisons and ultrasound findings. In a review of 19 studies, an average reduction of 14.67–28.5% fat was reported through caliper measurements, and average of 10.3–25.5% reduction was reported based on ultrasound measurements of various treatment areas (2a) [27]. Shek et al. [28] showed significant abdominal fat reduction of 4.5 cm after a single treatment. Three months after the initial treatment, a second treatment was administered and additional significant improvement was seen (0.4 cm, for a total of 4.9 cm from both procedures) when compared to baseline (4) [28].

In a multicenter, prospective, nonrandomized study of 32 patients treated with cryolipolysis in the flank and back, over 80% of the patients reported fat reduction at 4-month follow-up after just one treatment. Ultrasound of a 1/3 of the patients revealed 22.4% reduction in fat (4) [29].

Treatment of submental fat with a specialized applicator for the area was found to be safe and effective. After two cycles of treatment, ultrasound measurements showed a mean fat layer reduction of 2.0 mm (range + 2.00 mm to −5.9 mm), which correlates with a 20% reduction in the submental fat layer and was statistically significant ($P < 0.0001$). At follow-up 77% of the treated patients reported visible fat reduction (4) [30].

After one treatment of the inner thighs, there were 0.9 cm mean reduction in circumference and a 2.8 mm reduction of fat thickness at 16-week follow-up (4) [31]. In another study of 11 subjects treated with cryolipolysis in the inner thighs, there was an average 20% reduction in fat layer thickness corresponding to a 3.3 mm reduction (4) [32]. In a prospective, nonrandomized study, ultrasound images were analyzed, and a 2.6 mm fat layer reduction was calculated after just one treatment (4) [33].

A pilot study evaluating the use of cryolipolysis to reduce upper arm fat revealed a mean reduction of 15.3% in the fat layer, which corresponds to 2.03 mm, after one treatment cycle. The contralateral arm was not treated and served as a control (4) [34].

There have been multiple reports of effective fat reduction with off-label treatment of areas such as anterior brassiere rolls, lumbar rolls, hip, medial knee, and ankles, but patients need to have the appropriate distribution of fat in these areas so that the applicators can fit properly and not cause irregularities with treatment [27].

Long-term follow-up of two case studies showed enduring treatment effects even 6 or 9 years. Only one flank was treated and despite an extended period of time passing and weight fluctuations after the last treatment, the decrease in adipose tissue on the treated side persisted (3b) [35]. Enhanced clinical outcomes have been reported with 2 min of manual massage (1 min of kneading, 1 min of circular massage) immediately posttreatment. The mean fat reduction was 44% greater with massage than without when measured by ultrasound and with no increase in adverse effects (3b) [36].

Studies have not produced any significant adverse effects. No abnormal cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, or any decline in liver function have been detected even after multiple treatments in 1 day (4) [37]. Adverse effects are limited to mild discomfort during treatment, numbness and tingling (lasted a mean of 3.6 weeks, all resolved within 7 weeks), bruising, and transient erythema (4) [26, 38]. Some patients report posttreatment pain that occurs more commonly in women and neuropathic pain that is not responsive to medication. In a retrospective review of 125 patients, 19 developed posttreatment pain, 100% of which were female. Onset of pain occurred on average at 3 days and lasted anywhere between 2 and 60 days (mean 11 days). All cases were self-

limited and the majority of patients experienced pain relief with oral gabapentin (4) [39].

Incidents of paradoxical adipose hyperplasia (PAH) have been reported. Patients develop a well-demarcated, firm subcutaneous mass in the area of treatment approximately 3–6 months after treatment that persists. Although it was initially thought to be a rare phenomenon, as cryolipolysis gains popularity, the frequency has increased and occurs in 0.021% of treatments with 55% of the cases occurring in men. Of the reported cases, PAH was more commonly developed in the chest and anterior lower abdomen. The increased susceptibility of men developing PAH has been attributed to difference in fat distribution between men and women. Men have more visceral adipose tissue that is not appropriate for cryolipolysis. Differences in the orientation of the fibrous septa in fat may also contribute to differences as well as inadequate tissue draw (4) [40].

Contraindications to cryolipolysis include conditions exacerbated by cold exposure such as cryoglobulinemia, cold urticaria, and paroxysmal cold hemoglobinuria, as well as a hernia directly in the area to be treated [26]. Caution should be taken in patients with scars over the area to be treated. Patients that have unrealistic expectations and are looking for more than 20% reduction in adipose tissue from a single session are not ideal candidates. A second treatment can be performed to achieve more fat reduction as early as 6 weeks from the initial treatment. Patients that do not have an inch to pinch, do not have enough tissue to be drawn up into the vacuum-assisted applicators, and are better candidates for the flat applicator if there is enough fat for the flat applicator can sit on and do not create any drop-offs. Patients should be encouraged to return 2–6 months after the initial treatment. A study that took ultrasound measurements of subcutaneous fat 2 and 6 months after one treatment with cryolipolysis found a 20.4% reduction in the subcutaneous fat later after 2 months and 25.5% after 6 months [38].

High-Intensity Focused Ultrasound (HIFU) (Liposonix)

High-intensity focused ultrasound (HIFU) (2 MHz, >1000 W/cm^2) utilizes the energy behind high-frequency acoustic energy to target subcutaneous adipose tissue at depths that can be controlled by wavelength and energy level. The adipose tissue is ablated through thermal effects and mechanical (cavitational) effects. When the adipose tissue is raised to temperatures above 55 °C, it induces coagulation and necrosis causing virtually instantaneous cell death. Cavitation disrupts the adipocyte membrane through negative acoustic pressure. The Liposonix system (Valeant Pharmaceuticals, Hayward, CA) is the only FDA-cleared HIFU device for non-invasive waist circumference reduction. Energy depth with this device is fixed at 1.3 cm so patients need to have at least an inch of palpable fat in the area to be treated, especially over bony landmarks to avoid cutaneous burns and a BMI of ≤30. Areas that can be treated are limited by the size of the handpiece.

A retrospective chart review of 85 patients who underwent only a single treatment of the anterior abdomen and flank areas with HIFU found a 4.6 ± 2.4 cm mean reduction in waist circumference (range −9 cm to +4 cm) at 3-month follow-up. A total energy dose of 104–148 J/cm^2 (mean 134.8 J/cm^2) was delivered (4) [41]. Solish et al. [42] randomized patients to three passes of 47 J/cm^2 (total energy dose of 141 J/cm^2), 52 J/cm^2 (156 J/cm^2), or 59 J/cm2 (177 J/cm^2). They did not find significant differences in waist circumference between groups at 12 weeks. However, the group that received the highest energy treatment achieved a greater reduction in waist circumference at 4 weeks than the lower energy groups. At 12 weeks, participants' waist circumferences were an average of 2.5 cm smaller, and no significant differences in waist circumference measurements were seen between the different treatment groups (4) [42]. Jewell

et al. [43] reported statistically significant improvement in waist circumference in groups treated with energy levels of 59 J/cm^2 (177 J/cm^2) compared to a sham group in the intent to treat population. In a per-protocol population, statistical significance was seen in both the 59 J/cm^2 (−2.52 cm; p = 0.002) and the 47 J/cm^2 group (−2.10 cm; p = 0.04) when compared to the sham group (2b) [43].

Few patients reported prolonged tenderness, hard lumps, ecchymosis, or edema [41]. There were no reports of scarring or burns (2b) [44]. Typically patients only report mild to moderate pain during the procedure, which in practice sometimes requires a narcotic analgesic for pain mitigation. The pain severity seems to increase with the level of energy delivered. The procedure typically takes 1.5–2 h to treat the full abdomen and flanks. Bruising and edema resolved within 12–16 days. Lipid profiles, markers of inflammation, coagulation of liver or renal function, hematologic assessments, or blood chemistry after treatments did not reveal any abnormalities. Sixty to seventy-seven percent of patients felt that the treatment with HIFU met or exceeded their expectations. Up to 92% of the patients would be willing to undergo additional treatments for optimal results [43]. Contraindications for using HIFU include pregnancy, implanted electrical devices, current use of anticoagulant therapy, a coagulation disorder, cancer, hernia, and sensory loss in the treatment area.

Low-Intensity Focused Ultrasound (UltraShape)

Low-intensity focused ultrasound (UltraShape, Syneron Medical, Yokneam, Israel) is a device that emits low-intensity focused ultrasound (200 ± 30 kHz, 1.75 W/cm^2). It is FDA approved for non-invasive reduction of abdominal circumference via fat cell destruction. Three treatments are administered every 4 weeks. A single treatment session can last from 60 to 120 min. Newer platforms have reduced treatment times of 40–60 min. The acoustic waves cause changes in pressure within the fat cells creating bubbles in the fluid surrounding the adipocytes, which disrupt and lyse the fat cell membranes. The liquefied fat is then released as triglycerides. The ultrasound waves are focused on adipocytes and do not affect other tissues or skin appendages. The transducer delivers ultrasound energy 1.5 cm below the epidermis. Therefore an appropriate candidate for the device should have at least 3 cm of tissue that can be pinched. All areas can be treated with a single handpiece; therefore the treatment area is not limited by pre-determined applicator sizes. The majority of the available data evaluates treatments at 4-week intervals, but a study by Ascher showed significantly reduced circumferences in areas treated after three treatments every 2 weeks (4) [45].

A prospective study conducted in Spain treated 30 subjects with the UltraShape Contour I in the abdomen, flank, and off-label areas including the inner and outer thighs, inner knees, and breasts in males (4) [46]. Each area was treated three times at 1-month intervals. Participants showed significant progressive improvement after each treatment session in all treatment areas as measured by pre- and posttreatment photographs, ultrasound, and circumference measurements. The mean reduction in fat thickness was approximately 2.27 ± 0.8 cm by ultrasound measurements, while the mean abdominal circumference reduction was 3.95 ± 1.99 cm. The greatest reductions were seen in the outer thighs and the smallest changes were seen in the inner thighs [46]. A multicenter study (with centers in the United States, the United Kingdom, and Japan) reported a mean reduction of 2 cm in abdominal circumference and 2.9 mm in fat thickness after a single treatment session (2b) [47]. The findings were not as promising in a study evaluating the same number of treatment sessions in Southeast Asians. It was postulated that the smaller frame

of the participants made the treatment less effective or clinically apparent (4) [48].

Ascher [45] evaluated the effectiveness of three treatments with UltraShape at 2-week intervals instead of waiting 4 weeks between treatments, which is the schedule that the majority of the other studies followed. After the first treatment, the abdominal circumference of participants decreased by a mean of 2.47 cm (range 0.85 cm to −7.50 cm). After the second treatment, mean reduction was 3.52 cm (range, 0.5 to −8.00 cm) and − 3.51 cm after the third treatment. Eighty-four days after the last treatment, the mean reduction in abdominal circumference was 3.58 cm (range, 1.0–10.00 cm). These results were comparable to the results when treatments were administered 4 weeks apart. There were also no increased reports of adverse events [45].

No severe adverse effects have been reported. Infrequently patients experience transient pain during the treatment, mild erythema, and small blisters. No paresthesias, hematomas, ecchymoses, or edema, which may be seen more commonly with other body contouring treatments, has been reported. Cholesterol levels were not affected by the treatment; however mild increases in triglycerides were reported; however levels remained within normal limits. Since triglycerides are processed through the liver, there could potentially be concern for steatosis, but liver ultrasounds did not demonstrate any fat deposition in the liver [46].

Radiofrequency (Vanquish, Velashape)

Focused field radiofrequency energy (Vanquish, BTL Aesthetics, Prague, CR) is the first non-invasive focused field radiofrequency treatment for the reduction of subcutaneous fat. It is FDA cleared for non-surgical circumferential reduction of the abdomen. The technology is based on an oscillating electrical current that creates heat through collision of charged molecules and ions. Fat is an insulator with the ability of inner polarization. The electrical dipoles in the adipose tissue arrange in one direction against the polarization of the electrical field. The oscillating electrical current forces the electrical dipoles to oscillate also, creating heat in the subcutaneous adipose tissue. The applicator is designed to selectively deliver a focused energy with specific impedance that targets the adipose tissue layer. This limits energy delivered to the dermis, epidermis, and muscles. The adipose tissue is heated to 45–46 °C, while epidermal temperature remains under 42 °C. The radiofrequency is delivered through an applicator positioned over the targeted area approximately1cm above the skin. The applicator is large enough to simultaneously treat the abdomen and flanks. Patients are encouraged to stay well hydrated prior to and after the treatment to aid the body in eliminating dead fat cells. Recommended therapy consists of 30-min weekly sessions over a 4-week time period. Possible side effects include mild redness, swelling for approximately 1 h, and temporary increased sensitivity to heat (4) [49].

Biopsies taken from porcine tissue after one radiofrequency treatment showed desquamation of superficial layers in the epidermis, perivascular infiltration, alteration, and significant destruction of the adipose tissue [50]. After four treatments the biopsy revealed infiltration of foamy macrophages and neutrophil granulocytes. After a recovery period, histological examination of the skin biopsies revealed focal disintegration in adipose tissue and thick fibrotic septa. The epidermis, dermis, and adnexal structures were not affected. DNA analysis identified DNA damage indicating apoptosis of adipocytes (1c) [50].

In a prospective clinical trial of 35 patients, a mean reduction of abdominal circumference 4.93 cm (range 1–13 cm decrease) was reported 4 weeks after weekly treatments for 4 weeks [49]. Five subjects showed a reduction of 1 cm or less and four subjects had over 10 cm reduction of the abdominal circumference. Patients reported transient mild to moderate erythema over the treatment areas, which resolved within 60 min. 90.5% of the subjects did not report any pain.

Overall 71% were satisfied with the results. Three of the participants did show a significant response to the treatment, most likely due to a thin fat layer [49]. It was a well-tolerated treatment with no downtime and no need for additional use of compression garments or special posttreatment care. Clinical data regarding both the long-term effectiveness of focused field radiofrequency is limited at this time.

Other devices that utilize radiofrequency technology are the VelaSmooth and VelaShape (Syneron Medical Ltd., Yokneam, Israel), both of which make use of bipolar RF, infrared light (700–2000 nm), and a vacuum for mechanical tissue manipulation. VelaShape is FDA cleared for cellulite and circumferential reduction. The VelaShape III is a new high-power version of VelaShape (Syneron Medical Ltd., Yokneam, Israel) and is FDA cleared for reduction in cellulite and for the temporary reduction of thigh and abdominal circumference. The infrared light heats the tissue at 3 mm of depth and optimizes the penetration of the radiofrequency energy by preheating the target adipose tissue and minimizing impedance of this tissue. The bi-polar radiofrequency penetrates to a deeper level at 15 mm. The vacuum and massage rollers mechanically manipulate the tissue and increase local circulation and lymphatic drainage enhancing fat metabolism. The application of the thermal energy to the dermis induces collagen contraction and neocollagenesis. The vacuum further potentiates neocollagenesis through mechanical stress imposed on dermal fibroblasts. These effects correlate with clinical reduction in skin laxity and circumference reduction. There is no direct destruction of the adipocytes through this treatment, but there may be a decrease in adipocyte size due to cell dehydration and increased metabolic use of stored energy from the heat energy that is applied.

The recommended treatment frequency for the Velashape III is typically 1–3 treatments about 2 weeks apart. Each session lasts for approximately 20 min. It has been shown to be safe and effective in reducing the circumference of the arms, abdomen, and thighs. The ideal candidate should have a BMI of 30 or less. No specific recommendations are given based on minimum or maximum requirements of subcutaneous fat; however, the hand piece is a vacuum device and requires adequate suctioning of subcutaneous tissue.

In a prospective clinical trial, 35 female patients with skin laxity and unwanted subcutaneous fat in the abdomen/flanks, buttocks, or thighs were treated with the VelaShape II weekly for 6 weeks. The average reduction in circumference at 3-month follow-up was 1.4 cm in the abdomen/flanks, 0.5 cm in the buttocks, and 1.2 cm from the thighs. Ninety-three percent of participants demonstrated some type of change to the thickness of the fat layer, and on average, a 29% reduction was seen between baseline and 1-month follow-up visits. Patients experienced erythema, edema, and a strong heating sensation associated with treatments (4) [51]. In 2009, Brightman et al. [52] treated 29 postpartum subjects with VelaShape and found a significant reduction in abdominal circumference 3 months after the last treatment as well as improved skin laxity. The abdomen and flanks were treated once weekly for 4 weeks. The same study also treated the upper arms once a week for 5 weeks. A significant reduction in arm circumference was seen after the third treatment (0.387 cm, $P = 0.0076$) and continued reduction was seen through the fifth treatment. At 1- and 3-month follow-up post-procedure, the reduction in arm circumference remained significant, but not after 6 months. The average reduction in abdominal circumference after three treatments was 1.25 cm ($P = 0.0130$). At the 3-month follow-up evaluation, average abdominal circumference lost was 1.82 cm. Subjects tolerated the treatment well and at no point were any treatments discontinued due to patient discomfort. No adverse events were reported other than mild erythema which was noted immediately after the treatment and dissipated within an hour. Some patients had small ecchymoses that resolved in 5–7 days (4) [52]. There are no follow-up studies beyond the first few months after treatment with VelaShape to assess long-term outcomes.

Laser

Laser 1060 nm (SculpSure)

A 1060 nm diode laser (SculpSure, Cynosure, Westford, Massachusetts) was the first FDA-cleared laser for the non-invasive treatment of adipose tissue in the abdomen and flank in 2015. The device uses a 1060 nm diode laser that specifically targets the adipose tissue and heats the tissue between 42 °C and 47 °C with contact cooling to minimize damage to the epidermal or dermal layers of the skin. Melanin is also not highly targeted at this wavelength and therefore thought to be safe for all skin types. The device destroys adipocytes through the elevated temperatures. Each device has a bracket that is placed over the abdomen and flank, with four applicators applied to the skin that do not require suction assistance. The placement of the applicators can be personalized for each patient. The easy placement and size of the applicators allows for potential off-label use to treat other areas of the body. Each treatment takes only 25 min. There is no downtime and patients can resume all activities immediately after the procedure.

The clinical data specifically evaluating the 1060 nm diode laser for the treatment of adipose tissue is limited. In a prospective study, 49 subjects received treatment of 1 flank with the 1060 nm laser and the contralateral flank served as a control with no treatments [53]. Photos and ultrasound measurements of fat thickness were performed at baseline and follow-up at 6 and 12 weeks posttreatment. Board-certified dermatologists correctly identified the photograph of the treated flank 90.3% of the time. Statistically significant reductions in the treatment flank compared to the control side were seen at weeks 6 and 12 and 96% of the subjects were satisfied. Ultrasound measurements revealed a 13% reduction in fat thickness of the flanks 12 weeks after treatment. The most commonly reported side effects were mild to moderate tenderness, numbness, and stinging all of which resolved within 1–3 weeks (4) [53]. Seventeen patients treated in the abdomen or flank showed a 24% reduction in fat based on ultrasound, MRI, and photographic evaluation (4) [54]. However, clinical data regarding both the long- and short-term effectiveness of 1064 nm diode laser is still limited.

The advantages of the 1064 nm diode over cryolipolysis are shorter treatment sessions, less discomfort, and an additional benefit of collagen stimulation. There is also increased flexibility with treatment areas as the treatment is not limited to a minimum required volume of excess fat required to fit into handpieces as seen with cryolipolysis. Presently there are not comparative studies to confirm that one is superior or that patients prefer one to the other.

Appropriate Pre-op Evaluation and How It May Impact Procedure Selection

Body contouring treatments are most appropriate for people within normal weight range, limited skin laxity, and small problem areas. The patient must have fat that can be pinched, good skin quality, and realistic expectations of outcomes and potential side effects. Poor candidates for the procedure include those who are obese (BMI $\leq$ 30 kg/m^2), have excessive skin laxity or poor skin quality, and significant visceral fat. It is best to evaluate the patient unclothed and assess for muscle tone and excess fat that can be held between the fingers by squeezing the fat after the patient has engaged their transverse abdominis muscle.

Patients with significant skin laxity or large volumes of excess skin will likely be poor candidates for treatments that exclusively address excess subcutaneous fat. Additional treatments to address skin laxity should be recommended as well and may even require surgical intervention and appropriate referrals to plastic surgery should be made.

Devices such as cryolipolysis are limited by the size and shape of the adaptors. If there is not

enough tissue to create a strong vacuum suction, the treatment will be ineffective and increases the risk of adverse outcomes. A flat applicator can be used in areas where there is not enough fat to pinch, but there must be enough fat to be treated by the size of the applicator. In these cases, alternatives such as deoxycholic acid for submental fat may be a better option. For treatment of large areas such as the entire abdomen, devices such as the 1064 nm diode laser, HIFU, or focused field RF may be more appropriate depending on patient expectations, pain tolerance, and ability to return to the practice multiple times, respectively. Otherwise, tumescent liposuction remains the gold standard as it provides the most flexibility and control over the volume of fat removed and with the advantage of more precise contouring.

Understandably, many patients hesitate to undergo invasive procedures such as tumescent liposuction.

However, for the patient that is a good candidate and open to tumescent, they can be reassured that it is a safe and effective procedure and is still the gold standard for treatment of unwanted subcutaneous fat.

Prior to all treatments, it is important to obtain photos that are standardized for background, lighting, and positioning for the most accurate before and after photos. Monitoring and documenting weight gain/loss throughout the treatment period is highly recommended. There will not be significant changes in weight after the non-invasive treatments; however there will be inches lost which patients should be aware of and should be documented. Circumference can be measured at consistent points above and below the umbilicus. Patients should continue their current exercise and diet plan as to not regain any weight, as the pockets of unwanted fat are likely to recur. Most importantly, setting realistic expectations of results and number of treatments that may be needed should be communicated clearly with the patient prior to initiating any treatment plan.

Conclusion

The wide range of non-invasive devices now available is variably effective, but all with relatively similar safety profiles. The overall discomfort is tolerable or eased with oral analgesics or anxiolytics and most side effects are transient and self-limiting. Most devices are only FDA cleared for the reduction of abdominal circumference.

Deoxycholic acid and cryolipolysis are comparable in the treatment of submental fat. Both methods reduce submental fat by a mean of 20% [30]. Deoxycholic acid is invasive and requires injections, while cryolipolysis is not invasive, but cannot be used universally as it requires owning the device and being able to obtain a good fit with the adaptor. The prolonged and significant edema patients experience after deoxycholic acid injections may not be acceptable to patients. Cryolipolysis can cause bruising, erythema, and numbness but is short lived.

The bipolar RF, infrared light (700–2000 nm), vacuum, and mechanical tissue manipulation device (VelaShape) and cryolipolysis deliver similar reductions in thigh circumference, 1.2 and 0.9 cm, respectively, but differ in the number of treatments required to achieve those results. The 1.2 cm reduction after treatment with VelaShape was after weekly treatments for 6 weeks, while the 0.9 cm reduction seen after only one session of CoolSculpt [31, 51]. Based on Shek et al.'s [28] findings, cryolipolysis is more effective at reducing abdominal circumference. After just one treatment with cryolipolysis, a reduction of 4.5 cm was found compared to 1.25 cm after three treatments with VelaShape [28, 52].

A modest reduction in abdominal circumference of 1.25–1.4 cm was seen with the VelaShape even after three to six weekly treatments, while a 3.58–3.95 cm reduction was seen after three treatments with UltraShape [46, 51]. HIFU (Liposonix) and cryolipolysis both achieved significant reductions in abdominal circumference after only one treatment, 2.5–4.6 cm and 1–4.5 cm, respectively [31, 41, 43]. A 24% reduc-

tion in abdominal circumference was reported after one session using the 1064 nm diode laser (SculpSure), which is similar to the results seen with CoolSculpt [31, 53].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Tumescent liposuction remains the gold standard for removal of subcutaneous adipose tissue (A). The largest volume of subcutaneous tissue can be removed in one session and allows for contouring. It continues to be a safe treatment in the hands of trained dermatologists. Laser-assisted lipolysis has the added benefit over tumescent liposuction of improving skin laxity, but with a risk for thermal burns (B). Non-invasive modalities have gained popularity due to their ease of use, minimal adverse events, and reduced downtime. The tradeoff is that multiple treatments are often required to achieve desired results and even after many treatments, reduction in subcutaneous adipose tissue may still be modest (A). Of the non-invasive treatments, cryolipolysis has the most FDA-approved uses and data to support its effectiveness. Although other treatment modalities can eventually have similar outcomes, the results are achieved only after multiple treatments compared to one or two treatments with cryolipolysis (B). Deoxycholic acid is an effective treatment for submental fat but has significant discomfort and swelling for weeks after treatment. In practice, the advantage of deoxycholic acid is that it does not require large, cumbersome, and pricey devices and does not require the patient to fit perfectly within a set applicator size. This flexibility allows for more contouring and personalized treatment. The radiofrequency and ultrasound devices are effective but still relatively new; therefore data is still limited on the permanence of the treatments. All treatments reviewed have been found to be safe and effective, without significant adverse outcome, but with any treatment, discussion and clear counseling with patients prior to any procedure will allow for the best outcomes and patient satisfaction (B).

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Self-Assessment Questions

1. Cryolipolysis is contraindicated in patients with a history of:
   (a) Hypertension
   (b) Diabetes
   (c) Cryoglobulinemia

2. Which of the following statements regarding paradoxical adipose hyperplasia (PAH) is NOT true?
   (a) Occurs more frequently in male patients than female patients.
   (b) PAH is self-limiting and will resolve over time.
   (c) Most commonly develops in the chest and abdomen.

3. Which of the following statements is true regarding marginal mandibular nerve paresis seen with deoxycholic acid injections?
   (a) Presents with an asymmetrical smile.
   (b) Is likely due to injection 1.0–1.5 cm below the inferior border of the mandible.
   (c) Typically resolves without sequelae.
   (d) All of the above are true.

4. True or False? Tumescent liposuction is significantly less safe than non-invasive body contouring treatments.

5. True or False? It is necessary to monitor triglycerides and cholesterol levels and check hepatic panel prior to and after treatments that induce adipocyte lysis.

Correct Answers

1. c: Cryoglobulinemia
2. b: PAH is self-limiting and will resolve over time
3. d: All of the above are true
4. False
5. False

Skin Laxity

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Jingyun Gao and Diana Bolotin

Abstract

Over the past decade, there has been a surge in demand for minimally invasive treatments for aging skin. Patients seek non-surgical treatments due to reduced procedure-associated risks and faster recovery time compared to traditional surgical methods. One component of aging skin is the appearance of laxity, which is due to thinning of the epidermis, loss of dermal connective tissue and atrophy and/or redistribution of subcutaneous fat, or all of the above. Innovation in energy-based devices has created multiple avenues to address the various factors leading to skin laxity. This chapter will discuss the mechanism of action, efficacy and safety of ablative and non-ablative lasers, infrared light, ultrasound, and microneedling in treatment of skin laxity.

Keywords

Ablative laser · Non-ablative laser · Infrared light device · Radiofrequency device Microfocused ultrasound · Microneedling Skin laxity

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Epidemiology

Skin laxity is an acquired condition in which the skin becomes loose and redundant over time. Histologically, changes in all three layers of the skin contribute to appearance of lax skin. With aging, thinning of the epidermis and effacement of the rete ridges result in flattening of the dermal epidermal junction, which contributes to fine wrinkles and epidermal laxity. Loss of dermal connective tissue volume due to decreased production and altered organization of collagen bundles and elastic fibers leads to rhytids and dermal laxity. In addition, atrophy and redistribution of subcutaneous fat, as well as bone resorption such as that seen in cheekbones, can further accentuate the appearance of age-related skin laxity [1, 2].

Environmental and hormonal factors also contribute to the development of skin laxity. Smoking acts synergistically with ultraviolet radiation on the skin, causing superficial and deep dermal elastosis and reducing hydration of the stratum corneum, all of which contribute to appearance of lax skin [3–5]. Smoking also accelerates collagen degradation via upregulation of matrix metalloproteinases while inhibiting new collagen (types I and III) formation within the dermis [6–8]. In a cross-sectional study done in Japan, subjects' age, pack-years of smoking, and sun exposure were all independent factors in causing facial wrinkles [9]. Estrogen and progesterone have also been shown to induce keratinocyte

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proliferation and collagen synthesis and inhibit matrix metalloproteinase [10–12]. Hence, the loss of these hormones in post-menopausal skin leads to epidermal and dermal atrophy and subsequent formation of rhytids [13]. Finally, smoking and loss of estrogen together cause decreased water retention within the epidermis and dermis, giving the appearance of reduced turgor and perhaps explaining why female smokers have a higher risk of skin laxity and aged appearance than their male counterparts [14, 15].

Less commonly, medical and genetic conditions may be causal factors for focal and diffuse laxity of skin. This can be due to genetic disorders such as cutis laxa or pseudoxanthoma elasticum or acquired conditions such as granulomatous slack skin of mycosis fungoides. Evidence regarding treatment of these rare conditions is sparse and thus will not be addressed in this chapter.

Treatment Overview

Treatment options for skin laxity include surgical and non-surgical modalities. Surgical options include facelift, neck lift, brachioplasty, and abdominoplasty. Many of the surgical treatments covering a wide area (such as abdominoplasty) are performed by plastic surgery under general anesthesia. Recently, options for less invasive techniques for skin tightening have become available to the practicing dermatologist. Patients seek non-surgical options due to the overall reduced risk and faster recovery time in comparison with traditional surgical methods. In the 2013 data of the American Society for Aesthetic Plastic Surgery (ASAPS), there were 293,388 cases of non-surgical skin tightening, in comparison with 129,807 facelift and 27, 898 neck lift; and over 80% of patients who underwent these procedures were female [16]. The 2014 data showed that non-surgical tightening has become the 7th most popular procedure in the non-surgical category and 5th most popular among male patients [17]. Another 58% increase in non-surgical skin tightening procedures was noted in 2015 [18].

Given that epidermis, dermis, and the subcutis all contribute to appearance of skin laxity, tightening treatments can be organized by the depth and layer of skin each method and device targets. For example, ablative and non-ablative lasers, such as carbon dioxide (CO_2, 10,600 nm), erbium: yttrium-aluminum-garnet (Er-YAG, 2940 nm), and erbium: glass (Er-Glass, 1540 nm), target the epidermis and superficial dermis, while microneedling, filler, radiofrequency, ultrasound, and infrared devices act almost exclusively on the dermis and subcutis with minimal effects on the epidermis. This chapter will discuss each method and device in detail, including supporting evidence in the literature regarding their efficacy as treatments of skin laxity and their potential risks or side effects.

Literature Review

Lasers

Lasers and lights have been used as treatments of mild to moderate skin wrinkling for over a decade. These treatments primarily target epidermal and dermal skin laxity. They are typically classified into ablative and non-ablative categories. Both categories of lasers are available as fractionated and non-fractionated devices. In general, ablative lasers are more effective and require fewer sessions for treatment of skin wrinkling than non-ablative lasers, but they do require longer recovery time. Fractionating either laser further reduces recovery time and complication rate but may require multiple treatment sessions [3/B] [19].

Ablative Lasers

Ablative lasers, such as CO_2 (10,600 nm) and erbium:yttrium-aluminum-garnet (Er:YAG) (2940 nm) lasers, are both strongly absorbed by water within the tissue, which leads to instantaneous vaporization of the epidermis and denaturation of collagen within the superficial portion of the papillary dermis. This stimulates re-epithelialization and new collagen and elastin synthesis over time. The result is tighter skin tone, improved skin texture with reduction in fine

wrinkles and smoother skin surface. Non-fractionated ablative lasers are associated with potential hypopigmentation, hyperpigmentation, and scarring; however, overall the risks are low [20, 21]. Fractionated ablative lasers work on similar principles as described above but cause microscopic zones of thermal injury of the skin and hence reduce the risks associated with ablative lasers such as scarring while also allowing a shorter recovery time [22].

In an earlier small study by Fitzpatrick et al., nine patients (unspecified Fitzpatrick skin type) underwent one split-face treatment with non-fractionated CO_2 laser versus Er:YAG. Prior to treatment, four tattoo dots were applied to the upper eyelids and distance between them served as a marker for degree of skin tightening. On the CO_2 laser-treated side, there was an average of 43% tightening immediately and 34% tightening at the 6-month follow-up as measured by shortening of vertical distances between the tattooed dots. This is in comparison with the 42% and 36% seen on the Er:YAG laser-treated side at 1- and 6-month follow-up, respectively. Of note, scarring was not seen on the CO_2-treated side but three patients did develop scarring on the Er:YAG-treated side [4] [23]. Another retrospective study reported results for 47 patients (Fitzpatrick type I–III, except for one patient with type IV) who underwent non-fractionated CO_2 laser resurfacing of the entire face. Using pre- and post-operative photography and a facial rhytids score, the authors reported a 45% improvement at long-term follow-up with mean duration of follow-up of 2.3 years. Of note, 55% of the patients had some complications including milia, acne, hyperpigmentation, hypopigmentation, viral infection, and ectropion [4] [20].

The advent of fractionated ablative lasers allowed for retention of improvements in skin laxity seen with non-fractionated treatments while decreasing complication rates and recovery time. In a prospective, single-blinded study by Tierney et al., 25 patients (unspecified Fitzpatrick skin type) with varying degrees of eyelid laxity were treated with ablative fractional CO_2 laser. At 6-month follow-up, there was an average of 65.3% improvement in eyelid laxity based on blinded assessment by two physicians using pre- and post-operative photography and a pre-set laxity score. The authors also reported that an average of 2.44 sessions were required for significant improvement [4] [24]. This is further corroborated by the study by Bonan et al., in which 45 patients (Fitzpatrick type I–III) received 2–3 treatments of fractional CO_2 laser on periorbital skin. Before and after photographs, as well as photographs at 2 weeks, 4 weeks, 3 months, 6 months, and 12 months after the final treatment, were evaluated by three independent dermatologists. At the 12-month follow-up, all the patients were found to have improvements in eyelid skin tightening, skin laxity, skin texture, periorbital fine lines, and rhytids clearance; more specifically, 5 patients (11.1%) achieved excellent improvement, 11 patients (24.5%) marked improvement, 15 patients (33.3%) moderate improvement, and 14 subjects (31.1%) slight improvement [4] [25].

Non-ablative Lasers

Non-ablative lasers used for the treatment of skin laxity are generally in the infrared range, such as the neodymium:yttium-aluminum-garnet laser (Nd:YAG, 1064 nm, 1320 nm, and 1440 nm), erbium-doped glass fiber laser (1550 nm), and thulium-doped fiber laser (1927 nm). Similar to the ablative lasers, these infrared-range lasers target the water-containing tissues, allowing heating of the dermis to stimulate collagen production and remodeling. In contrast to the ablative laser, the epidermis is protected by various forms of cooling. Like their ablative counterpart, these lasers also come in fractionated form, allowing for fewer side effects and less downtime.

Of these lasers, the long-pulsed 1064 nm Nd:YAG has been most extensively studied. In a recent prospective blinded randomized split-faced study, 20 Korean patients (Fitzpatrick type III–IV) underwent 3 treatment sessions at 4-week intervals using long-pulsed Nd:YAG on one side of the face. Using the untreated side of the face as control, they found that the treated areas showed an average reduction of 45.1% in wrinkle grade. Furthermore, objective measurements using a Cutometer, which measures elasticity of the skin,

also showed significant improvement of the treated side. Biopsy of treated and untreated skin confirmed an increase in collagen and elastic fibers on the treated side [4] [26].

Combination treatments of different non-ablative laser modalities have also shown promise in synergizing improvements in skin tone. In a study of 150 patients (Fitzpatrick type I–V) with facial aging, 50 patients were treated with 532 nm KTP, 50 were treated with 1064 nm Nd:YAG, and 50 were treated with both. Pre- and posttreatment photographs were evaluated by an independent observer, and degree of redness, pigmentation, rhytids, skin tone/tightness, and texture were scored on a 0–10 scale. After 3–6 treatments, patients treated with the 532 nm KTP laser alone showed 35% improvement in skin tone/tightening and 27% in rhytids. Patients treated with the 1064 nm Nd:YAG laser showed 16% improvement in skin tone/tightening and 13.6% in rhytids. Patients treated with both KTP and Nd:YAG lasers showed the most significant improvement of 44.8% in skin tone/tightening and 37.6% in rhytids. Skin biopsy specimens from all treatment arms taken at 1-, 2-, 3-, and 6-month intervals demonstrated new collagen and elastin formation [2b] [27].

Another non-ablative device is the 1550 nm erbium-doped glass fiber (Er-Glass). In a study of 24 patients (Fitzpatrick type I–II) with mild to moderate periorbital and perioral rhytids, each patient underwent 3 monthly treatments with a fractionated Er-Glass laser, and pre- and posttreatment photography were evaluated by a blinded observer using a quantile grading scale. At 6 months posttreatment, mean improvement was 2.1 for the periorbital area, and 2.0 for the perioral area, which corresponded to 51–75% improvement [4] [28]. In a retrospective study of patients (Fitzpatrick I–IV) treated with 1550 nm Er-Glass system for upper and lower eyelids and using similar methodology of evaluation as above, all patients ($N = 31$) had some degree of eyelid tightening, with 25.8% of patients achieving 50–75% improvement and 19.4% achieving 75–100% improvement [4] [29].

In addition to treatment of rhytids, the 1550 nm Er-Glass laser has also been used for treatment of pigmentary disorders such as melasma. In a study of 50 patients (Fitzpatrick type I–III) with mild to moderate facial ($N = 30$) and non-facial ($N = 20$) photodamage, rhytids, and dyspigmentation, each patient underwent three successive treatments at 3–4-week intervals, and pre- and posttreatment photographs at 3-, 6-, and 9-month intervals were evaluated by a blinded assessor using the same quantile scoring system as above. Specific clinical attributes assessed included dyspigmentation, wrinkling, and surface irregularities. The authors found that maximum clinical improvement was noted at 3 months following treatment, with mean score of 2.23 for facial skin and 1.81 for non-facial skin. At the 9-month follow-up, 73% of patients treated on the face and 55% of patients treated on other areas achieved at least 51–75% improvement [4] [30]. The newer, 1927 nm thulium fiber glass laser has also been shown to be effective in reducing laxity and rhytids, in addition to being a treatment for melasma and other pigmentary abnormalities [4] [31].

Returning to the subject of epidermal versus dermal laxity, ablative and non-ablative lasers differ in their ability to improve epidermal laxity, with ablative lasers such as CO_2 and Er:YAG suitable for treatment of both epidermal and superficial dermal laxity and non-ablative lasers targeting primarily the dermal component. This limitation on the non-ablative laser can be ameliorated to some degree by combining it with a different device, such as the 532 nm KTP laser mentioned above [27]. The fractional 1550 nm Er-Glass laser has also been shown to improve epidermal textural irregularities [31]. Despite earlier reports of dyspigmentation and scarring, the overall risks are low in long-term studies [21]. Regardless, both ablative and non-ablative technologies are effective in inducing skin tightening, and the ultimate decision most likely depends on each individual patient's degree of skin laxity and preferences for recovery time and number of treatments.

Infrared Light

Like the non-ablative laser, infrared (IR) light devices target water molecules within the dermis

while protecting the epidermis with cooling. In a prospective cohort study of 13 female patients (unspecified Fitzpatrick skin type) who underwent two treatments using an infrared device in the 1100–1800 nm range, 11 of the 12 patients who completed the study were noted to have obvious improvement by an independent observer and continued to improve after the 1-month follow-up. The authors further noted that the changes were more dramatic for individuals with neck laxity due to excess pendulous skin than those with laxity due to excess submental fat [4] [32].

Because of its epidermal sparing properties, infrared devices have also been studied in patients with darker skin tone and found to be equally effective and safe. In a prospective split-face, single-blinded study of 13 Chinese women (Fitzpatrick type III–IV), the side of the face treated twice using an 1100–1800 nm IR device, 3 of 13 patients reported mild improvement and 7 reported significant improvement at 3-month follow-up. When evaluated by an independent assessor using comparison photography, 5 out of 12 patients were noted to have some degree of improvement of the treated side using the untreated side as control [3b] [33]. In another prospective study of 21 Asian patients (Fitzpatrick type IV–V) who underwent 3 treatments with the same device, 19% reported mild, 38% moderate, and 43% good improvement. Of note, there were seven episodes (of 63 total treatments) of superficial blistering. These occurred in the early phase of the study when higher fluences were used. Those patients did develop temporary post-inflammatory hyperpigmentation, which resolved by 6 months after the treatments [4] [34].

While infrared devices can also be used on non-facial sites, the improvement in laxity is usually more subtle than that of facial sites. In a study of 20 patients (Fitzpatrick I–IV) with mild to severe laxity of upper arm skin who underwent treatment using an IR device, there was very small (0.38 cm) but statistically significant decrease in measured arm circumference but minimal improvement in subjective and objective photographic assessment [4] [35]. In a larger study by Felici et al., 303 patients (unspecified Fitzpatrick skin type) underwent infrared treatments of the abdomen, legs, and buttocks; and although 60% of patients reported being satisfied or very satisfied, the degree of satisfaction was lower in patients who had had prior treatments on their face or neck [3b] [36].

In summary, IR is an effective treatment for facial laxity. Similar to the non-ablative lasers, it primarily targets dermal laxity while sparing the epidermis. With proper cooling, it can be safely used in patients with pigmented skin as shown above [33, 34]. However, while it has been shown to be effective on non-facial sites, the results were less impressive [35, 36]. Side effects such as blistering and post-inflammatory hyperpigmentation are infrequent and temporary, and most occur when higher fluence settings are used [34].

Radiofrequency

Radiofrequency (RF) devices were initially approved by the FDA for treatment of periorbital laxity. These devices work by delivering an alternating current through the skin. The current is converted into heat energy following Ohm's law (Energy = $I^2 \times Z \times t$, where I is the current, Z impedance, and t time). Like the laser and infrared devices, heating of dermal tissues leads to immediate collagen contraction followed by neocollagenesis and neoelastogenesis.

Unlike light-based modalities discussed previously, RF is not limited by scatter and absorption of energy by water molecules in the upper dermis and hence can penetrate deeper into the dermis and subcutis. This is particularly true for monopolar (with grounding pads) and unipolar (without grounding pads) RF devices. In the initial study by Fitzpatrick et al., 86 patients (Fitzpatrick type I–IV) underwent a single treatment of the periorbital area using a unipolar radiofrequency device. Following RF treatment, 83.2% of patients demonstrated at least a 1 point reduction on the Fitzpatrick Wrinkle Scale as evaluated by a blinded observer using comparison photography, and 66.4% of patients were noted to have a greater than 0.5 mm eyebrow lift posttreatment [2b] [37]. Subsequent studies using unipolar RF devices have shown similar efficacy for treatment

of skin laxity in non-periorbital regions. In a study by Alster et al., 28 of 30 patients (Fitzpatrick type I–IV) showed at least 25% improvement of nasolabial and mesolabial fold laxity after a single treatment, and 17 of 20 patients showed at least 25% improvement of neck laxity [4] [38].

This is further supported by Finzi et al. in which 25 patients (Fitzpatrick type I–V) underwent one treatment of RF using multipass vector (mpave) technique. In contrast to conventional RF protocol in which the treatment is delivered in one single pass with no overlap, the mpave technique takes into account the direction needed for facial lift and delivers progressively more passes in areas that require the most tightening. More specifically, the lower cheeks are treated in an expanding teardrop configuration centered on the pre-auricular region with the smallest teardrop receiving the most number of treatments. Similarly, more passes are utilized over either the mid-eyebrow or lateral-eyebrow forehead depending on the types of brow lift the patient is looking for. Using pre- and posttreatment photography and a quantile scoring system, 80% of patients showed at least 26% improvement 3 months after treatment [4] [39].

Similar to IR devices mentioned previously, RF devices are felt to be safe and effective in pigmented skin. In a study with 85 Japanese female (Fitzpatrick type III–IV) patients, the authors found 78.0% improvement in jowls, 69.5% in marionette lines and nasolabial folds, and 73.8% in other facial wrinkles when evaluated by an independent observer using comparison photography and pre-set 5-point scales. Complications were seen in 7 patients, including edema (3), burn (1), blister (1), and secondary hyperpigmentation (2). In all cases, the complications were transient and resolved by 3 months [4] [40].

More recently, studies have also been done using bipolar radiofrequency devices, which provide much better control of depth in comparison with the unipolar devices and theoretically reduce the amount of thermal damage and its potential complications [41]. Bipolar devices can also be coupled with microneedles to deliver energy to a precise depth within the skin without affecting the epidermis and have real-time temperature feedback to avoid overheating [42, 43]. In a prospective, open-label, multicenter trial of 100 patients (Fitzpatrick I–IV) with mild to severe facial and neck laxity, the authors found that 100% of the patients showed an improvement in rhytids, with mean improvement of 1.6 points (25.6%), and 95% of the patients demonstrated an improvement in laxity, with a mean improvement of 0.7 (24.1%) on the Fitzpatrick Wrinkle Scale after a single-pass treatment [2b] [42]. A later study by the same authors showed that optimal improvement is achieved when the skin temperature is maintained at 67 °C for 3–4 s [2b] [43]. In another study of 20 Japanese patients (Fitzpatrick type III–V) who underwent treatment for facial skin tightening using such a device, there was an average of 12.1 ml volumetric reduction of the face at 6-month posttreatment, calculated using three-dimensional volumetric photography [4] [44].

While theoretically unipolar and bipolar radiofrequency devices all have their own advantages and disadvantages, the clinical significance of these differences is yet to be determined. A randomized, split-face study showed no statistically significant difference between the devices. However, it should be noted that in the same study, neither device yielded significant improvement in skin laxity when subjects were evaluated using a comprehensive photoaging grading scale by a blinded observer [4] [45].

Both unipolar and bipolar RF devices can be used for tightening in all areas of the face, neck, and even the eyelids. There are devices currently on the market that allow for both unipolar and bipolar settings, which in theory allows for heating of the superficial and deep dermis [46]. Like the IR and microfocused ultrasound technology (discussed below), RF is also safe for pigmented skin. It should be noted that having a pacemaker and defibrillators are absolute contraindications for radiofrequency device use. Other relative contraindications include morphea, scleroderma, and other collagen vascular diseases [47, 48]. Given the unpredictable heating patterns of joint prostheses or other implants, it is also recommended to avoid using these devices directly over or within the vicinity of the prosthesis [49].

Ultrasound

Microfocused ultrasound (MFU or MFU-V for concurrent visualization) delivers energy to the dermis and subcutis by inducing molecular vibration within the tissue. This vibration is then translated into heat, which leads to thermally induced denaturation of collagen and subsequent dermal and subcutaneous remodeling. It can be calibrated to deliver different frequencies, with higher frequency affecting more superficial dermis and lower frequency penetrating into deeper subcutis. Because of its ability to precisely target different depths, MFU is able to spare the epidermis without the need for aggressive cooling. MFU also has the advantage over other devices in that it allows visualization of the dermis and subcutis during treatment. Unlike lasers and RF devices which deliver three-dimensional cones of energy to the skin, the MFU device emits energy in 25 mm lines. During treatment, the device is marched along this line (parallel to the direction of intended lift) at set spacing to deliver a uniform plane of energy. This process is repeated until the entire treatment area is treated with the parallel linear array of US pulses [50]. In the pivotal study by Alam et al., 30 of the 35 (86%) patients (unspecified Fitzpatrick skin type) who underwent treatment using intense focused ultrasound device on the face and neck showed significant brow lift 90 days after treatment, with mean brow lift of 1.7 mm [2b] [51]. In another study by Oni et al., 63.6% of patients (N = 93, most patients had Fitzpatrick type II skin) with lower facial and neck laxity showed objective improvement 90 days after the procedure [2b] [52]. These findings are later confirmed histologically in a prospective study by Suh et al., in which 22 Korean patients (Fitzpatrick type III–VI) underwent single treatment for facial laxity, and 73% and 77% of patients self-reported much improvement of jawline and nasolabial fold laxity, respectively. Skin biopsies obtained before treatment and 2 months after treatment from 11 patients demonstrated increased dermal collagen and straightening of elastic fibers [2b] [53].

In addition to the face, neck, and eyelid, MFU devices have also been studied on other anatomic locations. In two small studies, 9–15(56%) patients had aesthetic improvement in elbow skin laxity and 24 of 28 patients (86%) had improvement of knee skin laxity following treatments when evaluated by blinded assessors [4] [54, 55]. In another study of 31 patients who underwent treatment of the right buttock, 81.5% (N = 27) showed overall improvement by physician global assessment at 90 days posttreatment, and 89.5% (N = 19) at 180 days posttreatment. It is interesting to note that majority of patients in the study stated that they would not recommend treatment to family or friends on posttreatment survey; however, the author did not further comment on the reason for this [4] [56].

When comparing the efficacy of this modality on different anatomic sites, Park et al. concluded that MFU is most effective on the jawline, followed by cheek and perioral areas, in decreasing order [4] [57]. In a different study, Alster et al. showed that MFU appears to be more effective for tightening of the upper arm and knee than the thigh and that the dual-depth treatment of the upper arm, knee, and thigh was also found to be slightly better than single-plane treatment [4] [58].

Since the ultrasound devices can be calibrated to deliver energy at different frequency and depth, combinations of different settings to treat superficial and deep dermal laxity have also been studied. In a small-scale study by Pak et al., seven Korean patients (unspecified Fitzpatrick skin type) underwent treatment for periorbital laxity; a 1.5 mm probe was used for eyelid skin, and a 3.0 mm probe was used for the orbicularis oculi muscle and septum. Each patient had before and after computed tomography imaging, which demonstrated a mean of 0.5 mm increase in distance between the orbital rim and most protruding portion of the lower eyelid. Clinically, this translated to increased fullness of the infraorbital rim [4] [59]. In another retrospective analysis of 28 Korean patients (Fitzpatrick type III–VI) who underwent MFU device treatment for facial laxity, each patient had 3 sessions, 4 weeks apart, with 200–300 treatment lines per session using 4 MHz with 4.5 mm transducer followed by 8 MHz with 3 mm transducer. Evaluation by independent assessors and comparison photography showed

that 32.1% of the patients had significant improvement and 57.1% had some degree of improvement 3 months after the last treatment [4] [60]. Contrary to the Alster study above, a more recent study of MFU treatment of the neck ($N = 41$, Fitzpatrick type I–III) showed that the differences between using single depth (7 MHz, 3 mm) and double depth with two transducers (4 MHz, 4.5 mm, and 7 MHz, 3 mm) were insignificant [4] [61].

MFU devices can be used for lifting and tightening of many anatomical locations, including the face, neck, arm, knee, thigh, and buttock. It has the advantage of inducing energy at precise depth within the dermis and subcutis, while sparing the epidermis from thermal damage, and hence is safe to use in all skin types. Its noninvasive and non-ablative nature also allows the patient to resume work and social activity immediately after the treatment. However, because it does not induce any injury to the epidermis, it is also unlikely to have effect on the epidermal component of skin laxity. And like many of the other energy devices, it is associated with intraoperative discomfort and potential bruising. MFU devices have also been observed to cause temporary motor nerve paresis and dysesthesia lasting up to several weeks. Only a few cases have been reported in the literature thus far, with branches of the facial nerve being most commonly affected and deep branch of the supraorbital nerve more rarely affected [4] [62, 63].

Combination Devices/Multimodality Treatment

Given the advantages and limitations of each individual modality discussed thus far, there is great interest in the industry in combining the different modalities into one single device. There are currently several devices on the market approved by the FDA that combine RF and light-/laser-based technology, collectively called ELOS (electro-optical synergy) device. However, whether combination devices are significantly better than single devices has yet to be determined. In a study using a combination of broadband IR (700–2000 nm) and bipolar radiofrequency, 19 Chinese patients (Fitzpatrick III–V) underwent 3 treatments at 3-week interval. At the 3-month follow up, 17 of the 19 (89.5%) patients reported moderate to significant improvement in skin laxity of cheek, jowl, periorbital area, and upper neck, and 15 of 19 (78.9%) patients reported moderate to significant improvement of the nasolabial fold. However, when evaluated by blinded observers using comparison photography and numerical scoring (−1 to 3), the improvement was less remarkable, with 26.3% of patients achieving mild to moderate improvement in periorbital, nasolabial, and upper neck laxity, 36.9% in jowl, and 47.3% in cheek laxity. Zero of the 19 patients achieved the level of significant improvement [4] [64]. In two studies examining the combination device of radiofrequency and diode laser, only modest improvements were noted in facial rhytids after three treatments at 3-week intervals [4] [65, 66].

In a later study examining the use of a combination of bipolar radiofrequency, infrared, vacuum, and mechanical massage device, 19 post-partum patients (Fitzpatrick type I–V) who underwent 5 weekly treatments for the upper arms showed a statistically significant decrease of arm circumference of 0.625 cm at the 5th treatment. At 1- and 3-month posttreatment follow-ups, mean reductions of upper arm circumference were 0.71 cm and 0.597 cm, respectively. Ten patients also underwent four weekly treatments of the abdomen and flanks, and the noted reduction of abdominal circumference at the 3rd treatment was statistically significant at 1.25 cm. At 1- and 3-month follow-ups, the reduction in abdominal circumference was 1.43 and 1.82 cm, respectively [4] [67].

Microneedling

Unlike the energy-based technologies discussed thus far, microneedling is performed with micron-sized puncture devices that are designed to breach the uppermost layers of the skin without vaporization or heating of tissue. Depending on the shape, length, and width of the microneedle, it can be designed to penetrate through different layers of the epidermis and/or dermis. Microneedle puncture of the upper dermis has been shown to induce neocollagenesis via induction of physiologic wound-healing cascades, a process commonly

referred to as percutaneous collagen induction (PCI) [68].

While microneedling has been most well-studied in scar revision, literature on its use in skin tightening remains scarce. In one small study of ten patients (Fitzpatrick type III–IV) with Glogau class II–III wrinkles, all patients underwent six sessions of microneedling at 2-week intervals. At the 3-month follow up, the authors note an approximately 60% improvement in facial wrinkling and an 80–90% rate of patient satisfaction with the treatment. Biopsies obtained at baseline and at 1 and 3 months after initiation of therapy showed increased epidermal thickness and increased type I, III, and VII collagen in the dermis [4] [69].

As previously mentioned, microneedling has also been coupled with bipolar radiofrequency devices for treatment of skin laxity. It works by allowing the current to pass between the microneedles, thus allowing precise depth and energy delivery while sparing the epidermis from thermal injury. Details of the studies regarding such technologies are summarized in the RF section earlier.

Effectiveness of Treatments

In general, it is accepted that minimally invasive skin tightening treatments achieve more subtle effects on skin laxity in comparison with the traditional surgical approaches. However, there have been very few studies examining and quantifying the differences in outcomes between these approaches. One study examined the relative improvement of patients who underwent RF treatments versus patients who underwent traditional surgical lift, in which before and after images of 15 patients who had radiofrequency and 6 patients who had surgical lifts were blindly evaluated using a four-point laxity grading scale. The average improvement was 0.44 among RF-treated patients and 1.20 among the surgical group ($P < 0.001$). The improvements relative to baseline were 16% for RF treatment and 49% for the surgical facelift [4] [70].

Comparisons between noninvasive treatment modalities are also lacking in literature. It was thought that laser-based devices tend to perform slightly better than other energy devices such as radiofrequency. However, whether this translates into clinical significance is yet to be determined. In a split-face study in which patients were treated with a long-pulse Nd-YAG device on one side of the face and a radiofrequency device on the other, improvement was greater on the laser-treated side in terms of laxity and wrinkles but essentially the same in terms of texture and pigmentation [4] [71]. In another split-face study of the same design, upper face improvements, including forehead and periorbital lines, brow, and eyelid positions, were essentially the same on both sides (30.2% and 31.3% improvement for laser and RF, respectively, $P = 0.89$), while lower face improvements, including malar cheeks and jowl positioning, nasolabial fold depth, and fold extension, were greater on the laser-treated side (35.7% and 23.8% improvement for laser and RF, respectively). However, the differences were not statistically significant ($P = 0.074$). Yet, when the entire face was evaluated, improvement in facial laxity was significantly greater on the laser-treated side (47.5% and 29.8% improvement for laser and RF, respectively, $P = 0.028$) [4] [72].

Safety

Infrared, radiofrequency, and ultrasound devices are generally safe for all skin types with low risk of adverse events reported in the literature [20]. Transient erythema and edema are to be expected and often used as a treatment endpoint. The most common adverse event with these devices is overheating, which, in mild cases, causes patient discomfort. If not recognized immediately, however, it can then lead to superficial burn and full-thickness permanent scar [73, 74]. To reduce the potential risks for overheating and scarring, lower fluence settings with higher numbers of passes are preferred over more traditional high fluence settings. Some newer devices provide temperature feedback which helps mitigate the risk of overheating. In the event of overheating, treatment should be aborted immediately, and a

cooling device should be applied until all symptoms and signs of overheating resolve.

Ablative nonfractional lasers, such as the CO_2 laser, are associated with potentially more serious complications, including bleeding, crusting immediately following procedure, severe acne flare, hyper- and hypopigmentation for several weeks to months following procedure, and potential scarring. And while the introduction of fractionated lasers, use of higher fluences, and shorter pulse widths have lessened the collateral thermal damage associated with traditional ablative lasers, these resurfacing lasers still have the potential of causing scarring, discoloration, and infection. Fortunately, a recent large multicenter study has shown very low rates of adverse events reported with CO_2 resurfacing (0% for fractional and nonfractional pulsed) [2a] [60]. However, smaller studies over the years have reported complications which should be taken into consideration when planning treatments and obtaining informed consent from patients. One such study, mentioned previously, showed that 55% ($N = 47$) of the patients who underwent non-fractionated CO_2 resurfacing for rhytid and solar aging had some form of complication, most commonly milia and acne which occurred in 14 cases (30%), hyperpigmentation in 8 cases (17%), and hypopigmentation in 6 cases (13%). In the same study, one patient developed infection and another developed ectropion. Most of the complications were resolved within 1 year with the exception of one case of hypopigmentation and one case of hyperpigmentation which were resolved by 2 years [4] [20].

The side effects of microneedling and microneedling coupled with radiofrequency have not been well documented, particularly when used for the treatment of skin laxity. It is more commonly used for the treatment of acne scars, from which the safety data may be extrapolated to some extent. Reported complications include mild erythema, edema, superficial bleeding, and desquamation as well as more serious consequences such as delayed local hypersensitivity reaction and scarring [75–78]. In a case series by Soltani-Arabshahi et al., three women developed foreign body-type of granulomatous reactions following procedures. All three women had applied topical serum (two cases of vitamin C and one case of a gel product) prior to the microneedling session. These cases were thought to be delayed-type hypersensitivity granulomas due to intradermal tattooing of the topical product [4] [77]. A long-term adverse effect of radiofrequency microneedling is thought to be similar to traditional radiofrequency, and limited to pain during procedure, as well as self-limited erythema, edema, and dyspigmentation [4] [79].

Preoperative Evaluation and Patient Selection

Given all the available treatment options, patient preferences play a major role in choosing the most appropriate treatment modalities. While the current trend is for more patients to prefer the idea of noninvasive tightening procedures over traditional surgical approaches, patients should be made aware during the initial surgical consultation that surgical lifts usually provide more dramatic improvement in laxity. Patients should also be informed of the potential side effects of each individual modality that they are considering. Specifically, a discussion of the potential for scarring or pigmentary changes, the recommended number of treatment sessions, timeline between each treatment and peak effect, as well as the length of recovery time is critical before deciding on the best treatment option.

During initial evaluation, the following patient factors should be noted: (1) degree of skin laxity, (2) depth of skin laxity, (3) patient's Fitzpatrick skin type, (4) history of prior treatments including injectables, and (5) other medical conditions and comorbidities. The ideal candidates for noninvasive tightening procedures are those who are relatively young, and with mild to moderate skin laxity. Patients with severe deep wrinkling and skin laxity may not be satisfied with the more subtle improvement offered by noninvasive modalities. Patients with epidermal laxity will benefit the most from laser resurfacing procedures unlike those with deep dermal and subcutaneous laxity who may do better with surgical lifts or IR, RF, or MFU devices, depending on the degree of involvement. Radiofrequency, ultrasound, and

infrared devices are generally safe for patients with type III–V skin; however, if concerned, a test spot can be done to evaluate for potential dyspigmentation several weeks prior to scheduled procedure. Furthermore, in patients with a pacemaker and/or a defibrillator, RF devices should be avoided. Other medical conditions to consider include morphea, scleroderma, as well as a history of joint prosthesis or other implants [47, 48].

There has been much debate in the field regarding use of noninvasive skin tightening devices in patients who have had dermal filler treatment. It was postulated that the heat generated by these devices may break down the injectable filler, which may have unpredictable remodeling and/or inflammatory effects in the skin. However, surprisingly, in a pilot human study and in animal models, patients saw greater improvement when radiofrequency is used in conjunction with hyaluronic acid [80, 81]. Additionally, studies have not shown any adverse events when laser, light, or ultrasound modalities are used on human skin injected with polymethyl methacrylate (PMMA) [82]. Similar lack of adverse events was reported for calcium hydroxyapatite filler combined with RF therapy [83].

In a recent consensus recommendation by Fabi et al., a stepwise treatment approach using neuromodulators first, followed by soft-tissue filler, and then MFU were recommended. The experts further recommended spacing individual treatments by 1–2 weeks to allow resolution of local side effects from each treatment, such as swelling and bruising. This timing also allows assessment and re-assessment of patient's need after each treatment. However, for patients who desire all treatments within the same day, MFU was recommended before injections to avoid contamination of the transducer as well as unintended manipulation and displacement of filler material [84].

Typical Treatment Plan: Case scenario

Case study 1: Patient JS is a 53-year-old Asian female with Fitzpatrick type IV skin who presented to the clinic complaining of "wrinkling around her eyes and droopy eyelids." She reported that one of her friends just had a facelift but she is interested in something that is less dramatic. She works as an account manager at a local bank and prefers to be able to return to work with minimal recovery time. On examination, there were static and dynamic medium-depth rhytids involving bilateral lateral canthi as well as mild laxity of upper eyelid skin. She was not interested in injectable therapies and strongly preferred a noninvasive option for her skin laxity.

Given patient's skin type, radiofrequency, infrared laser, as well as microfocused ultrasound treatment options were discussed. After explaining the potential risks for pain, erythema, and bruising for either procedure, patient proceeded with MFU-V. Dual-depth protocol was used to target the deep dermis, subcutaneous fat, as well as orbicularis oculi muscle and septum (15 lines with 1.5 mm probe and 15 lines with 3 mm probe for each infraorbital area) as described by the study by Pak et al., [49]. The patient's pain was controlled with an intramuscular ketorolac injection and she did not require nerve blocks. After the treatment the patient had mild erythema and edema at the treated sites and was able to return to work the following day. At her 3-month follow-up, her periorbital skin appeared tighter and she was very pleased with the outcome.

The patient then returned to the clinic a few months later and complained of loose skin on her bilateral upper arms. Her daughter is getting married in about 6 months, and she would like to wear a sleeveless dress but feels self-conscious about her "saggy" upper arms. She asked whether the same procedure she had around her eyes can be done for the arms. On examination, the patient had mild to moderate skin laxity of bilateral upper arm as well as moderate amount of subcutaneous fat.

Given the degree of subcutaneous fat, noninvasive devices such as MFU, IR, or RF alone are unlikely to provide significant result for the patient. However, she would be a good candidate for sequential treatment that involves traditional liposuction or noninvasive fat removal such as cryolipolysis (not discussed in this chapter) followed by MFU or IR to tighten the dermal component of the laxity. Alternatively, this patient

may also benefit from brachioplasty. However, there is a higher risk of visible scar at the incision sites and a longer recovery time associated with an invasive procedure. After discussing all treatment options, patient opted for traditional liposuction followed by MFU. At her 6-month follow-up, she brought you a picture of her at her daughter's wedding and informs you that again she is pleased with the result.

Of note, there are very few reports in the literatures specifically addressing the timing between different modalities of treatment for skin laxity and even fewer addressing the timeline between traditional liposuction and noninvasive tightening procedures. This could be due to the fact that most studies excluded individuals who had undergone other surgical or non-surgical tightening procedures. However, in general, combinations and successive treatments were thought to be safe and even possibly synergistic [50, 85, 86].

Case 2: Patient HG is a 59-year-old Caucasian female with Fitzpatrick skin type II who presented for evaluation of loose skin around her lower cheeks and chin. She endorsed multiple blistering sunburns as a child and years of tanning bed use in her youth. She also informed you that she has tried over-the-counter retinol cream in an attempt to reduce her wrinkles and correct her skin tone but has not seen any benefit. On examination, patient had numerous tan macules with feathered borders on forehead, nose, and cheek consistent with solar lentigines; she also had prominent nasolabial fold and marionette lines. Overall, her skin appeared thin and crinkly. She brought a picture of herself from 10 years ago, which showed more prominent cheekbones and slimmer jawline.

This patient is a good example of epidermal and dermal thinning, redistribution of subcutaneous fat, and skeletal bone resorption with aging. Her history of UV exposure also contributed to the epidermal and dermal process, in addition to development of solar lentigines. After performing a thorough skin exam to ensure that this patient does not have any evidence of skin cancer, treatment options including ablative lasers such as the CO_2 laser (fractional), non-ablative lasers such as the Q-switched Nd:YAG, as well as dermal fillers, to reconstitute volume, were discussed. The potential side effects and recovery time for each procedure were discussed. The patient proceeded with fractional CO_2 laser as she is retired, was able to devote time to recovery from a more aggressive therapy, and wished to minimize the number of treatments. Patient was provided with verbal and written care instruction as well as valacyclovir for prophylaxis to be started prior to her procedure.

The patient tolerated the treatment well but called the clinic the following day asking how long she would stay red, oozy, and crusted. She apologized that she could not recall all the details of the conversation and she was having a hard time putting on her reading glasses to read the written instructions. The care instructions and expectations of healing time were again reviewed with the patient. At her 1-month follow-up, the patient's facial skin appeared tighter and more luminescent. The fine wrinkling of her skin completely abated. In addition, solar lentiginosis was markedly improved. She informed you that while the recovery process was longer than she had imagined, she is very pleased with the result.

Postoperative Care and Follow-Up

For non-ablative lasers, radiofrequency devices, and infrared and microfocused ultrasound devices, heating and denaturing of collagen is instantaneous, and the patient may experience immediate skin tightening during and after the procedure. However, neocollagenesis and elastogenesis may take weeks to months to take effect. Majority of the studies evaluated patients at 1, 3, and 6 months post-op. In some studies, effects were sustained to slightly diminished at 1 year after the procedure.

After treatment with ablative lasers, patients will invariably experience oozing and crusting post-operatively. Even the newer short-pulse CO_2 laser requires a 1–2-week recovery period following the procedure depending on the settings used. It is essential to follow up with patient during and after the recovery to ensure proper

healing. Similar to non-ablative technologies, dermal remodeling continues to occur after the initial treatment, and patients' skin laxity may continue to improve months after the procedure.

Depending on the modality used and settings implemented, improvements can be subtle, as evidenced by multiple studies showing subcentimeter improvement in arm/abdomen circumference and 1–2 mm in brow lift. Hence, pre- and posttreatment photography and measurements are crucial. Many studies used commercially available standardized photography systems that take high-resolution photographs from multiple angles with controlled lighting and exposure allowing both the patient and physician to objectively evaluate the results.

Conclusions

Given current trends and demand for minimally invasive approaches to treating skin laxity, light-based devices, radiofrequency, and ultrasound can offer modest degrees of improvement for patients with mild to moderate degree of skin laxity. With the exception of ablative nonfractional lasers, these devices have the advantage of minimal side effect profiles and recovery times in comparison with surgical procedures. However, more research is needed to determine optimal settings of these devices on different anatomic locations (particularly non-facial sites), and further comparative studies are needed to evaluate relative efficacy of various devices compared to each other. Furthermore, given the rapid technology development and increasing popularity of these treatment modalities, it is important that practitioners maintain continuous education on the mechanisms and logistics of these devices.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Noninvasive devices are thought to be less effective than surgical lifts; however, they have the advantage of less downtime, no requirement of general anesthesia (local anesthesia may still be needed), and less risks of scars	B
RF, IR, and US can all lead to some degree of improvement in skin laxity objectively and subjectively	B
RF, IR, and US have been extensively studied in patients with Fitzpatrick IV–V skin and are thought to be safe	B
Ablative lasers, and some of the non-ablative lasers, have the advantage of targeting both epidermal and dermal components of skin laxity	B
Most studies were focused on skin laxity on the face. IR and US can also be used on other anatomical site, though usually they are less effective on non-facial site. Patient satisfactions are also lower for non-facial site, especially if patient had had treatment of the same device on the face	B

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Self-Assessment Questions

1. Which of the following is an absolute contraindication for the use of a radiofrequency device?
   (a) Presence of joint prosthesis
   (b) Presence of bare-metal coronary stent
   (c) Presence of defibrillator and/or pacemaker
   (d) Presence of dental implants
   (e) Presence of dermal and subcutaneous filler material
2. Which of the following devices has been shown to cause temporary motor nerve paralysis and dysesthesia?
   (a) Ablative laser
   (b) Radiofrequency
   (c) Infrared
   (d) Microfocused ultrasound
   (e) Microneedle
3. Which of the following devices are considered safe to use on darkly pigmented skin?
   (a) Radiofrequency
   (b) Infrared
   (c) Ultrasound
   (d) A & B
   (e) All of the above
4. If patient reports pain or intense heat during an IR procedure, the operator must perform which of the following?
   (a) Move the device to a different area of treatment
   (b) Remove the device entirely from the patient
   (c) Turn off the IR device but allow the cooling device to stay on the patient with cooling on
   (d) Apply topical lidocaine to the affected area
   (e) Reassure the patient that this is normal response
5. All of the following patients may benefit the most from noninvasive skin tightening procedure alone or in combination with other treatments. Which of the following is most likely to benefit the most from noninvasive procedure alone?
   (a) 69-year-old with loose sagging chin
   (b) 70-year-old with moderate to severe jowls
   (c) 48-year-old with excess skin on abdomen after bariatric surgery
   (d) 37-year-old with mild abdominal skin laxity after three pregnancies
   (e) 72-year-old with “bat wing” arms

Correct Answers

1. c: The presence of defibrillator and/or pacemaker is an absolute contraindication to use of a radiofrequency device. The presence of joint prosthesis may lead to abnormal heat conduction and RF devices should be avoided within the vicinity of prosthesis but can still be used elsewhere on the body. The presence of filler has not been shown to cause abnormal tissue response when used in conjunction with radiofrequency devices. In fact, in animal models and a pilot human study, the patient saw greater improvement when radiofrequency is used in conjunction with hyaluronic acid.
2. d: Ultrasound devices have also been observed to cause temporary motor nerve paresis and dysesthesia lasting up to several weeks. Only few cases have been reported in literature thus far, branches of the facial nerve being the most common locations and rarely the deep branch of the supraorbital nerve.
3. e: RF, IR, and US have been extensively studied in patients with Fitzpatrick IV–V skin and are thought to be safe. In particular, the US devices can be calibrated to deliver energy to a precise depth within the skin while sparing thermal damage of the epidermis. However, if dyspigmentation is ever a concern, a test spot can be done weeks prior to the procedure.
4. c: The most common adverse event during IR procedure is overheating of the skin leading to a superficial burn. When patient complains of intense heat or pain, it is imperative that the operator turn off the energy-delivering portion of the device but still allow the handpiece to be in contact with the affected skin so that the tip may continue to cool the area.
5. d: The ideal candidates for noninvasive tightening procedures are those with mild to moderate skin laxity. The 70-year-old with moderate jowls may benefit from RF, IR, or MFU-V, but younger patients typically do better than older patients. The other patients listed most likely will require surgical procedures to achieve desired results.

Lentigines and Dyschromia

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Hao Feng and Arielle N. B. Kauvar

Abstract

Lentigines are benign, pigmented macules that are frequently a cosmetic concern for patients. Solar lentigines are an early sign of dermatoheliosis and are common in lighter skinned individuals. Procedures used alone or in combination to treat solar lentigines include topical creams, cryotherapy, microdermabrasion, chemical peels, intense pulsed light, and lasers. Nanosecond domain lasers and intense pulsed light sources are the workhorse modalities for treatment of lentigines, and experience is growing with picosecond lasers. Other methods include cryotherapy, millisecond domain long-pulsed lasers, non-ablative fractional lasers, and lightening creams, which can be used alone or in combination. Treatment approaches are tailored for each patient based on the skin and lesion color, as well as tolerance for downtime and multiple treatment sessions. Test treatments can help the clinician find the treatment with the most efficacy and the least side effects. Most treatment modalities are extremely well tolerated without significant adverse events. Strict sun protection is required to prevent post-inflammatory pigment alteration and lesion recurrence.

Keywords

Lentigo · Solar lentigines · Treatment · Laser Topical · Intense pulsed light (IPL) Cryosurgery

Epidemiology

Lentigines are benign pigmented macules that result from an increased number and activity of epidermal melanocytes with increased melanin in keratinocytes and melanocytes [1, 2]. Solar lentigines result from both chronic sun exposure and acute sunburn [3] and are the earliest sign of dermatoheliosis. They occur on sun-exposed skin, including face, neck, hands, forearms, and upper chest [4, 5], and patients often seek treatment for aesthetic concerns. Solar lentigines are commonly seen along with seborrheic keratosis, actinic keratosis, and both melanocytic and keratinocytic skin cancer [6–8]. Other types of lentigines include lentigo simplex (ephelides or freckles) and mucosal melanotic macules. Patients with xeroderma pigmentosum who are hypersensitive to ultraviolet radiation due to

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defective DNA repair mechanisms develop solar lentigines at a very young age [9]. Rarely, lentigines are seen in resolving plaques of psoriasis [10, 11]. We will focus our discussion in this chapter primarily on solar lentigines.

Solar lentigines may be seen in any skin type, but are most common in Caucasian populations due to their low levels of melanin, which protects from the effects of ultraviolet radiation. In whites, solar lentigines can be found in 20% of individuals younger than 35 years of age and more than 90% of individuals older than 60 years of age [12, 13]. Solar lentigines are seen in individuals after the age of 20 who had two or more sunburns.

Treatment Overview

Procedures used to treat lentigines include topical creams or gels that inhibit melanogenesis and non-specific destructive modalities including chemical peels, cryotherapy, microdermabrasion, lasers, and light sources. Lasers may be used to ablate tissue or for their selective targeting of melanin [20].

Topical treatments aim to disrupt melanin synthesis pathway. The most commonly used agents are hydroquinone and tretinoin [14]. Other topical agents that have been used effectively include azaleic acid, tazarotene, adapalene, and mequinol [14]. Botanical therapies for the treatment of solar lentigines produce mixed results [15]. Topical therapies are often used as a first-line treatment for patients who desire a more conservative, nonphysical treatment modality.

Cryotherapy is widely available and has been used as a safe and effective treatment option. It utilizes melanocyte's vulnerability to injury at temperatures around −4° C to −7° C [14]. A single freeze-thaw cycle is usually sufficient and effective.

A variety of chemical peels, including trichloroacetic acid, Jessner's solution, salicylic acid, glycolic acid peels, have been used individually or in combination to treat solar lentigines [14]. Patients with large areas of involvement and uneven pigmentation may benefit from peels.

Microdermabrasion removes solar lentigines through mechanical abrasion of the pigmented epidermis and superficial dermis [14]. This may be effective for a few localized and focal areas on the extremities, but would not be a desirable option for widespread lesions.

Both ablative and pigment-specific lasers and light sources have been used to treat solar lentigines. Continuous-wave CO_2 (10,600 nm), erbium yttrium aluminum garnet (Er:YAG) (2940 nm), krypton (520–530 nm), copper vapor (511 nm), potassium titanyl phosphate (532 nm), argon diode (488–630 nm), and tunable dye lasers were used in the 1970s and 1980s. They produced non-specific destruction of pigmented lesions and, with excellent technique, could be used to remove superficial pigmented lesions with acceptable outcomes. Due to diffusion of thermal damage, scarring and dyspigmentation was a significant risk.

The development of the concept of selective photothermolysis by Anderson and Parish enabled the creation of a new generation of pulsed lasers that could selectively target pigmented lesions without the risk of non-specific tissue heating and limit the risk of adverse effects [16]. Selective photothermolysis of pigmented lesions requires the use of wavelengths that are preferentially absorbed by melanin and pulse durations that confine thermal injury to the targeted chromophores (i.e., melanosomes within pigmented melanocytes or keratinocytes) [16, 17]. In theory, this requires pulse durations in the nanosecond (or less) domain to match the thermal relaxation times of these targets. In practice, however, longer microsecond and millisecond domain pulses may be used in the case of lentigines because the pigment is confined to the epidermis, and focal epidermal destruction can heal without scarring. Pigment-specific nanosecond lasers used to treat lentigines include the quality-switched (QS) ruby (694 nm), QS alexandrite (755 nm), QS neodymium-doped yttrium aluminum garnet (Nd:YAG) (532 nm and 1064 nm), and the 510-nm pulsed dye laser [14, 17]. Novel picosecond domain lasers also produce excellent results for epidermal pigment. Millisecond-pulsed ruby, alexandrite, Nd:YAG, and the 595-nm pulsed dye [18–22] lasers as well as intense pulsed light sources (IPLs) can be safely used as well for the aforementioned reasons.

IPLs use a filtered flashlamp to produce noncoherent light in the 500–1200-nm range in

conjunction with cutoff filters to adjust the spectrum of light emitted to achieve more vascular or pigment selectivity. Similar to a laser, the range of wavelengths is chosen for selective chromophore absorption and the millisecond pulse durations render it safe for use in the treatment of pigmented epidermal and vascular lesions [14, 23]. Posttreatment downtime is minimal, but multiple treatments at 2- to 4-week intervals are often needed to achieve maximal results.

When treatment of diffuse photodamage is sought, controlled ablation or heating of tissue layers with full-surface, short-pulsed CO_2 and Er:YAG lasers can safely remove the epidermis and variable portions of the dermis. Fractional photothermolysis is another approach to selective removal of epidermal or dermal tissue that relies on spatial selectivity, where thousands of microscopic foci of tissue are damaged and replaced by wound repair. Because of the fractional nature of these injuries, a greater number of treatment sessions is usually required for pigmented lesions. A more in-depth discussion of these modalities can be found in Chaps. 47 and 49.

Effectiveness of Treatments

The effectiveness of cryotherapy for treating solar lentigines has been examined in several studies. Zouboulis et al. studied six patients with large, solitary solar lentigines in a prospective case series and found full remission of all lesions with excellent cosmetic results. At 10-month follow-up, there was no evidence of recurrence or dyspigmentation at the site of treatment (4) [24]. The same group also reported a randomized, controlled, prospective trial of 20 patients with small solar lentigines and found substantial improvement in 80% and 100% of patients with minimal skin atrophy observed at follow-up in 10% and 60% of patients treated for 5 and 10 s of contact cryotherapy, respectively (1b) [25]. In a randomized, controlled, comparative study with blinded observers, the distribution of graded response rate to liquid nitrogen were 11%, 12%, 20%, 59%, and 32% for poor (0–25%), fair (26–50%), good (51–75%), excellent (76–90%), and clear (91–100%) responses, respectively (1b) [26]. Stern et al. also found good responses (at least moderate lightening and no more than slight textural change) in 61% and excellent responses (substantial decrease in pigmentation or return to normal skin color and no textural change) in 23% of patients treated with cryotherapy (1b) [27]. The rate of recurrence is not well studied although one paper reported a rate of 55% at 6 months [28].

IPLs can safely treat solar lentigines in phototype I–IV skin. Kawade et al. found 18 of 45 (40%) Asian patients with facial lesions showed more than 50% improvement, and 16% had more than 75% improvement as evaluated by photography and observation after an average of four IPL treatments at 2–3 weeks intervals. There were no complications of hyperpigmentation or scarring (2b) [29]. Sasaya et al. studied the effectiveness of IPL with a 515-nm filter on dorsal hand lentigines. They found 62% of patients had more than 50% improvement, and 23% had more than 75% improvement with no patients showing hyperpigmentation or scarring after treatments (2b) [30]. Tanaka et al. assessed treatment of solar lentigines in 40 Asian subjects using short-wavelength (500–630 nm) IPL, delivered with a targeted tip and contact cooling. Ninety percent of patients were satisfied with the results and no serious adverse events were observed (2b) [31]. Bjerring and Christiansen treated 18 patients with solar lentigines and found pigment reduction was achieved in 96% of the patients with the average clearance of 74.2% (2b) [32]. Galeckas et al. treated ten patients three times at 3–4-week intervals, and blinded investigators found improvement in 82% of dark and 62.5% of light lentigines (2b) [33].

The CO_2 and argon lasers were the first lasers used to treat lentigines. Dover et al. treated 146 lesions in 5 patients with 1 treatment session of CO_2 laser and found a gradual dose-response clearance with 81% of lesions substantially lightened or cleared at the highest tested fluence (2b) [34]. In a retrospective study, Fitzpatrick et al. treated 83 lentigines in 26 patients with a CO_2 laser and found all lentigines had 100% clearance (2b) [35]. Stern et al. conducted a randomized, controlled, prospective trial and found 25% and

62% of lentigines had excellent and good results, respectively, with the argon laser, while 23% and 61% of lentigines had excellent and good results, respectively, with the CO_2 laser (1b) [27].

Nanosecond domain, QS lasers produce excellent results for lentigines. These include the frequency-doubled QS Nd:YAG (532 nm), QS ruby (694 nm), QS alexandrite (755 nm), and QS Nd:YAG (1064 nm). In general, one to two treatment sessions are required to achieve a satisfactory response.

Tse et al. found a 67% mean percentage clearing after one treatment in six patients treated with QS ruby laser (4) [36]. Kopera et al. achieved good clearance of 196 solar lentigines on the forearms of eight female patients with one treatment session and observed no recurrence or adverse events during 6–8 weeks of follow-up (2b) [37]. The effects of QS ruby laser on solar lentigines in 91 patients with skin type II, III, and IV were studied by Sadighha et al. (2b) [38]. Complete clearance was achieved in all patients after one or two treatments. Post-inflammatory dyspigmentation occurred in 7.8% of patients with Fitzpatrick skin type II, 9.8% of patients with type III, and 16.6% of patients with type IV; all improved over a 6-month follow-up period [38]. Treatment of dorsal hand lesions in 11 patients showed a response in all subjects after 1 treatment; 24 weeks following three treatments, the numbers of subjects showing 51–75%, 26–50%, and 1–25% improvement were five, four, and one, respectively, with one patient dropping out due to pain (1b) [39].

Kilmer et al. performed a multicenter, single-impact, dose-response study of lentigines with the frequency-doubled QS Nd:YAG laser and found greater than 75% pigment removal was achieved in 60% of those lesions treated at higher-energy fluences (2b) [40]. Tse et al. found a 58% mean percentage clearing after one treatment in six patients [36]. Treatment of 12 subjects by Suh et al. produced 51–100% and 26–50% improvement in 83% and 17%, respectively (4) [41].

Kaminaka et al. conducted a prospective, randomized, split-face comparative study in eight Asian patients with facial solar lentigines using low-fluence 1064-nm QS Nd:YAG weekly for ten sessions on one cheek. They found 62.5% of patients had greater than 50% clearance after the final treatment with a recurrence rate of 13% at 6 months follow-up. 75% and 62.5% of patients were satisfied with their clinical response at the end of ten treatments and at 6 months follow-up, respectively (1a) [42].

Using the QS alexandrite laser, Kagami et al. retrospectively studied a cohort of 49 Japanese patients following 1–5 treatments with at least 3-month intervals and found 2%, 24.5%, 26.5%, 20.4%, and 8.2% of patients had 96–100%, 76–95%, 51–75%, 26–50%, and 0–25% clearance, respectively (2b) [43].

Millisecond duration long pulse alexandrite and pulsed dye lasers can be safely used to treat lentigines, because the pigment is confined to the epidermis and dermal-epidermal junction. In a prospective trial with a blinded investigator and control groups, Rosenbach et al. treated 21 lentigines in 11 patients with Fitzpatrick skin types II–IV and found 25%, 67%, and 10% of lesions had 91–100%, 76–90%, and 51–75% improvements, respectively, with one to two treatments at 4-week intervals (1b) [44]. The long pulse alexandrite laser successfully treated lentigines in two Japanese patients without pigmentary changes, scarring, or recurrence (4) [45]. Vano-Galvan et al. treated five patients with ten light-colored solar lentigines using the combination of cryotherapy plus long pulsed alexandrite laser and found all lesions showed substantial lightening with no adverse events during treatment and after 1 year of follow-up (4) [46]. Trafeli et al. found improvement in lentigines 6 weeks after treating 16 subjects. The darker lentigines achieved the best lightening with few side effects and minimal downtime (2b) [47].

The pulsed dye laser was safe and effective for the treatment for lentigines in multiple studies. Kono et al. showed 83.3% clearance rate (1b) [22]. The group did a follow-up validation study with 54 Asian patients using similar settings with the pulse dye laser and found 70% excellent, 24% good, and 4% fair responses with only 1 patient developing post-inflammatory hyperpigmentation (2b) [21]. Kauvar et al. showed that pulsed

dye laser with a modified pulse sequence and compression handpiece produced objectively moderate (26–50%) improvement in pigmented lesions in 24 phototype I–III patients with photoaged skin (4) [18]. In a study of 12 Caucasian female patients using the 595-nm pulse dye laser with a compression handpiece and no epidermal cooling, Garden et al. demonstrated clearance of 75–100% in 43%, 59%, 76%, and 79% of the lesions treated after one, two, three, and four treatments, respectively, at 4–6-week intervals (4) [19].

Non-ablative and ablative fractional lasers successfully treat photodamage-associated lentigines and dyschromia [14, 17]. The non-ablative devices heat microscopic foci of tissue, with typical microscopic thermal zones measuring 150 microns in diameter and the depth and density of beams can be varied. The resulting damaged tissue, comprised of thermally denatured columns of tissue, is eliminated trans-epidermally, and new epidermis and dermis replace the treated tissue [17, 48]. Multiple treatment sessions, typically 4–6, are needed for pigmented lesions because of the fractional nature of the treatment. Multiple wavelengths are currently available including 1927 nm, 1320 nm, 1440 nm, 1550 nm, and 1565 nm. An advantage of these treatments is that they also produce improvements in texture and vascularity, as they target tissue water, and treat everything in the path of the laser beams. Treatment with the fractional 1927-nm laser also reduces actinic dysplasia. Brauer et al. in a prospective, multicentered study investigated the safety and efficacy of a fractionated 1927-nm non-ablative thulium laser for the treatment of photoinduced pigmentation in 40 subjects. Moderate to very significant improvement in solar lentigines was observed in 68% of subjects at 1 month and in 51% of subjects at 3 months after the second treatment (2b) [49]. Treatment is safely performed in all skin types and also on non-facial skin. Healing is associated with edema, erythema, and desquamation lasting 4–7 days. Fractional ablative lasers (CO_2, Er:YAG, and YSGG) are typically used on the face only because of the higher risk of adverse events when used on adnexal-poor skin. Treatment of photodamage with fractional ablative and non-ablative lasers is addressed in depth in Chaps. 17 and 18.

Comparative Effectiveness of Common Treatments

Given the multitude of therapeutic modalities in the physician's armamentarium to treat solar lentigines, we now review the relative effectiveness of these procedures. These various therapies are not mutually exclusive, as they may be used in combination or sequentially. For example, Hexsel et al. in 2014 published their investigator-blinded, randomized clinical trial of 50 patients and found that triple combination cream consisting of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% enhanced the effects of cryotherapy in the resolution of solar lentigines (1b) [50].

Chemical Peel Versus Laser

A split-lesion study comparing trichloroacetic acid (TCA) 35% peel and frequency-doubled QS 532-nm Nd:YAG laser therapy of 37 facial lentigines in 20 Asian patients with skin types III–IV showed better improvement on the laser-treated areas in 65% of patients, superior improvement on the TCA-treated areas in 14%, and similar improvement in 21%, with similar safety profiles (1b) [51].

Topical Cream Versus Laser

A prospective, open-label trial in 15 patients, Fitzpatrick skin types I–IV, with symmetrically distributed solar lentigines on the back of both hands compared one or two treatments with a QS ruby laser versus triple-combination cream (hydroquinone 5%, tretinoin 0.03%, and dexamethasone 0.03%) for 7 weeks accompanied by ultraviolet protection. The QS ruby was found to provide a statistically significant superior lightening when compared with topical therapy at the end of therapy and at 12-week follow-up. Both had acceptable side effect profiles although QS ruby laser caused more hyperpigmentation and crusting, all of which resolved by 20 weeks (1b) [52].

Cryotherapy Versus Laser

Stern et al. conducted a randomized, controlled, prospective trial comparing liquid nitrogen cryotherapy, argon laser, and low-fluence carbon dioxide laser in the treatment of solar lentigines at 99 sites in 13 patients. Cryotherapy produced significantly better results than either the continuous-wave argon or CO_2 laser treatment. There was infrequent skin atrophy for all three treatment modalities (1b) [27]. In another randomized, controlled, comparative study with blinded observers comparing liquid nitrogen, the frequency-doubled QS Nd:YAG laser, the continuous-wave HGM K1 krypton laser, and the 532-nm diode pumped laser in 27 individuals with solar lentigines on the backs and dorsal hands. The frequency-doubled QS Nd:YAG laser provided the best lightening with the fewest adverse effects (1b) [26]. Seirafi et al. enrolled 24 patients with Fitzpatrick's skin types II–IV with facial or hand lentigines and performed an evaluator-blinded randomized clinical trial comparing pulse dye laser and cryotherapy. They found pulse dye laser was more likely to produce substantial lightening of the solar lentigines than cryotherapy, especially in subjects with skin types III and IV, but there might be no difference in those with type II skin (1b) [20].

IPL Versus Lasers

In a split-face trial of 17 Asian patients, examining 2 treatments of IPL versus 1 treatment of QS alexandrite laser, there were similar rates of improvement. The laser caused post-inflammatory pigmentation in eight patients, which resolved within 6 months, and there was no hyperpigmentation following IPL treatment. The results after IPL were better than QS alexandrite laser among those with post-inflammatory hyperpigmentation after laser treatment (1b) [53].

Between Lasers

Negishi et al. conducted a prospective, randomized, parallel-group study with 196 Asian subjects comparing a single treatment with either QS ruby or QS frequency-doubled Nd:YAG laser with mild (endpoint of slight immediate whitening of the lesion) or aggressive (endpoint of very obvious immediate whitening) irradiation. They found no differences in efficacy both between the two lasers or between the mildly and aggressively irradiated groups. Aggressive treatment with QS lasers resulted in a high post-inflammatory hyperpigmentation incidence (33% and 23% vs 7% and 8%), while having no advantage in efficacy (1b) [54]. Noh et al. reported a prospective, randomized, double-blinded, split-face comparison pilot study with a QS 660-nm or QS 532-nm Nd:YAG laser in seven Asian women with facial solar lentigines. This new 660-nm wavelength ruby-like Nd:YAG laser uses a handpiece equipped with a solid dye to convert the 532-nm QS Nd:YAG laser energy to 660 nm. There were no significant differences between the two groups at 4- and 8-week follow-up [55].

In comparison trials, QS lasers are more effective than fractional ablative CO_2 lasers. Schoenewolf et al. conducted a randomized, controlled trial of an intra-individual, side-to-side comparison of 11 patients and found better clearance with the QS ruby laser compared to a fractional ablative CO_2 laser used to treat dorsal hand lentigines [39]. A prospective, single-blinded, randomized, intraindividual controlled trial study in 25 Thai patients with skin phototypes III–IV found significantly better outcomes with the 532-nm QS Nd:YAG laser compared to the fractional CO_2 laser by both colorimeter assessment and physician grading scale with no significant difference in post-inflammatory hyperpigmentation. Eighty percent of the patients treated with 532-nm QS Nd:YAG laser had excellent self-assessment results versus 8% in fractional CO_2 laser group. There was faster healing time and a lower pain score with the fractional CO_2 laser treatment (1b) [56].

Single-session treatment with thin-layer Er:YAG laser "micropeel" was compared with QS Nd:YAG laser [57] in a split-face, evaluator-blind, randomized controlled study in 15 Asian patients. The immediate effects were better with the QS Nd:YAG at 2-week follow-up, but that group had a higher incidence of hyperpigmentation at 4-week follow-up (1b) [58]. The same group performed a second split-face, evaluator-blind, randomized controlled study and

found similar improvement with QS Nd:YAG laser alone as compared to QS Nd:YAG laser plus Er:YAG micropeel combination therapy at 2 weeks. However, there was a higher incidence of post-inflammatory hyperpigmentation in the combination group (73% vs 40%), thus making the QS Nd:YAG monotherapy to be more favorable (1b) [59].

Kono et al. compared treatment of solar lentigines with a pulsed dye laser (1.5-ms pulse duration) used with a compression handpiece to reduce competing absorption by hemoglobin and a QS ruby laser in 18 Asian patients with facial lentigines with Fitzpatrick skin types III–IV. Clearance rates were 70.3% and 83.3% for QS ruby and pulsed dye lasers, respectively, with higher rates of posttreatment erythema and dyspigmentation in QS ruby group (1b) [22]. Chan et al. conducted a split-face, randomized control study in 34 Asian patients and found similar results with a millisecond domain and nanosecond domain frequency-doubled 532-nm Nd:YAG laser with respect to both clinical efficacy and adverse effects, including post-inflammatory hyperpigmentation, which resolved with bleaching agents and glycolic acid creams (1b) [60]. Ho et al. conducted a retrospective analysis of four different lasers in the management of solar lentigines in Asians. Each patient received 1–4 treatments (mean of 1.8), at 4–6 weeks intervals, depending on the clinical response. They found no statistically significant differences in efficacy with the pulsed dye laser, QS 532-nm Nd:YAG, and long-pulsed 532-nm KTP lasers. The long-pulsed alexandrite laser did not produce significant clearance of lesions. The post-inflammatory hyperpigmentation occurred in 20% of patients following long-pulsed alexandrite treatment, 10% after QS Nd:YAG laser treatment, and in none after pulsed dye and long-pulsed KTP laser treatment (2b) [61].

In summary, QS lasers, long-pulsed lasers, and IPLs are effective in treating solar lentigines with an excellent safety profile. In Asian patients, treatment with less aggressive laser parameters and longer pulse durations is associated with a lower risk of post-inflammatory hyperpigmentation.

Preoperative Evaluation and Patient Selection

A thorough medical history including medical conditions, current and previous medications, allergies, and results of prior treatments should be obtained at the initial consultation. Patients should be questioned about a history of systemic gold therapy (which is a risk factor for laser-induced chrysiasis when treating with nanosecond and picosecond lasers), herpes simplex virus in the treatment area (which can be reactivated with treatment), and a history of keloid formation, abnormal wound healing, and post-inflammatory hyperpigmentation. The patient's expectations and allowable downtime should be carefully considered and weighed when planning treatment and deciding between various modalities.

On physical exam, the clinician should evaluate the patient's skin phototype, the number, extent (scattered vs diffuse), and location of lentigines of interest. It is important that the clinician is confident of the diagnosis, especially if another provider is referring the patient. Differentiating solar lentigines from other pigmented lesions can sometimes be difficult. Lesions that are clinically suspicious for melanoma or dysplastic nevi should be appropriately evaluated prior to laser treatment. There have been reported cases of malignant melanoma being referred to as solar lentigines for cosmetic treatment [62]. These reports highlight the importance of careful evaluation of pigmented lesions before treatment. If there is any doubt, it is prudent to perform a biopsy to confirm diagnosis before treatment.

It is important to emphasize the need for using broad-spectrum sunscreens and practicing sun-protective habits in order to optimize treatment results. Pre- and posttreatment with bleaching agents could minimize posttreatment dyspigmentation and further optimize results, particularly in individuals with a tendency toward hyperpigmentation [63]. Discussing realistic expectation is also important, as the greater the contrast between background skin and lesion, the more likely the clinician is to achieve success and avoid adverse outcomes.

Impact of Patient Preference

Patient preferences may significantly impact the treatment selection. Topical therapies are considered first-line treatments for patients who desire a more conservative, nonphysical treatment modality. Cryotherapy is widely available and may be utilized in patients who are limited by their budgets. Patients with large areas of involvement and uneven pigmentation may benefit from peels, such as trichloroacetic acid. In deciding between QS laser treatments and IPL, patient's preference regarding cost-effectiveness, number of sessions, and downtime tolerance need to be carefully weighed. QS lasers will generally only require one to two treatment sessions and are thus more cost-effective than IPL, but they carry a greater risk of erythema and post-inflammatory hyperpigmentation, especially in darker-skinned individuals. IPLs are a good option when treating a large surface area, such as the chest or arms, as most systems come equipped with large rectangular spot sizes that can be used to paint in the whole cosmetic unit, but usually require more treatment sessions. Familiarity with individual device settings as well as clinical endpoints during treatment is essential as aggressive treatment with IPL in darker-skinned or sun-tanned individuals can produce adverse events including blistering, hypopigmentation, and scarring. Nonablative fractional lasers can also be considered to achieve both skin rejuvenation through collagen remodeling and simultaneous removal of pigmented lesions including solar lentigines.

Typical Treatment Plan

The treatment plan for each patient will vary depending on the patient's skin type, the number, density and color of lentigines, the tolerance for downtime, multiple treatment sessions, and the cost. Standardized photographs should be taken prior to and after each treatment session. The patient should not be suntanned at the time of treatment, especially if planning to treat with IPL or laser devices. Topical bleaching creams, chemical peels, microdermabrasion and cryotherapy should be considered first if budget considerations are primary. The following discussion centers on device-based treatment of lentigines.

If the patient has light phototype skin and scattered lesions, a QS laser is the first line of treatment. For patients with darker skin types or those prone to hyperpigmentation, treatment with a millisecond duration laser, IPL, or low-fluence QS 1064 nm should be considered as first-line treatment. Concomitant use of bleaching cream should be considered in patients at high risk for post-inflammatory hyperpigmentation. When numerous lesions are present on the background sun-damaged skin, non-ablative fractional lasers should be considered, as they will address additional concerns.

For the experienced clinician, laser test spots are not usually required for treating individuals with light phototype skin and a low risk of post-treatment pigment alteration. In an individual with a higher risk of adverse events, test treatments are desirable with one or multiple devices, and results and complications are evaluated at approximately 4 weeks. Some of the most common complications to look for include textural change, scarring, pruritus, hypo- or hyperpigmentation, and immediate pigment change. If the clinical outcome is satisfactory, full treatment of all lesions can then be pursued. If post-inflammatory hyperpigmentation develops at the test sites with lasers, consider using IPL for treatment. In patients who are prone to develop hyperpigmentation, consider using topical bleaching creams such as hydroquinone for 1–2 weeks before treatment and then adding a topical corticosteroid immediately after laser treatment for 2–3 days. Patients should be counseled on adhering to daily sunscreen use to optimize treatment outcomes and maintain results. Patients should return for a follow-up visit at 4–6 weeks, at which time re-treatment may be performed if necessary.

Novel Treatments

Lasers with picosecond domain pulses have recently been commercialized. With pulse durations 100–1000 shorter than nanosecond

lasers, these high peak power devices disrupt pigment such as melanin or tattoo ink primarily via photoacoustic effects and cavitation rather than thermal effects. The physics of laser-tissue interactions predict that picosecond pulses should produce faster clearance of tattoo ink with a lower incidence of adverse effects compared to nanosecond lasers, which is being borne out in recent literature. Early studies and anecdotal reports also suggest that picosecond lasers may be able to clear pigmented lesions more quickly with fewer side effects.

The picosecond 755-nm alexandrite and 532-nm Nd:YAG picosecond lasers have been used successfully to treat solar lentigines. Chan et al. published on their early experience with the picosecond 755-nm alexandrite laser and found a fair (25–49%) improvement in the one patient treated for lentigines (4) [64]. Treating with a picosecond 532-nm Nd:YAG laser, Guss et al. found greater than 75% clearance in more than 78% of the lesions in a retrospective chart review of 255 treated solar lentigines in 6 Fitzpatrick skin type IV individuals. Five of the 6 patients only required one treatment and in only 2 of the 255 lesions developed post-inflammatory hyperpigmentation (2b) [65]. The higher safety profile of picosecond laser in darker-skinned individuals is supported by a retrospective study by Levin et al., where the investigators found 4 of 25 (15%) darker-skinned patients treated with QS lasers for pigmented lesions developed permanent dyspigmentation, while all side effects, including post-procedural hyperpigmentation, in the 755-nm picosecond laser treatments were temporary and resolved within 3 months (4) [66].

A new 660-nm ruby-like laser, which used a handpiece equipped with a solid dye that converts the 532-nm QS Nd:YAG laser energy to 660 nm, is effective in treating facial solar lentigines [55]. Noh et al. conducted a prospective, randomized, double-blinded, split-face comparison pilot study in seven Asian women and found no significant difference in improvement was found between the 660-nm ruby-like laser and 532-nm QS Nd:YAG laser based on both subjective and objective measures. There was decreased post-inflammatory hyperpigmentation at 8 weeks after treatment with the 660-nm laser, which likely related to the lower coefficient of absorption for melanin and hemoglobin at 660 nm compared to 532 nm [55, 67]. The 660-nm ruby-like laser potentially provides another treatment option for lentigines in Asian skin based on this study.

Safety

Generally, both selective and nonselective physical modalities and topical treatments are safe in the treatment of lentigines. The most common side effects are erythema and dyspigmentation. Textural change and scarring are rare, and when they do occur, they are usually preceded by post-treatment blistering or ulceration from excessive tissue damage.

Treatments that result in prolonged erythema and edema, such as cryotherapy, continuous-wave, and ablative lasers, have an increased risk of post-inflammatory hyperpigmentation in darker phototype skin.

In general, pulsed lasers that selectively damage pigment by confining thermal damage to lesional tissue carry a very low risk of textural change and scarring in all skin phototypes, but transient hyperpigmentation has been reported to occur in up to 20–25% of darker skin, and in Asian skin with the use of QS lasers, 532 nm in particular. The risk is very low in white, non-suntanned skin. The risk is highest when treating with the 532-nm lasers due to enhanced absorption by melanin as well as hemoglobin, compared to longer wavelength devices. There is more erythema and edema after treatment, as well as purpura due to strong absorption by hemoglobin. At 532 nm and 694 nm, care must be taken to use the lowest possible fluence and avoid pulse stacking to minimize these risks [56, 57]. The risks are lower with the 755-nm alexandrite and 1064-nm Nd:YAG lasers due to lower absorption by melanin, but clearing low contrast, lightly pigmented lesions become more of a challenge.

The estimated risk of post-inflammatory hyperpigmentation in darker-skinned patients using QS lasers is approximately 25%, although studies show various results ranging from 0% to 47% [38, 53, 65, 68]. Kang et al. in a retrospective multicenter study involving 5 hospital clinic sites and 516 patients found the overall incidence of post-inflammatory hyperpigmentation was 20.3% during treatment of solar lentigines using a QS 532-nm Nd:YAG laser (2b) [69]. For patients at high risk for post-inflammatory hyperpigmentation, QS 1064-nm YAG laser can be used in conjunction with good sun protection. Gradual fading, rather than rapid clearing of lentigines, occurs with successive laser treatments.

Millisecond lasers have been used to treat dark-skinned patients in an attempt to cause less non-lesional epidermal damage and post-inflammatory hyperpigmentation. In the case of millisecond pulse duration lasers and IPLs, selective photothermolysis predicts slow heating of the lesion rather than photomechanical disruption of the melanosomes and pigment-containing cells observed with nanosecond domain lasers. At appropriately chosen fluences, post-inflammatory hyperpigmentation will be minimized. When too high a fluence is used with millisecond pulse widths, adverse effects may be even greater due to non-specific absorption of thermal damage. In a study done comparing long-pulsed and QS Nd:YAG 532 nm in Asians showed long-pulsed is safer with lower risk of post-inflammatory hyperpigmentation [60].

Postoperative Care and Follow-Up

Patients should follow up around 4–6 weeks to evaluate for efficacy and post-procedure complications. Patients should be counseled on rigorous ultraviolet protection as solar lentigines can recur and new lesions may develop. Since solar lentigines are markers of dermatoheliosis, patients should also be screened for skin cancer as dictated by the individual's circumstances.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Solar lentigines are common, especially in sun-exposed areas and in lighter skinned individuals	A
Benign lentigines can sometimes be difficult to differentiate from benign pigmented lesions	B
A variety of topical and physical procedures effectively treat solar lentigines	A
Lasers are generally more effective than topical creams, chemical peels, and cryotherapy	B
IPL has minimal downtime but requires more treatment sessions for solar lentigines than lasers	B
IPL and fractional non-ablative lasers can be used to simultaneously improve skin tone and texture in addition to treating lentigines	B
Patients with darker skin color are more prone to complications such as dyspigmentation after physical treatments with lasers and cryotherapy	B

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Self-Assessment Questions

1. A 57-year-old man with Fitzpatrick skin type II was referred by a colleague for cosmetic removal of a pigmented lesion that has been changing and growing in size over the past year. The patient said the referring colleague told him it was a lentigo, and he desires a treatment with minimal downtime. On dermoscopy, the lesion is asymmetrical and has multiple colors. What should you do next?
   (a) Treat with liquid nitrogen cryotherapy
   (b) Treat with intense pulsed light
   (c) Treat with QS ruby laser
   (d) Treat with topical hydroquinone cream
   (e) Biopsy the lesion
2. Which of the following laser is generally the safest for treating solar lentigines in darker-skinned patients?
   (a) QS 532-nm Nd:YAG laser
   (b) QS 694-nm ruby laser
   (c) QS 755-nm alexandrite laser
   (d) QS 1064-nm Nd:YAG laser
   (e) CO_2 ablative laser
3. A 45-year-old woman with Fitzpatrick skin type III desires treatment for multiple solar lentigines on her face and cannot have anything more than minimal downtime. Which treatment modality do you recommend?
   (a) QS 532-nm Nd:YAG laser
   (b) Intense pulsed light
   (c) Ablative CO_2 laser
   (d) Non-ablative 1927-nm laser
   (e) Picosecond 755-nm laser
4. Which of the following is not a treatment for solar lentigines?
   (a) QS lasers
   (b) Cryotherapy
   (c) PUVA therapy
   (d) Topical bleaching agents
   (e) Fractional non-ablative lasers
5. A 64-year-old woman with Fitzpatrick skin type III desires treatment for multiple solar lentigines on her dorsal hands and bilateral upper extremities. She wants the least number of treatments, does not mind downtime, and has a history of post-inflammatory hyperpigmentation. You have multiple light-based and laser modalities available. What is the next best step in management?
   (a) Treat all lesions with IPL
   (b) Treat all lesions with QS 694-nm ruby laser
   (c) Treat all lesions with QS 532-nm Nd:YAG laser
   (d) Treat all lesions with cryotherapy
   (e) Do test spots treatments with various modalities

Correct Answers

1. e: Biopsy the lesion. Solar lentigines can sometimes be diagnosed incorrectly. If the clinician sees evidence that suggests a different diagnosis and especially if there are worrisome signs (multiple colors, asymmetry, changing), then a biopsy is needed to confirm diagnosis before treatment.
2. d: QS 1064-nm Nd:YAG laser. QS 1064-nm Nd:YAG laser emits a longer, near-infrared ray that is capable of penetrating into the deeper regions of the skin. It tends to spare the epidermis and avoid damage there which would cause posttreatment dyspigmentation in darker patients who have higher concentration of melanin at the dermal-epidermal junction.
3. a: Intense pulsed light. Of all the treatment modalities listed, IPL has minimal to no downtime. However, patients will need multiple treatment sessions.
4. c: PUVA therapy. PUVA has been demonstrated to cause PUVA lentigines. All other options have been shown to be effective in treating solar lentigines.
5. e: Do test spots treatments with various modalities. To ensure efficacy and avoid unwanted complication such as post-inflammatory dyspigmentation, it is best to spot test with different treatment modalities to evaluate for efficacy and complications. This ensures that the best treatment can be established quickly per patient preference and full treatment for all the lesions can then be pursued.

Melasma

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Abstract

Melasma is a common acquired disorder of hyperpigmentation characterized by symmetric brown macules and patches on sun-exposed skin. The treatment of melasma often necessitates a multifaceted approach combining broad-spectrum photoprotection, topical agents, and, in refractory cases, chemical peels and laser/light therapy. Superficial chemical peels, including glycolic, salicylic, and trichloroacetic acid, are safe and cost-effective procedures that remove excess cutaneous pigment through controlled chemical injury followed by skin regeneration. Lasers and light-based devices, including fractional resurfacing and Q-switched lasers, are also effective in the treatment of refractory melasma, particularly when used in combination with topical depigmenting agents. Microneedling and picosecond lasers have more recently been added to the treatment armamentarium. This chapter provides an evidence-based approach to the treatment of melasma with laser and light-based devices, chemical peeling agents, and other dermatologic procedures. Herein, the authors review the safety and efficacy of dermatologic procedures and provide evidence-based recommendations for procedural selection and peri-procedural care in melasma.

Keywords

Melasma · Hyperpigmentation
Hypermelanosis · Laser treatment · Fractional resurfacing · Chemical peel

Epidemiology

Melasma is a common acquired disorder of hyperpigmentation characterized by symmetric light to dark brown macules and patches on sun-exposed skin. This condition most commonly affects the forehead, cheeks, and chin of individuals with Fitzpatrick skin types (FST) III and IV, but can be seen in any skin type [1, 2]. Melasma may be divided into three distinct types—epidermal, dermal, and mixed—depending on the depth of melanin pigment within the skin, which can typically be determined via Wood's lamp examination [3, 4].

Melasma affects approximately five to six million individuals in the United States [5]. The prevalence varies by ethnic group and may be as high as 8–36% in skin of color, including people of Middle Eastern, Hispanic, and African descent [6–9].

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It more commonly occurs in women, often between pregnancy and menopause, with a mean age of 34 [2]. Men may also develop this condition, and studies in India have reported that as many as 20.5–25.83% of melasma cases occur in males [10].

Although there are numerous etiologies implicated in the pathogenesis of melasma, the strongest contributor is exposure to sunlight [2]. Other contributory factors include pregnancy [11, 12], hormonal changes [2], use of oral contraceptives or hormone replacement therapy [13], thyroid disease [14], and family history of melasma, especially in those with darker skin types [2]. In males, the development of melasma has been attributed to subtle testicular resistance, resulting in low levels of testosterone [15].

The pathogenesis of melasma, regardless of the underlying etiology, is thought to be due to an increased number of melanocytes (melanocytosis) and increased melanin production (melanogenesis) within the skin as a result of alterations in gene expression and cellular signaling pathways [4, 16–18]. Melasma skin exhibits upregulation of genes involved in melanin biosynthesis and melanocyte markers, including TYR, MITF, SILV, and TYRP [18]. Increased vascularization due to elevated levels of vascular endothelial growth factor and downregulation of lipid metabolism genes have been implicated in its development and are important to consider when choosing an optimal therapy [17, 18].

Treatment Overview

The treatment of melasma often requires a multifaceted approach combining broad-spectrum photoprotection, sun avoidance, topical compounds, and, in refractory cases, chemical peels and laser/light therapy. Sunscreens with SPF 30+ and topical medications that target melanin production are first-line therapies. Hydroquinone and triple combination creams (TCC) containing hydroquinone, corticosteroids, and retinoids are the most commonly used topical therapies and are considered the gold standard of treatment due to their high efficacy [19–23]. For those who achieve insufficient response with topical therapy alone, additional improvements can be observed when combined with procedures such as chemical peels, light therapy, and laser treatments, which are typically considered to be second- and third-line [1, 19].

Chemical peeling is a safe and cost-effective procedure that aims to remove excess epidermal, and perhaps some dermal, pigment through controlled chemical injury followed by regeneration of the skin [20]. Typically, superficial peels are the most appropriate therapy for melasma, and medium-depth and deep peels should be used with caution or avoided altogether due to increased risk of dyschromia [21]. The peels most commonly used for melasma include glycolic acid (GA), salicylic acid (SA), and trichloroacetic acid (TCA) [1]. Other options include 1% tretinoin, Jessner's solution (salicylic acid, lactic acid, and resorcinol), and fruit peels. While published utilization data for chemical peeling agents are not available, expert opinion suggests that GA peels are the most frequently used peels for melasma worldwide.

Several lasers have also been studied in the treatment of melasma (Table 53.1). Melanin within the skin is targeted best at wavelengths of light ranging from 600 nm to 1100 nm, and, therefore, lasers that emit wavelengths within this range are often chosen for its treatment [22]. These lasers can be divided into the following categories based on their unique properties:

- Ablative non-fractionated lasers: 10,600 nm carbon dioxide (CO_2), 2940 nm erbium-doped yttrium aluminum garnet (Er:YAG) [*reported but not widely utilized in melasma due to high risk for adverse events; contraindicated in Fitzpatrick skin types IV–VI*]
- Fractional ablative lasers: 10,600 nm fractional CO_2, 2940 nm fractional Er:YAG
- Fractional non-ablative lasers: erbium (1410 nm, 1540 nm, 1550 nm), diode (1440 nm, 1927 nm), and thulium fiber (1927 nm)
- Quality-switched lasers:
  - Green light—frequency doubled quality-switched neodymium-doped yttrium aluminum garnet (FD QS-Nd:YAG or QSNYL) (532 nm)

Table 53.1 Laser and light therapies for the treatment of melasma

Author	Device	n	FST/Race	Treatment	Results	Side effects and recurrence
Ablative non-fractional lasers						
Nouri et al. [24]	950 μs pulsed CO_2 Open-label, 2 groups: 1. CO_2 laser alone 2. CO_2 + 2nd pass QSAL 755 nm	8	IV–VI	1 session **CO_2 laser** 300 mJ/cm^2 950 μs pulse **QSAL** 6 J/cm^2	Complete resolution of melasma in test spot at 6 months in combination group	Peripheral hyperpigmentation in 50% of subjects in CO_2 laser only group No recurrence at 6-month follow-up
Angsuwarangsee and Polnikorn [25]	Ultrapulse 950 ms CO_2 Prospective, split-face: 1. CO_2 laser plus QSAL 2. 750 nm QSAL alone	6	II–V	1 session **CO_2** 300–350 mJ/cm^2, 60 W, 8 mm OR collimated, 300 mJ, 5Ws, 3 mm **QSAL** 5–7 J/cm2, 5 Hz, 60 ns, 3 mm	MASI decreased in 83.3% of subjects on combined side versus 50% on QSAL side. MASI increased on QSAL side in 16.6%	Contact dermatitis and hyperpigmentation observed in combined group Severe PIH at 6-month follow-up in skin types V–VI
Manaloto and Alster [26]	Er:YAG 2940 nm	10	II–V	1 session Collimated 5.1–7.6 J/cm^2, 8 Hz, 5 mm, 3 passes	Mean MASI decreased from 19.1 at baseline to 10.6 at 6 months Melanin reflectance spectrometry score decreased from 48.8 at baseline to 43.6 at 6 months	PIH at 3–6 weeks' post-treatment with associated increase in MASI above baseline (100%)
Attwa et al. [23]	Er:YAG 2940 nm	15	II–IV	Monthly, 6 sessions 1.0 J, 5 Hz, 5 mm, 2 passes	Statistically significant decrease in MASI from 5.95 ± 3.3 before treatment to 2.47 ± 1.7 at 6-month follow-up Physician assessment demonstrated 50–100% improvement in 80% of subjects	Oozing and facial edema PIH at 2–4 weeks after last session (20%) Recurrence at 6-month follow-up in 33%
Ablative fractional lasers						
Diosti et al. [27]	Fractional Er:YAG	10	III–V	Monthly, 3 sessions 1400 mJ/P, 2 Hz, 7 × 7 tip, 3 passes	Change in MASI not statistically significant At 6-month follow-up, 70% of subjects reported subjective mild or moderate improvement in melasma Considerable reduction in melanin pigment in the basal layer in 70%	PIH (10%) Recurrence at 4-month follow-up in 40% of subjects

(continued)

Table 53.1 (continued)

Author	Device	n	FST/ Race	Treatment	Results	Side effects and recurrence
Trelles et al. [28]	Fractional CO_2 3 groups: 1. Anti-pigment cream 2. Fractional CO_2 laser 3. Fractional CO_2 laser + anti-pigment cream	30	II–IV	1 session 350 ms, 7.5 W	Subject self-assessment demonstrated 100% efficacy in all 3 groups at 1 month and 70% efficacy in combined group only at 10 months (0% efficacy in monotherapy groups)	Mild stinging, burning, erythema, crusts
Non-ablative fractional						
Naito [29]	1550 nm Er:glass	6	III–IV	Monthly, 3–4 sessions 6–8 mJ, 250 MTZs/ cm^2	At least 20% physician-graded improvement in melasma in all subjects	PIH (16.6%)
Wind et al. [30]	1550 nm Er:glass Single-blinded, split-face RCT: 1. 1550 nm Er:glass + TCC 2. TCC alone	18	II–V	4–5 sessions 15 mJ, 8 passes, 14–20% coverage	Physician global assessment, melanin index, and L-value showed a significant worsening of pigmentation at the laser-treated side Majority of patients preferred TCC at 6-month follow-up	Erythema, burning sensation, edema, and pain PIH after two or more laser sessions (31%)
Rokhsar and Fitzpatrick[31]	1550 nm Er:glass	10	III–V	Weekly or bimonthly 4–6 sessions 6–12 mJ 2000–3500 MTZ/cm^2	Physician-rated improvement of 75–100% in 6/10 subjects	PIH in FST V (10%)
Kroon et al. [32]	1550 nm Er:glass Observer-blinded RCT: 1. 1550 nm Er:glass 2. TCC	20	II–V	Bimonthly, 4 sessions 10 mJ, 2000–2500 MTZ/cm^2, 8 passes, 14–20% coverage	No objective difference in physician global assessment between groups Mean treatment satisfaction higher in laser group at 3-week follow-up	Erythema, burning sensation, facial edema, and pain No PIH or hypopigmentation Recurrence in 50% of subjects in each group at 6-month follow-up
Goldberg et al. [33]	1550 nm Er:glass	10	III–IV	Bimonthly, 4 sessions 6–10 mJ, 2000–2500 MTZ/cm^2	Good improvement (51–75% lightening) in FST III and fair improvement (26–50% lightening) in FST IV at 3 months Decreased melanocytes on light and electron microscopy	No PIH
Manela-Azulay and Borges [34]	1540 nm Er:glass	10	II–VI	Monthly, 3 sessions 8 mJ–15 mJ/MB, 15 ms, 5 mm	75–100% improvement in 29% and 50–75% in 71% of subjects who completed study	Second-degree burns (20%) and polymorphic light eruption (10%) No recurrence at 3 months

Tourlaki et al. [35]	1540 nm Er:glass	78	II–IV	Monthly, 3 sessions 15 mJ, 3600/4000 MTZs/cm^2, 15 ms, 15 mm spot, 4 passes, 50% overlap	Mean MASI significantly reduced compared to baseline at 1 month and 6 months' post-laser treatment	Transient edema and erythema No PIH Partial recurrence at 6-month follow-up
Polder and Bruce [36]	1927 nm fractionated thulium	14	II–IV	Monthly, 3–4 sessions 10–20 mJ, 6–8 passes	Statistically significant reduction in MASI at 1 month (51%), 3 months' (33%), and 6 months' (24%) post-treatment	Moderate erythema and mild edema No PIH Marginal recurrence at 6 months but improved from baseline
Brauer et al. [37]	1927 nm diode	23	I–IV, VI	Bimonthly, 4–6 sessions 5 mJ, 5–10% density, up to 8 passes	Investigator-rated marked or significant (51–100%) improvement in melasma in 40% of subjects and moderate improvement in 25–30% at 1 month and 3 months' post-treatment	Mild edema, mild-to-moderate erythema, flaking Transient perioral PIH (4.3%) No recurrence at 3 months
Quality-switched lasers						
Taylor and Anderson [38]	QSRL (694 nm)	4	II–VI	1–6 sessions 1.5–7.5 J/cm^2, 40 ns, 5 mm	No change in pigmentation or worsening of pigmentation in all patients No change in epidermal melanin on biopsy specimens at 2 months' post-treatment	Edema, erythema PIH (25%), confetti-like hypopigmentation (25%)
Tse et al. [39]	Frequency-doubled QS Nd:YAG and QSRL 2 test spots within the same lesion	3	NA	1 session	Subjects demonstrated no improvement in melasma with either laser	
Zhou et al. [40]	Low-fluence QS Nd:YAG	50	III–IV	Weekly, 9 sessions 2.5–3.4 J/cm^2, 10 Hz 6 mm spot	Mean MASI scores decreased 61.3% from baseline to end of study (10.6–4.1, $p < .001$). Mean decrease in MI was 35.8%	Burning sensation, erythema, urticaria, tiny purpura No PIH Recurrence rate of 64%
Brown et al. [41]	Low-fluence, large spot QS Nd:YAG	20	II–IV	Weekly, 8 sessions 2–4 J/cm^2 8–10 mm spot	19 out of 20 subjects demonstrated 25–100% lightening in melasma	Results maintained at 1-month follow-up Melasma flares seen at 3 months after last treatment

(continued)

Table 53.1 (continued)

Author	Device	n	FST/ Race	Treatment	Results	Side effects and recurrence
Sim et al. [42]	Low-fluence QS Nd:YAG	50	Asian	Weekly, 15 sessions 2.8 J/cm2, 10 Hz, 8 mm	Based on physician assessment, 59% of subjects demonstrated good (50–75%) improvement and 42% demonstrated excellent (75–100%) improvement	Erythema, transient burning, mild edema No PIH or hypopigmentation
Wattanakrai et al. [43]	Low-fluence QS Nd:YAG Split-face, investigator-blinded RCT: 1. QS Nd:YAG laser +2% HQ 2. 2% HQ	22	II–V	Weekly, 5 sessions 3–3.8 J/cm^2, 6 mm	92.5% improvement in relative lightness and 75.9% improvement in mMASI in laser group vs. 19.7% and 24% improvement, respectively, in HQ-only group	Mottled hypopigmentation (13.6%) and rebound hyperpigmentation (18%) on laser-treated side At least partial recurrence in all subjects at 12-week follow-up
Jeong et al. [44]	Low-dose QS Nd:YAG Split-face, crossover, RCT: 1. TCC then QS Nd:YAG 2. QS Nd:YAG then TCC	13	III–IV	Weekly, 8 sessions 1.6–2.0 J/cm^2, 7 mm, 2 passes	Mean MASI decreased significantly after laser treatment compared with TCC cream Side 1: mean MASI improved from 3.42 to 3.0 after TCC cream and to 2.09 after 8 weeks of laser Side B: mean MASI score decreased from 3.20 to 1.74 after laser and increased to 2.22 with TCC	Mild pain and erythema. No PIH or hypopigmentation Relapse seen in 85% at 11-month follow-up
Vachiramon [45]	Low-fluence QS Nd:YAG Split-face, investigator-blinded, RCT: 1. QS Nd:YAG 2. QS Nd:YAG +30% GA peel	15	III–V	Weekly, 5 sessions 2.2–2.8 J/cm^2, 10 Hz, 6 mm	52.3% improvement in mean RLI and 37.6% decrease in MASI at 4-week follow-up in combination group (vs. 37.6% and 14.6% reduction, respectively, in laser monotherapy group)	Burning, stinging, erythema, edema Guttate hypopigmentation (8%), PIH (17%) Rebound increase in RLI and mMASI score, but not complete relapse, at 16-week follow-up
Polnikorn [46]	QS Nd:YAG	35	NA	Weekly, 10 sessions followed by monthly, 2 sessions 3–3.4 J/cm^2, 10 Hz, 6 mm, 10 passes, 10% overlap	After 6 months of treatment, 30% of subjects demonstrated excellent clearance (>81% reduction of melasma) and 36.7% demonstrated good clearance (51–80% reduction)	Discomfort, erythema, whitening of fine hair, urticaria Mottled hypopigmentation (8.57%) Recurrence of melasma in 5.71% at study completion

Kang et al. [18]	Dual-toning QS Nd:YAG	30	IV	Bimonthly QS mode: 1.2 J/cm^2, 5 ns, 8 mm, multiple passes Micropulsed mode: 7 J/cm^2, 300 μs, 5 mm, multiple passes	67% of subjects with fair to excellent improvement, 23% with visible improvement, and 10% with little or no improvement	Erythema, stinging No recurrence at 6-week follow-up
Yue et al. [47]	Fractional-mode QS Nd:YAG	30	III–IV	Bimonthly, 8 sessions 2.6–3.6 J/cm^2, 8.5 mm, 42.4% coverage	Mean MASI decreased from 12.84 to 7.29, and mean MI decreased from 56.52 to 32.75 after treatment	Slight burning, tingling, and erythema No PIH or hypopigmentation Partial recurrence in 40% patients at 3 months and 82.4% at 6 months after last treatment
Kim et al. [48]	Low-fluence photoacoustic twin pulse (PTP) mode Nd:YAG	22	III–IV	Bimonthly, 5 sessions 2.5 J/cm^2, 7 mm, 5–7 passes	Significant improvement in melasma in 59.1% of subjects based on physician assessment and 86.4% based on subject assessment Mean MASI scores decreased by 20.4%	Erythema, dryness, pain, and itching No PIH or hypopigmentation Partial relapse in 18%
Jang et al. [49]	Low-dose fractional QSRL (694 nm)	15	III–IV	Bimonthly, 6 sessions 2–3 J/cm^2, 40 ns, 7.1 mm, 300 μm, 27.7% coverage	MASI decreased from 15.1 ± 3.3 before treatment to 10.6 ± 3.9 at 16 weeks	Transient erythema, mild pain Slight increase in MASI between 4 and 16 weeks' post-treatment
Picosecond lasers						
Choi et al. [50]	Picosecond Nd: YAG (1064 nm and 595 nm) Split-face, unblinded RCT: 1. Picosecond +2% HQ 2. 2% HQ	40	III–V	Weekly, 5 sessions **1064 nm** 1.5 J/cm^2, 5 or 10 Hz, 7–10 mm, 2–4 passes **595 nm** 0.55 J/cm^2, 2 or 5 Hz, 750 ps, 5 mm	At 1 week post-treatment, RLI decreased by 76.92% in the laser group and 2.56% in the HQ group. There was greater improvement in mMASI and better treatment satisfaction in the laser group at this time point Only RLI remained significantly improved on the laser-treated vs. HQ side at 12-week follow-up	Mild dermatitis, pain, and erythema

(continued)

Table 53.1 (continued)

Author	Device	n	FST/ Race	Treatment	Results	Side effects and recurrence
PDL						
Passeron et al. [51]	PDL (595 nm) Single-blind, split-face, RCT: 1. PDL + TCC 2. TCC	17	II–IV	Every 3 weeks, 3 sessions 1st pass: 7 J/cm^2, 1.5 ms, 10 mm 2nd pass: 10 J/cm^2, 20 ms, 7 mm, 10% overlap	In the entire cohort, there was a greater decrease in MASI in the PDL group (6.20 ± 3.02–2.79 ± 2.70) vs. TCC only group (6.76 ± 3.25–4.35 ± 2.76). When stratified by FST, patients with FST II–III demonstrated significantly greater improvement with PDL + TCC. There was no difference in treatment response for FST IV	Transient irritation from TCC PIH only in FST IV (18%)
IPL						
Bae et al. [52]	Low-fluence, short-pulse IPL (550 nm–800 nm) Double-blinded RCT: 1. IPL with 10 J/cm^2 fluence 2. IPL with 13 J/cm^2 fluence	20	IV–V	Weekly, 6 sessions 10 J/cm^2 or 13 J/cm^2, 70 μs, 2 passes	Statistically significant decrease in MASI and MI compared to baseline at weeks 2–9 in both groups Slightly greater numeric improvement in melasma with 13 J, but this was not statistically significant	Transient erythema, burning
Figueiredo Souza and Trancoso Souza [53]	IPL (560 nm) Evaluator-blinded, open-label, RCT: 1. IPL + TCC 2. TCC alone.	62	II–V	1 session 12–22 J	49.4% reduction in MASI at 6 months and 44.9% at 12 months in IPL + TCC group Significantly better response in the IPL + TCC group than TCC alone	Pain, microcrusts, mild transient erythema PIH (25%)
Goldman et al. [54]	IPL (560 nm) Split-face RCT: 1. IPL + TCC 2. IPL + inactive cream	56	I–IV	Monthly, 2 sessions 14–18 J/cm^2, 3.0–3.5 ms, 2 pulses, delay of 20 ms (II) or 30 ms (III–IV)	Physician-rated improvement of clear or almost clear in 57% of patients with IPL plus TCC vs. 23% with inactive cream	Skin erosion, erythema, scaling, dryness, burning, edema, telangiectasia
Wang et al. [55]	IPL (570 nm–615 nm) RCT, 2 groups: 1. IPL + 4% HQ 2. 4% HQ	17	III–IV	Monthly, 4 sessions 26–33 J/cm^2, 3–5 ms, 2 pulses, 30–35 ms delay	39.8% improvement in relative MI in IPL + HQ group (vs. 11.6% in HQ group) at week 16 35% of patients had >50% improvement in melasma severity	Erythema, microcrusts, pain PIH (12%) Recurrence in 2 patients in IPL group at 24 weeks' post-treatment
Li et al. [56]	IPL	89	III–IV	Every 3 weeks, 4 sessions	Mean MASI decreased from 15.2 to 4.5 Investigator evaluation demonstrated 75.3% improvement after 4 sessions and 77.5% improvement at 3-month follow-up	Transient erythema, slight edema, microcrusts PIH (4.5%)

Chung et al. [57]	IPL Split-face RCT: 1. IPL + topical 2% tranexamic acid (TA) 2. IPL + vehicle	13	NA	Monthly, 4 sessions 8.0–9.4 J/cm^2 2.5 ms Double pulse 10 ms pulse delay	MI and mMASI decreased significantly from baseline to 12 weeks after the last IPL treatment on the topical TA side only	Rebound prevented by continued TA use at 3-month follow-up
Chung [58]	Pulse in pulse (PIP) IPL (550–800 nm) Split-face RCT: 1. PIP IPL 2. IPL + low-fluence QS-Nd:YAG (IPL/NDY)			Group 1: **IPL** Bimonthly, 7 sessions 12–15 J/cm^2, 2–3 passes Group 2: **IPL** 1 session 9.0–9.4 J/cm^2, 2.5 ms double pulse, 10 ms delay, 1 pass **Nd:YAG** Bimonthly, 6 sessions 1.0–1.2 J/cm^2, 10 ns, 8 mm, multiple passes	54.4% vs. 50.0% reduction in mMASI score in the PIP-IPL and IPL/NDY treatment groups, respectively, at 2 weeks after last treatment	No significant recurrence of melasma at 6 months' post-treatment

n number of patients, *FST* Fitzpatrick skin type, CO_2 carbon dioxide, *QSAL* q-switched alexandrite laser, *MASI* melasma area and severity index, *mMASI* modified melasma area and severity index, *PIH* post-inflammatory hyperpigmentation, *Er:YAG* erbium:yttrium aluminum garnet, *Er:glass* erbium:glass, *TCC* triple combination cream, *RCT* randomized controlled trial, *QSRL* Q-switched ruby laser, *QS Nd:YAG* q-switched neodymium-doped yttrium aluminum garnet, *HQ* hydroquinone, *GA* glycolic acid, *RLI* relative lightness index, *PDL* pulsed dye laser, *IPL* intense pulsed light, *TA* tranexamic acid

  - Red light—quality-switched ruby (QSRL) (694 nm), quality-switched alexandrite (QSAL) (755 nm)
  - Near-infrared—quality-switched neodymium-doped yttrium aluminum garnet (QS-Nd:YAG or QSNYL) (1064 nm)
- Picosecond laser (532 nm Nd:YAG, 755 nm alexandrite, 1064 nm Nd:YAG)
- Pulsed dye laser (PDL) (595 nm)

Ablative lasers emit a high wavelength that targets water and, through indirect tissue vaporization, reduces the number of melanocytes and overall melanin content within the epidermis and dermis [23]. These are not widely utilized in the treatment of melasma due to considerable recovery periods and a high risk of dyspigmentation or scarring, especially in higher Fitzpatrick skin types. Fractional resurfacing using non-ablative fractional lasers is a newer technology that, rather than causing full-thickness epidermal wounds, creates microscopic treatment zones (MTZs) that result in a reduction in melanocytes and number of melanin granules in keratinocytes without as much inflammation and pigmentary sequelae [33]. Quality-switched lasers, also referred to as "laser toning" devices, use photoacoustic and photothermolytic effects to destroy melanosomes [22]. Multiple passes of a low-fluence laser (i.e., 1.6–3.5 J/cm^2) over a large spot size (i.e., 6–8 mm) optimize energy delivery while minimizing tissue damage [22, 42]. Pulsed dye lasers (PDLs) are preferentially absorbed by hemoglobin within cutaneous vessels, thereby allowing this laser to target the vascular component of melasma [51]. Picosecond lasers are a newer class of lasers that use shorter pulse durations, which results in a greater photoacoustic (rather than photothermolytic) effect and thereby minimizes thermal injury to adjacent tissue [59, 60].

Intense pulsed light, a spectrum of light ranging from 500 to 1200 nm applied over a long pulse width (milliseconds), is another treatment option for melasma [52]. Research on monopolar radiofrequency devices [61] and light-emitting diodes (LED) [62] is limited, and, therefore, these modalities will not be addressed in this chapter. The most widely used energy-based devices for melasma are non-ablative fractional lasers (especially the 1927 nm wavelength), QSNYL, and IPL.

Effectiveness of Treatments

Fractional Resurfacing

Fractional resurfacing is currently the only FDA-approved laser treatment for melasma and, therefore, is widely used for this indication. Yet research on these lasers has yielded mixed results, with some studies even suggesting that TCC may be superior (2b) [30, 31, 34].

An early pilot study using 1550 nm Er:glass laser without hydroquinone pretreatment demonstrated 75–100% clearing of melasma in six out of ten patients after 4–6 treatments, although long-term follow-up was lacking (2b) [31]. Subsequent small observational studies demonstrated between 20% and 75% improvement in melasma in all subjects, with better results seen in those with skin type III as opposed to darker phototypes (2b) [29, 33].

A pilot study of 1540 nm Er:glass laser alone in ten subjects with FST II–VI showed at least 50% improvement in all who completed the study, although two subjects withdrew due to second-degree burns (2b) [34]. A larger trial studying 1540 nm plus TCC in Indian females demonstrated > 50% improvement in 46 out of 76 subjects at 1 month post-treatment and only 16 out of 76 at 6 months [35].

Similarly, 1927 nm thulium and 1927 nm diode lasers have been shown to result in at least 50% improvement in almost half of individuals treated with laser alone, with a statistically significant 51% reduction in MASI at 1 month post-treatment (2b) [36, 37]. Brauer et al. found no relapse at 3 months post-treatment with 1927 nm diode, while Polder et al. found a marginal increase in severity at 3 and 6 months post-treatment with the thulium laser, although melasma remained improved from baseline [36, 37].

Interestingly, randomized controlled trials comparing fractional laser (+/− concurrent TCC) to TCC alone have failed to demonstrate superi-

ority of laser therapy (1b) [30, 32, 63]. Wind et al. performed a split-face study of 1550 nm plus TCC versus TCC alone and found relative worsening of hyperpigmentation on the laser-treated side compared to the topical therapy side [30]. After two or more laser sessions, 31% of the patients developed post-inflammatory hyperpigmentation (PIH). Although treatment density (rather than fluence) of fractional lasers is most closely related to the development of PIH, the authors attributed the high rate of PIH to the use of high fluence in combination with springtime treatment (and subsequent high sun exposure) [64]. Kroon et al. randomized patients to either 1550 nm laser or TCC and found no difference in physician global assessment between the two groups [32]. Nonetheless, mean treatment satisfaction was higher in the laser group at 3-week follow-up [32].

Data on the frequency of relapse after treatment success with fractional resurfacing is inconsistent. Overall, there appears to be partial recurrence by 6-month follow-up, although often patients maintain some benefits of laser therapy at this time point [32, 35, 36].

Ablative Lasers

There are few studies evaluating the efficacy of ablative lasers in the treatment of melasma, and those that exist are limited by small sample sizes. Initial studies using 10,600 nm CO_2 laser plus Kligman's formula to treat dermal melasma demonstrated complete resolution of melasma within a test spot in all subjects. No recurrence was seen at 6-month follow-up; however, 75% of the subjects experienced either post-inflammatory hypo- or hyperpigmentation (level 4) [24]. The small sample size (four subjects) and small test spot treated limit the quality of these results. A high risk of PIH at 3–6 weeks' post-treatment has also been observed with Er:YAG 2940 nm lasers [23, 26]. One case series of ten females demonstrated that, after just one laser treatment, mean MASI decreased from 19.1 at baseline to 10.6 at 6 months, although MASI increased to >20 at weeks 3 through 6 due to the occurrence of PIH (2b) [26]. A recent observational study similarly showed a statistically significant decrease in MASI at 6-month follow-up, with 50–100% improvement in the majority of subjects; however, recurrence was seen in 33.3% (2b) [23].

Fractional Er:YAG and CO_2 lasers appear to have limited efficacy in the treatment of melasma, albeit mitigating the risk of PIH compared to traditional ablative lasers. A study of fractional Er:YAG in ten patients with FST III–V demonstrated mild-to-moderate clinical improvement in 70% of patients, although the reduction in MASI score was not statistically significant. PIH was observed in one out of ten subjects (2b) [27]. Trelles et al. demonstrated 90% efficacy of fractional CO_2 laser in achieving good-to-excellent results at 1 month post-treatment in skin types II–IV; yet all results were lost at the 10-month follow-up (1b) [28]. Nonetheless, use of fractional CO_2 laser in combination with anti-pigment cream was associated with 80% efficacy at 10 months' post-treatment, and the results were maintained at 12-month follow-up. Of the 30 females studied, none developed PIH [28].

A retrospective study of 48 Koreans treated with fractional long-pulsed alexandrite laser was associated with 42.7% improvement in epidermal melasma and 16.5% improvement in dermal melasma (2b) [65].

Quality-Switched Lasers

Quality-switched lasers, particularly QSNYL, are the most commonly used lasers for the treatment of melasma [66]. Initial observational studies using QSRL (694 nm) and QSNYL (1064 nm or 532 nm) in the treatment of melasma demonstrated unchanged or worsening pigmentation (2b) [38, 39]. A significant risk of PIH and hypopigmentation was observed, especially with the use of high fluences [38].

More recently it has been suggested that repetitive subthreshold-pulsed 1064 nm QSNYL is more effective in the treatment of refractory melasma than traditional Q-switched lasers (level 4) [67]. Zhou et al. studied the use of low-fluence QSNYL in 50 patients with skin types III–IV and

demonstrated a mean decrease in MASI of 61.3% after nine weekly treatments (2b) [40]. Brown et al. observed 25–100% lightening of melasma in 19 out of 20 subjects after 8 weekly treatments (2b) [41]. In a cohort of 50 Asians, 42% demonstrated excellent (75–100%) improvement and 59% demonstrated good (50–75%) improvement in melasma based on physician assessment after 15 weekly treatments (2b) [42]. Research on low-fluence photoacoustic twin pulse (PTP) mode, dual-toning QSNYL, and fractional mode QSNYL has also indicated positive results (2b) [18, 47, 48].

Randomized, controlled studies have shown that combined low-fluence QSNYL and topical therapy (hydroquinone and TCC) is more effective than topical therapy alone (1b) [43, 44]. It is typically believed that laser therapy plus topical therapy is superior to laser alone, although studies to prove this are needed.

Data on the use of QSRL in melasma is lacking, although a recent study in 15 Korean patients showed promising results (2b) [49]. After treatment with low-dose, fractional QSRL, mean MASI decreased significantly from baseline to week 16 (15.1 ± 3.3–10.6 ± 3.9), with the lowest MASI observed at 4 weeks' post-treatment (2b) [49]. A retrospective study of 25 Caucasians with FST I–III treated with QSRL showed a 72.3% reduction in MASI after 1–3 treatments; however, PIH and recurrent melasma occurred in 28% and 44% of patients, respectively, at 3-month follow-up (2b) [68].

While Q-switched lasers appear to be effective in reducing melasma severity, prior studies suggest that optimal results only can be expected to be maintained for approximately 4–6 months' post-treatment [18, 41]. Most studies have demonstrated at least partial relapse of melasma by 12 weeks' post-treatment [40, 43, 45, 47, 49], with approximately 80% relapse after 6–11 months [44, 47].

Picosecond Laser

Picosecond lasers are being used increasingly for the treatment of pigmentary disorders, including melasma, and have been shown to be efficacious and safe, even in highly pigmented skin [50, 69–71]. A recent split-face, randomized controlled trial of dual-wavelength picosecond laser (1064 and 595 nm) plus topical hydroquinone 2% versus hydroquinone monotherapy in 40 Korean females (FST III–IV) demonstrated the superiority of combination picosecond laser therapy [50]. One week after final laser treatment, there was greater than 50% improvement in melasma in 76.92% of the subjects on the laser-treated side versus 2.56% on the topical-only side. There was a significant improvement in mMASI and relative lightness index (RLI) on the laser-treated (compared to topical only) at 1 week post-treatment, and RLI continued to be significantly improved at 12-week follow-up. The rate of melasma recurrence was similar on both sides of the face [50].

Pulsed Dye laser

Pulsed dye lasers (PDLs), which target the vascular component of melasma, have been shown to be effective in reducing melasma severity and recurrence [51, 72]. Passeron et al. conducted a randomized, single-blind, split-face clinical trial of PDL plus TCC versus TCC alone in 18 white women (FST II–IV). They found that PDL plus TCC was beneficial in treating melasma in skin types II and III, but not skin type IV given that 50% of subjects with FST IV developed PIH [51]. A later case report of a woman enrolled in the aforementioned study suggested that, in addition to reducing melasma severity, PDL may also help minimize rebound of melasma within the treated areas [51]. Further studies of PDL in the treatment of melasma, particularly in darker skin types, are needed to quantify the degree of improvement that can be expected with the use of vascular-targeting therapies.

IPL

Conventional IPL is thought to have a limited effect on melasma [56]. Low-fluence and short-

pulse duration IPL, however, appears to be more effective [52, 56]. In one study, treatment with IPL was associated with a 77.5% improvement in melasma severity at 3 months' post-treatment without concurrent use of anti-pigment cream (2b) [56]. Bae et al. evaluated 20 Korean subjects with FST IV–V and demonstrated moderate to marked improvement in 55% of the subjects treated with 10 J and in 65% of the subjects treated with 13 J; the difference in improvement between the fluences was not statistically significant (1b) [52].

The efficacy of IPL appears to be increased when combined with hydroquinone, TCC, or topical tranexamic acid (1b–2b) [53–55, 57]. One randomized, split-face study of IPL plus TCC versus IPL plus inactive cream demonstrated physician-rated improvement of clear or almost clear in 57% who received TCC as compared to 23% who received inactive cream (1b) [54]. In another split-face study, Chung et al. demonstrated a statistically significant decrease in mMASI (14.77–9.38) on the side treated with IPL plus topical tranexamic acid, but no statistically significant change on the IPL plus vehicle side (1b) [58]. The use of topical tranexamic acid following IPL was also thought to help prevent rebound of melasma at 3-month follow-up [53, 57]. Figueiredo et al. demonstrated maintenance of IPL results at 12 months' post-treatment (MASI reduction of 49.4% at 6 months and 44.9% at 12 months) with continued use of TCC [53].

The response to IPL is better in subjects with epidermal melasma (rather than dermal) and those without forehead involvement; frontal and malar melasma do not appear to respond as well to IPL (2b, 1b) [53, 55].

Chemical Peels

The majority of research on chemical peels in melasma has focused on Glycolic Acid (GA) peels (Table 53.2). Javaheri et al. evaluated the efficacy of 50% GA peel plus nightly 10% GA in the treatment of 25 Indian females with epidermal and mixed melasma and demonstrated improvement in MASI in 90% of the subjects (2b) [74]. Average MASI decrease was 46.7% in epidermal-type and 27.8% in mixed-type melasma [74]. Rendon et al. similarly showed improvement in 90% of subjects treated with GA peel plus TCC at 12 weeks, with 65% rated as clear or almost clear (2b) [79].

Randomized controlled trials and observational studies have evaluated GA peels following or in conjunction with hydroquinone, topical GA, TCC, modified Kligman's formula, azelaic acid, and adapalene. Several studies suggest that serial 20–70% GA peels plus topical therapy are superior to topical therapy alone [73, 75, 78]. However, one prospective, split-face study showed no significant difference between combined peel and 4% hydroquinone versus hydroquinone alone (2b) [76]. A single-blind, split-face, randomized controlled trial of ten Asian females showed greater improvement in melasma and fine wrinkling with the use of 20–70% GA peel plus topical 10% GA/2% hydroquinone than topical therapy alone (1b) [73]. Although it is difficult to compare the relative efficacy of these combinations due to differences in study design, it can be concluded that the use of pre- and post-peel topical lightening agents enhances the efficacy of GA peels and decreases the risk of post-treatment pigmentary sequelae [73, 78].

Based on current data, one could expect to see an improvement in melasma in approximately 90% of subjects treated with GA peels and skin lightening agents (2b) [74, 79, 80] with improvement in MASI ranging from 46.7% to 79.99% (1b) [78, 83]. Some suggest that the efficacy of GA is inversely proportional to the duration of disease (1b) [84], while others have found no effect of age of onset and duration of melasma on treatment response [74]. One author suggests that a minimum of four chemical peels should be performed before pursuing a different peel or therapeutic modality (level 5) [21]. Few studies have reported on recurrence of melasma after chemical peel, although one study demonstrated relapse in 5.9% of patients at 3-month follow-up [84].

GA peels are most effective for epidermal melasma, followed by mixed-type, and are unlikely to have effect in dermal melasma (2b) [74, 77]. Although concentrations of 20–30%

Table 53.2 Studies evaluating glycolic acid and salicylic acid chemical peels in melasma

Author	Study design/ treatment	Concentration and regimen	n	FST/ race	Results	Side effects and recurrence
Glycolic acid						
Lim and Tham [73]	Single-blind, split-face 1. GA peel +10% GA + 2% HQ 2. 10% GA + 2% HQ BID	20–70% GA 4–5 min Every 3 weeks 8 treatments	10	IV–V Asian	Greater improvement in melasma and fine facial wrinkling on peel side ($p = 0.06$) 60% lightening on peel side in 4/10 vs. 1/10 on topical only side	Stinging Redness Burning Transient hyperpigmentation
Javaheri et al. [74]	Observational GA peel + 10% GA	50% GA 2–5 min Monthly 3 treatments	25	Indian	MASI improved in 90% of patients Average decrease in MASI was 46.7% in epidermal-type melasma vs. 27.8% in mixed-type	Mild hyperpigmentation (1/25)
Sarkar et al. [75]	Open-label, pilot 1. GA peel + modified Kligman's (2% HQ, 0.05% tretinoin, 1% hydrocortisone) 2. Modified Kligman's	30–40% GA 1–3 min Every 3 weeks 6 treatments	40	III–V Indian	Greater decrease in MASI score at 12 and 21 weeks in combined group (week 21: 79.99% vs 63.14%, $p < .01$)	Mild cutaneous erythema and burning Superficial desquamation Persistent erythema (10%) Superficial vesiculation PIH (10%)
Hurley et al. [76]	Single-blind, split-face 1. GA peel + 4% HQ 2. 4% HQ	20–30% GA 3–5 min Bimonthly 4 treatments	21	IV–V Hispanic	Decrease in MASI and lightening of pigmentation in both groups. No significant difference between peel + HQ versus HQ alone	Significant erythema (4/21)
Grover and Reddu [77]	Observational GA peel + tretinoin 0.025%	10–30% GA Bimonthly 7 treatments	15	III–V	Good to fair response in patients with epidermal and mixed melasma. No significant improvement in dermal melasma	Mild discomfort and irritation of skin PIH (13.2%) GA-induced hypopigmentation (6.7%)
Erbil et al. [78]	Randomized, single-blind 1. GA peel + azelaic acid + adapalene 2. Azelaic acid 20% BID + adapalene 0.1% QD	20%–70% GA 3–5 min Bimonthly 8 treatments	28	NA	83.08% decrease in MASI in peel group vs. 69.34% decrease in MASI in control group Better results when GA concentration is >50%	Moderate-to-severe epidermolysis with PIH (10.7%)
Rendon et al. [79]	Pilot GA + TCC (fluocinolone acetonide 0.01%, HQ 4%, and tretinoin 0.05%)	Bimonthly 5 treatments	20	II–VI	Hyperpigmentation significantly reduced on spectrophotometric measurement, with 65% of subjects rated as clear or almost clear at 12 weeks 90% of subjects showed improvement by 12 weeks	Erythema Desquamation Pruritus Burning sensation

Table 53.2 (continued)

Author	Study design/ treatment	Concentration and regimen	n	FST/ race	Results	Side effects and recurrence
Godse and Sakhia [80]	Observational study GA peel + TCC (tretinoin 0.05%, HQ 4%, mometasone furoate 0.1%)	57% GA 2–6 min Every 3 weeks 4 treatments	20	IV–V Indian	Significant reduction in melasma with 50% physician-rated improvement in 10/20 subjects and 75% improvement in 3/20	Irritation and hyperpigmentation (5%)
Salicylic Acid						
Kodali et al. [81]	Single-blinded, split- face 1. SA peel + 4% HQ 2. 4% HQ	SA 20–30% 4–5 min Bimonthly 4 treatments	20	III–V Hispanic	No statistically significant difference in MASI improvement or melasma severity between the 2 groups	Erythema Burning Peeling
Grimes [82]	Observational SA peel + 4% HQ	20–30% SA Bimonthly 5 treatments	6*	V–VI African American/Hispanic	Moderate to significant improvement in melasma in 66% of patients	Temporary crusting Hypopigmentation Transient PIH

n number of subjects, *FST* Fitzpatrick skin type, *GA* glycolic acid, *HQ* hydroquinone, *MASI* melasma area and severity index, *TCC* triple combination cream, *PIH* post-inflammatory hyperpigmentation, *SA* salicylic acid
*6 out of 25 patients studied had a diagnosis of melasma

should be used initially, 50–70% GA is most effective in decreasing the severity of melasma [73, 74, 76, 78]. In this author's experience (AFA), patients will typically demonstrate improvement by the third or fourth peel; patients who do not respond by the fourth peel are unlikely to demonstrate a clinically meaningful response [74].

Data on the use of salicylic acid (SA) peels in the treatment of melasma is limited [1, 85]. One study suggests that peels containing 20–30% SA within an ethanol base are effective when used in conjunction with daily application of hydroquinone 4% cream (2b) [82]. However, a subsequent single-blinded, split-face study comparing combination SA peel and 4% hydroquinone to hydroquinone alone showed no statistically significant difference in MASI or spectrophotometer-measured hyperpigmentation between the two groups (1b) [81].

It is important to note that many of the studies on chemical peels have been performed in Indian populations, which may limit the applicability of the results to other skin types, particularly darker-skinned individuals of African descent [74, 75, 77, 80, 83, 84]. Several studies have been performed in Hispanic and Middle Eastern populations [78, 79, 81].

Other Procedures

Tranexamic acid (TA) microinjections and microneedling have recently been studied in the treatment of melasma. A randomized, open-label, split-face study in 60 dark-skinned patients with moderate-to-severe melasma demonstrated 38% and 44% improvement in MASI scores with the use of TA microinjections and microneedling followed by topical TA (Dermaroller MS4), respectively (1b) [86]. No adverse events were reported in this study. Another split-face study of rucinol and sophora-alpha depigmentation serum with and without microneedling in office (Dermaroller CIT 8) and at home (Dermaroller C8) demonstrated greater improvement in MASI with the use of a microneedling device (1b) [87]. Microneedling (Dr. Roller®) followed by daily TCC and sunscreen has also demonstrated good results with the maintenance of skin lightening at 24 months in all patients who followed up at this time point (11/22 subjects) (level 4) [88].

Comparative Effectiveness of Common Treatments

Relative Effectiveness of Lasers

Due to the limited number of studies comparing laser modalities, it is difficult to develop strong evidence-based conclusions regarding the relative efficacy of different lasers. Additional randomized controlled trials, particularly split-face studies, are needed to further evaluate this question. Relevant studies are discussed below.

A randomized, split-face study of QSNYL versus QSRL demonstrated a clinical decrease in melasma severity in both treatment groups, with faster recurrence of melasma on the QSRL side (1b) [89]. Histological examination of biopsy specimens taken from skin treated with each laser suggested that QSNYL leads to a decrease in the number of melanin granules without significantly altering the cellular architecture, whereas QSRL induces greater epidermal and dermal damage that may contribute to subsequent melanogenesis [89]. Omi et al. concluded that QSNYL yields superior results with a longer recurrence-free interval [89].

A randomized, investigator-blinded, split-face study comparing low-fluence QSNYL and low-fluence QSAL in 20 subjects with FST I–IV demonstrated no difference in mMASI or subjective patient assessment between the two sides, although it is important to note the absence of skin types V–VI in this study (1b) [90].

A single RCT of 40 females with symmetric melasma suggested the superiority of low-power fractional CO_2 laser over low-fluence QSNYL. Based on patient self-assessment, there was complete improvement in 62.5% and 15% of patients treated with fractional CO_2 laser and QSNYL, respectively. At 2 months' post-treatment, the reductions in MI and mMASI score were significantly greater on the side treated with fractional CO_2 laser for subjects with both epidermal and dermal melasma (1b) [91]. The incidence of side effects was equal on both sides, and there were no cases of post-inflammatory hypo- or hyperpigmentation [91].

Several studies have also suggested that the combination of certain lasers may be superior to laser monotherapy. Early research on CO_2 lasers in melasma demonstrated the superior efficacy of combination CO_2 laser plus 750 nm QSAL. More specifically, CO_2 laser followed by 750 nm QSAL appeared to be more effective than either laser alone without additional risk of post-inflammatory dyspigmentation or other side effects (2b) [24, 25]. This has been attributed to the fact that, in addition to destroying hyperactive melanocytes, the CO_2 laser removes the epidermis, allowing for better activity of the QSAL on remaining, deeper dermal pigment [25]. It is important to note that CO_2 lasers are not suitable for treating melasma in FST IV–VI due to a high risk of pigmentary complications in this population. A report of two cases also suggests that a combination of fractional 2940 nm followed by 1064 nm QSNYL leads to rapid improvement in melasma with sustained results at 6-month follow-up; however, larger studies involving a broad range of skin types are needed to confirm this (level 4) [92]. Treatment with PDL followed immediately by 1927 nm fractional diode laser was suggested to be effective in a single case report [72]. While the synergistic targeting of vascular and melanin components is compelling, further research is needed to confirm the efficacy and safety of combined treatment (level 4). Current evidence does not support the combination of QSNYL plus 1550 nm, as one study demonstrated no substantial benefit over the use of QSNYL alone (1b) [93].

Relative Efficacy of Lasers Versus Chemical Peels

Although there are few direct comparison studies of lasers and chemical peels, overall the literature suggests that the efficacy is similar between the two treatments [94–96]. A split-face study in Asian women showed no difference in outcome, adverse events, or recurrence rate between 1550 nm fractional thermolysis and 15% TCA chemical peel (1b) [94]. Another study randomly

assigned 75 Indian patients to either high-fluence QSNYL, low-fluence QSNYL, or 30–75% GA peel and found that improvement of melasma was best in the low-fluence QSNYL group, followed closely by the GA group (1b) [95]. The low-fluence laser also was associated with a lower risk of erythema, burning, and PIH [95]. Unfortunately, MASI scores increased in all groups at week 12. Lastly, a study of 30 patients treated with either 1550 nm Er:glass or 70% GA peel demonstrated equivalent improvement in melasma with both procedures. Recurrence was seen in the majority of patients at 6-month follow-up regardless of treatment group (2b) [96].

Combination of Lasers and Chemical Peels

Two studies have suggested that low-fluence QSNYL in combination with 30% GA peels may be more effective than laser therapy alone (1b) [45, 97]. Vachiramon et al. demonstrated a 52.3% improvement in mean RLI and 37.6% decrease in MASI at 4-week follow-up in men treated with monthly laser and weekly chemical peels, as compared to 37.6% decrease in mean RLI and 14.6% reduction in MASI with laser monotherapy [45]. Park et al. performed a randomized, split-face study in which they studied six weekly sessions of QSNYL on the entire face and three biweekly sessions of 30% GA on just one side. The combined therapy side demonstrated an average improvement in MASI of 37.4% as compared to 16.7% on the laser-only side [97]. It is important to note the use of 30% GA in these studies, which is lower than the 50–70% concentration typically used for monotherapy.

Combination of Lasers and IPL

In a study of Chinese patients with melasma, the combination of three successive sessions of QSRL followed by one session of IPL was shown to result in mild-to-moderate improvement of melasma in 73.6% of Chinese patients, with significant decrease in mean MASI from 14.66 to 5.70 after treatment (2b) [98]. One IPL treatment followed by four weekly sessions of low-fluence QSNYL was associated with a 59.35% improvement in MASI in patients with mixed-type melasma in one retrospective review (2b) [100]. A randomized, split-face study of 18 subjects treated with QSNYL (five weekly treatments) and IPL (three biweekly treatments) or QSNYL alone demonstrated more rapid improvement in mMASI and relative lightness on the combined side. However, recurrence was more frequent on the combined side (33%) than the monotherapy side (11%) at 12-week follow-up (1b) [46].

Combination of Lasers and Other Procedures

A study of 26 patients treated with fractional QSRL (4–6 treatments) and sonophoresis with vitamin C demonstrated a 35% decrease in MASI at 3 months' post-treatment (2b) [101]. A split-face study of QSNYL plus ultrasonic application of vitamin C versus laser therapy alone showed better fading of melasma with combined therapy (60–80% versus 40–60% improvement, respectively) (2b) [102]. A retrospective study of QSNYL followed by vitamin C sonophoresis similarly showed excellent outcomes in 91.3% of patients treated (1b) [103].

Low-fluence QSNYL plus microdermabrasion has been attempted successfully in an observational study, but has not been compared to either treatment individually (2b) [104].

Relative Effectiveness of Chemical Peels

GA is typically considered the peel of choice for treatment of refractory melasma, although numerous studies have demonstrated non-inferiority of other peeling agents (Table 53.3) [19]. Research suggests that 10–20% TCA is as effective as 20–35% GA, with decrease in MASI of 73–79%

Table 53.3 Studies comparing chemical peeling agents for the treatment of melasma

Author	Study design/ treatment	n	FST/ race	Results	Side effects and recurrence
Kalla et al. [84]	Design unclear, 2 groups 1. 55–75% GA 2. 10–15% TCA	100	Indian	Response to TCA was rapid and produced better results than GA GA was more effective with onset of melasma <1 year, and TCA was more effective with onset of melasma >1 year	Relapse was more common in the TCA group (25%) than in the GA group (5.9%) TCA was associated with more local irritant effects, i.e., tingling, burning, and post-peel cracking than GA
Khunger et al. [105]	Open-label, split-face 1. 70% GA 2. 1% tretinoin	10	III–V Indian	A significant decrease in mMASI was observed on both facial sides, with no significant difference observed between the two sides	GA: vesiculation (30%) and PIH (10%) Tretinoin: erythema and superficial desquamation (20%)
Kumari and Thappa [106]	Randomized, single-blinded 1. 20–35% GA 2. 10–20% TCA	40	Indian	79% reduction vs. 73% reduction in MASI at 12 weeks with GA and TCA peels, respectively TCA showed more rapid initial improvement	GA: mild burning (95%) TCA: moderate-to-severe burning (75%), post-peel cracking (35%)
Puri [107]	Unclear design, 2 groups 1. 20–35% GA 2. 15% TCA	30	Indian	Both peels associated with significant reduction in MASI scores (82% in GA and 79% in TCA), although there was no statistically significant difference between the two groups	GA: burning (6.6%), erythema (10%), pain (3.3%), PIH (6.6%) TCA: burning (26.6%), erythema (20%), pain (6.6%), PIH (13.35%), post-peel cracking (6.6%)
Faghihi et al. [108]	Randomized, double-blinded, split-face 1. 70% GA 2. 1% tretinoin	63	III–IV	31% reduction in MASI in tretinoin group and 29% reduction in GA group	Post-procedure discomfort was significantly lower with tretinoin
Lawrence et al. [109]	Randomized, single-blinded, split-face 1. 70% GA peel 2. Jessner's peel	16	II–VI	Similar improvement in lightness was observed on both sides	All side effects were observed on the GA side: extensive epidermolysis leading to PIH (6.25%), persistent erythema (12.5%), scattered crusting (37.5%)
Sarkar et al. [83]	1. 35% GA 2. 20% salicylic and 10% mandelic acid (SM) 3. 50% phytic acid (PA)	90	Indian	At 12 weeks, reduction in MASI was 62.36% in GA group, 60.98% in SM group, and 44.71% in PA group There was no statistically significant difference between SM and GA, but both were better than PA	GA: mild erythema and desquamation (19.2%), hyperpigmentation (15.4%), persistent erythema (15.4%) SM: burning sensation (25%) PA: burning sensation (31.8%), HSV (18.2%)

n number of subjects, *FST* Fitzpatrick skin type, *GA* glycolic acid, *TCA* trichloroacetic acid, *mMASI* modified melasma area and severity index, *MASI* melasma area and severity index, *PIH* post-inflammatory hyperpigmentation, *SM* salicylic-mandelic acid, *PA* phytic acid, *HSV* herpes simplex virus

versus 79–83%, respectively (2b) [96, 107]. It is important to note, however, that this low concentration of GA is not as effective as higher concentrations [78]. The faster onset of results and superior efficacy in the treatment of chronic pigmentation (duration > 1 year) makes TCA an appealing option [84]. Yet there appears to be a higher risk of relapse and hyperpigmentation in those treated with TCA peels (25% in TCA vs. 5.9% in GA) as well as increased risk of local irritant effects including prolonged erythema, tingling, burning, and post-peel cracking of the skin [84, 96, 107].

While there are no comparative studies of GA and SA alone, a study of 35% GA versus

combination 20% SA/10% mandelic acid (SM) demonstrated that the reductions in MASI of 62.36% and 60.98%, respectively, were not significantly different (1b) [83]. Both GA and SM were shown to be more effective than phytic acid, which demonstrated a 44.71% decrease in MASI [83].

Research suggests that tretinoin 1% peel is as effective as 70% GA peel in the treatment of melasma with lower risk of post-procedure discomfort and adverse events, such as erythema and superficial desquamation (2b,1b) [105, 108]. A recent randomized, double-blind, split-face study showed reduction in MASI of 31% versus 29% with tretinoin 1% and GA 70% peels, respectively (1b) [108]. Similarly, use of Jessner's solution and 70% GA are associated with comparable improvement in melasma based on change in colorimeter-measured light reflectance, with fewer adverse events seen with the former (2b) [109].

Lastly, a study by Sobhi et al. suggests that combination of 70% GA and iontophoresis with vitamin C is more effective than GA peel alone (2b) [110].

Preoperative Evaluation and Patient Selection

Wood's lamp examination to determine melasma depth remains the first step in evaluation, as the depth of melanin pigment, whether epidermal, mixed, or dermal, affects the efficacy of available therapies. For example, chemical peels are most effective in epidermal melasma and are less efficacious in dermal melasma [74, 77]. For those with dermal pigmentation, management with lasers such as non-ablative fractional or low-fluence QSNYL would likely offer greater efficacy, although efficacy with all modalities is generally less than that with epidermal melasma [23, 24, 49, 65, 67].

Additionally, patients should be evaluated for concomitant disease of the face, including acne, rhytides, or photodamage that may indicate superiority of a particular therapeutic modality. Fractional resurfacing is FDA approved for treatment of periorbital rhytides, pigmented lesions, acne scars, and surgical scars, and would be an appropriate choice for patients who also seek treatment of these conditions [111]. Chemical peels would have additional benefits for patients with oily skin, acne, acne scars, fine wrinkling, and texturally rough skin [85]. SA is typically used for the treatment of acne alone and may be more effective and better tolerated than the traditional GA peel for acne and post-acne scarring [112]. Nonetheless, several studies have demonstrated significant improvement in inflammatory and non-inflammatory lesions as well as atrophic acne scarring with serial GA peels [113, 114].

Skin pigmentation and ethnicity also play a large role in choice of treatment, as darker skin tones have a higher risk of PIH after laser and chemical peel procedures [115]. Traditional laser resurfacing devices, including ablative CO_2 and Er:YAG, result in high rates of dyspigmentation and even scarring in dark-skinned patients and, therefore, should be avoided [115]. IPL appears to be effective in the treatment of melasma in Asian skin when used at conservative settings, but should be avoided in skin types IV–VI due to a high risk of PIH [116]. PDL should also be avoided in FST IV+ due to a high risk of PIH [51]. Non-ablative and fractional lasers are thought to be safer for use in pigmented skin; however, lower treatment densities are recommended to minimize the risk of pigmentary sequelae (2b) [63, 64, 114, 115]. Lasers with ultrashort-pulse durations, including picosecond lasers, have also been associated with a lower risk of pigmentary sequelae [70, 71, 117].

Like with lasers, low concentrations and duration of chemical peels should be used in darker skin types and titrated up slowly and carefully to avoid excessive peeling, burning, or frosting that may result in PIH or hypopigmentation [21]. Given the relative paucity of studies evaluating the safety and efficacy of laser treatment of melasma in FST V–VI, the decision to use a laser for melasma in this cohort should be based on careful evaluation of the potential risks and benefits.

Lastly, medical and medication history as well as history of sensitivity or allergies are important considerations when evaluating a patient for therapy. Chemical peels should be avoided in subjects

with active dermatitis at the peeling site, acute viral infection (involving the treatment area), skin malignancies (involving the treatment area), pregnancy (category C) and contact allergy to salicylates (for salicylic acid) [85]. For those with a history of herpes simplex infection (not active infection), prevention with an antiviral should be considered post-peel. Subjects should be asked about history of keloids, which may put them at unacceptable risk of scarring from any procedures. For those taking isotretinoin, procedures should be avoided or postponed until 3–6 months after discontinuing treatment [85].

Impact of Patient Preference

Patient preferences regarding pain, post-procedure downtime, frequency of office visits, and risk/benefit ratio play an important role in choosing a procedural therapy for melasma.

For patients with low pain thresholds or who would like to avoid painful procedures, chemical peels would generally be preferred over laser/light therapies. Most studies have demonstrated at least mild-to-moderate pain in subjects treated with lasers and IPL [23, 30–32]. Therefore, superficial chemical peels would be a superior initial choice for these patients.

As for post-procedure downtime, non-ablative fractional lasers (especially the low energy, low density 1927 nm diode) and low-fluence QSNYL appear to have the shortest downtime, with resolution of erythema and edema usually occurring within 24 h after treatment [40, 48]. Erythema from resurfacing may take up to 4 days to resolve [30, 35]. Transient facial redness due to ablative lasers and IPL may last up to 7 days and may be associated with crusting, edema, and oozing [23, 28, 53]. Persistent erythema has been reported in approximately 15% of patients treated with GA peels [83].

Most laser, light, and chemical peel procedures require four to eight treatments spaced every 2–4 weeks, depending on the depth and severity of melasma. Patients who are unable to attend at least monthly office visits may not be good candidates for procedural therapy. One study suggests that a single treatment with IPL followed by TCC is associated with significant improvement in melasma up to 1 year post-treatment (superior to TCC alone), although further studies are needed to confirm this [53]. At this time, topical therapies would be the best choice for such patients.

Side effects associated with each procedure, and patients' willingness to endure these side effects, are also important to consider. These will be discussed further below. Post-inflammatory hypo- and hyperpigmentation are the most concerning sequelae. Although there is limited data comparing the prevalence of pigmentary sequelae between different procedures, ablative lasers should be avoided in darker-skinned patients due to the high risk of dyspigmentation [24].

Typical Treatment Plan

A 45-year-old Indian woman with FST IV presents to your dermatology clinic with a 4-year history of hyperpigmentation of the bilateral cheeks and forehead that has been worsening over time. She has tried over-the-counter skin brightening creams without success and notes significant embarrassment due to the pigmentation on her face. She reports a history of hypothyroidism for which she takes levothyroxine and is otherwise healthy. Upon examination of the skin, she has hyperpigmented dark brown patches on the bilateral malar cheeks and forehead that are consistent with a diagnosis of melasma.

The first step in the management of this condition should be educating the patient about risk factors and preventative measures, including the role of UV light in the progression of melasma and the importance of using sun protection [2]. The patient should be instructed to use broad-spectrum sunscreen with SPF 30 or higher on a daily basis and to use protective clothing, such as a hat, when in the sun for extended periods of time.

Initially, she should be started on a topical agent that targets melanogenesis with the goal of reducing the severity of hyperpigmentation. Our first-choice agent would be TCC (i.e., 4% HQ,

0.05% tretinoin, 0.01% fluocinolone), as this compounded medication has been shown to be most effective in the reduction of melasma severity [118]. Hydroquinone 4% alone would also be an appropriate choice. The patient should be advised that it may take up to 3–6 months to see an optimal effect and that she should return to clinic in 6–8 weeks for follow-up to review compliance, response, and possible side effects.

This patient returns to clinic for a second visit after 2 months. She has been using the TCC twice daily and, although she sees a slight reduction in her melasma, she is still very bothered by the dark spots on her face. For this patient, second-line therapy would be chemical peels. GA would be the best option given the strength of data supporting its efficacy in the treatment of melasma. Initially, 20–30% GA should be applied for approximately 2–3 min with the goal of titrating up by about 10–20% and increasing the time by 1–2 min with each subsequent peel (up to a maximum of 70% for 4–5 min). Typically, about six to eight peels every 3–4 weeks will be required for optimal results. The patient should be instructed to continue use of TCC after the peels to minimize the risk of PIH. TCC is discontinued 72 h prior to each peel to avoid irritation from concomitant use of topical retinoids (e.g., tretinoin found in TCC).

If this patient still has not responded appropriately to chemical peels, laser and light therapies would be the next step in the treatment ladder. For this woman with a darker skin type, nonablative fractional resurfacing (e.g., low-energy, low-power 1927 nm diode or 1550 nm erbium-doped laser with low density) provides the best safety profile and good efficacy data. Low-fluence Q-switched Nd:YAG used weekly for six to eight sessions would be another appropriate choice. Ablative lasers should be avoided due to high risk of post-inflammatory pigmentary abnormalities.

Safety

Lasers and chemical peels are commonly used in clinical practice and typically are associated with a low risk of adverse events when tailored to patients' skin types and treatment preferences. Although studies have not looked at the frequency of adverse events in the treatment of melasma specifically, a retrospective review of 362 Korean patients (FST III–IV) treated with non-ablative fractional thermolysis for any reason demonstrated significant adverse events in approximately 5% of patients (2b) [119]. These included prolonged erythema (1.8%), PIH (1.1%), aggravation of melasma (0.9%), herpes simplex outbreak (0.6%), and acneiform eruptions (0.2%). Transient erythema, burning, and edema were not considered adverse events [119].

Nonetheless, burning sensation, erythema, and mild edema immediately after laser treatment are the most commonly observed side effects of laser therapy, regardless of the device used [30, 32, 42, 44, 47, 48, 50, 51, 117]. With use of low-energy, low-density 1927 nm diode laser, QSNYL, and picosecond lasers, these findings tend to be mild and typically resolve within 2–24 h [40, 48, 50, 117]. Fractional resurfacing with Er:glass laser, however, has been reported to cause sunburn-like erythema in 99% of subjects that may take up to 4 days to resolve [30]. Erythema due to ablative lasers may last up to 7 days and may be associated with crusting, edema, and oozing [23, 28].

Although pain can occur during any laser treatment, studies demonstrate a numerically higher level of pain with Er:glass and CO_2 lasers than QSNYL or picosecond lasers, with average pain scores of 5.4–6.4 out of 10 [23, 30–32, 50]. A study by Wattanakrai reported an average pain score of 4.7/10 with QSNYL [43], and others have demonstrated absence of pain in the majority of patients treated with this modality [48]. A study of picosecond 1064 nm/595 nm laser in melasma demonstrated only mild (<4/10) pain during treatment [50]. Nonetheless, there are no comparative studies to corroborate the higher pain level with certain lasers compared to others.

The greatest concern with the use of lasers is the risk for pigmentary alterations as a result of post-laser inflammation and/or damage to melanocytes. Fractional resurfacing devices have a therapeutic window and using a high density (or inappropriate fluence) may result in undesired

pigmentary sequelae [22]. The majority of studies using low-fluence QSNYL have failed to demonstrate immediate or long-term dyschromias [40, 42, 44, 47, 48], although some suggest that PIH and guttate hypopigmentation may occur in as many as 16–18% and 8–14% of patients, respectively. [43, 45] The rate of PIH is also inconsistent in studies of non-ablative fractional lasers, including 1550 nm, 1540 nm, and 1927 nm. Rates of PIH range from 0% to 31%, with the majority of studies demonstrating no PIH at all [29–33, 36, 37]. Typically, the use of lower fluences and lower densities is thought to decrease the risk of PIH in darker-skinned patients (2b) [30, 119, 120]. A recent retrospective study of 37 Chinese patients treated with fractional resurfacing demonstrated no significant difference in the rate of PIH with use of high-energy/low-density versus low-energy/high-density settings, although density seems to be more associated with the development of PIH (2b) [64, 120]. Ablative non-fractional lasers may result in PIH in up to 50% of subjects [24, 25]. Fractional and CO_2 lasers may be associated with a slightly reduced risk of hyperpigmentation, although several studies have not commented on presence/absence of PIH [27, 28]. Picosecond Nd:YAG and alexandrite lasers demonstrate a low rate of PIH, with studies demonstrating PIH in 0–7% of patients [50, 70, 117].

For all lasers, the risk of PIH is higher in individuals with higher skin phototypes and may be reduced by using conservative settings [23, 25, 43, 64, 120]. Further, the risk increases with each laser treatment and, for QSNYL, may be more common in those receiving ten or more treatments [43]. Fortunately, mottled hypopigmentation and hyperpigmentation typically resolve within a few months with appropriate treatment [67].

Similar to lasers, side effects from IPL include mild-to-moderate pain, mild transient erythema, burning, edema, microcrusts, skin erosion, dryness, and scaling [52–54, 56]. Crusting has been documented to last up to 1–2 weeks after treatment [55, 56]. PIH may occur in up to 25% of patients treated with high fluences, with PIH more commonly seen in those with higher Fitzpatrick types [53]. Nonetheless, the majority of studies have demonstrated lower rates ranging from 0% to 12% [52, 55, 56].

GA and SA peels are associated with minor side effects in approximately 15–20% of patients [82, 83, 121]. Patients commonly experience mild erythema, discomfort, stinging, or burning of the skin [73, 75, 77, 80–82]. Minor peeling or a pulling sensation of the skin may occur [82, 83, 121]. Less common adverse events include moderate-to-severe epidermolysis, superficial vesiculation, and superficial burns, which ultimately result in the development of PIH [73, 75, 78, 83, 121]. As with lasers, PIH is usually self-limited and resolves after ~2 months [73].

TCA peels are associated with more local irritant affects than GA, including tingling, burning, post-peel cracking, and erythema [84, 96, 107]. Puri et al. also demonstrated a higher rate of PIH in the 15% TCA versus 20–35% GA groups [96]. Conversely, tretinoin 1% peel is associated with significantly lower post-peel discomfort, although there is debate about whether tretinoin is a peeling agent at all [105, 108].

Studies directly comparing the adverse events associated with lasers and GA peels are limited [45, 94, 97]. A study of 75 Indian patients treated with either high-fluence QSNYL, low-fluence QSYNL, or 35–70% GA peel demonstrated the fewest adverse events in the low-fluence QSYNL group. GA peels were also well tolerated [95].

In terms of combination therapy, one study suggests that combination of QSNYL and 30% GA peel is associated with a higher risk of burning, stinging, erythema and edema, but not hyperpigmentation or hypopigmentation [45]. Another study, however, showed no increased risk of adverse events with use of QSNYL and 30% GA [97]. Hong et al. performed a split-face, comparative study of 1550 nm plus 15% TCA versus 15% TCA alone and demonstrated no significant difference in adverse events, including PIH [94]. Combination of low-fluence QSNYL with 1550 nm or microdermabrasion similarly does not appear to be associated with an increased risk of adverse events [93, 97]. Combination of CO_2 laser and QSAL is associated with higher rates of PIH, despite greater improvements in melasma severity [25].

Postoperative Care and Follow-Up

The monitoring schedule for melasma varies based on what mode of treatment is chosen and the frequency with which it is performed. Typically, lasers and chemical peels are performed every 2–4 weeks. Patients should follow the recommended schedule in order to achieve optimal results.

Once the patient has attained satisfactory improvement in melasma, maintenance therapy with topical agents should be initiated. Follow-up is recommended every 3 months to monitor adherence to maintenance therapy and evidence of recurrence. Typically, recurrence will be seen by 6–12 months after laser or light therapy, although some studies have suggested recurrence as early as 12 weeks after treatment [27, 28, 32, 35, 36, 43–45, 47, 55]. There is limited data on relapse with chemical peels [84]. When relapse occurs, patients may be restarted on topical depigmenting agents, if they are not already using one, or repeat procedure(s) could be considered.

Observations and Recommendations

Evidence based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Glycolic acid is the most efficacious peeling agent for the treatment of melasma	B
Chemical peels should be used in combination with a topical depigmenting agent to maximize efficacy and minimize the risk of pigmentary sequelae	A
Fractional resurfacing has been associated with moderate improvement in melasma when lower fluences and treatment densities are used	B
Low-fluence QSNYL, fractional resurfacing, and IPL may have benefit in the treatment of melasma when combined with topical depigmenting agents	B
There is insufficient evidence to support the use of ablative lasers (fractional and non-fractional) in the treatment of melasma	C
A combination of lasers and chemical peels may play a role in the treatment of melasma, but further studies are needed to evaluate optimal combinations and to outline which patients would particularly benefit	C
Patients should be counseled on the risk of PIH and relapse after treatment with chemical peels, lasers, and light therapies	A
The importance of post-procedure sun protection and maintenance therapy with topical agents must be emphasized	A
There is a paucity of data pertaining to the treatment of melasma in Fitzpatrick skin types V and VI	C

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Self-Assessment Questions

1. Which of the following laser modalities is considered to be safe and effective in the treatment of melasma in skin types IV–VI?
   (a) Low-fluence 1064 nm Nd:YAG laser
   (b) 1550 nm Er:glass laser
   (c) 2940 nm Er:YAG laser
   (d) 755 nm Q-switched alexandrite laser
   (e) a and b
   (f) All of the above
   (g) None of the above

2. The efficacy of IPL in the treatment of melasma may be enhanced by the addition of which topical therapy:
   (a) Tretinoin 0.025%
   (b) Hydrocortisone 2.5%
   (c) Tranexamic acid 2%
   (d) Hydroquinone 2%
   (e) Glycolic acid 10%

3. A 32-year-old Indian female with melasma of the bilateral malar cheeks presents to your office after failing multiple prescription and over-the-counter topical skin lightening agents. She is interested in more aggressive interventions and would like to know what the most effective treatments are. When counseling the patient on available treatment options, which of the following would be an appropriate statement regarding the efficacy of procedural therapies for melasma?
   (a) The use of quality-switched Nd:YAG lasers is associated with complete resolution of melasma in the majority of patients after five to seven sessions.
   (b) GA chemical peels are a good choice for the treatment of melasma and should be started at a concentration of 50–70% given the increased efficacy of peels at this concentration.
   (c) Research suggests that, overall, laser modalities are more effective than chemical peels, and, therefore, fractional resurfacing or QSNYL should be the next step in management of this patient.
   (d) It would be appropriate to start with either low-fluence QS-Nd:YAG lasers or GA peels initially, and these two modalities may be combined in the future with additional improvement.
   (e) Fractional resurfacing is associated with at least 25% improvement in most patients, and those results are maintained up to 1 year after the last treatment.

4. The above patient decides to pursue laser therapy. What directions would you give her regarding the use of her topical skin lightening agents?
   (a) Discontinue use of skin lightening agents, as there is a higher risk of adverse events when lasers and topical therapies are used in conjunction.
   (b) For optimal results, continue daily use of triple combination cream prior to and following laser therapy.
   (c) For optimal results, continue your current skin over-the-counter brightening regimen prior to and following laser therapy.
   (d) You may continue to use topical lightening agents, but it is unlikely that you will attain additional benefits from their use.
   (e) Additional improvement may be seen if you use triple combination cream up until laser treatment, but you should discontinue use immediately after to avoid excessive skin lightening.

5. What is the most common side effect of fractional resurfacing when used for melasma?
   (a) Sunburn-like erythema
   (b) Post-inflammatory hyperpigmentation
   (c) Post-procedure pain
   (d) Oozing and crusting
   (e) Herpes simplex outbreak

Correct Answers

1. e: Low-fluence 1064 nm Nd:YAG laser and fractional resurfacing devices, including 1550 nm Er:glass, are considered to be safe for use in darker skin types and have been associated with improvement in melasma severity. Ablative lasers, including Er:YAG and CO_2 lasers, are associated with a significant risk of PIH and, therefore, should be avoided in skin of color. There is insufficient research on QSAL to support its use in skin of color.
2. c: Use of topical 2% tranexamic acid (or hydroquinone 4% or TCC) in combination with IPL has been shown to be more effective than IPL alone in the treatment of melasma. Tranexamic acid is also thought to help prevent rebound of melasma. The other topical compounds above have not yet been studied in conjunction with IPL.
3. d: Both lasers (QSNYL or laser resurfacing) and chemical peels (particularly GA peel) are effective in the treatment of melasma, and current research does not support the superiority of one treatment over another. Therefore, either would be an appropriate next choice. If optimal results are not achieved, it would be reasonable to combine the two treatment modalities. Studies suggest that combination of low-fluence QSNYL and 30% GA is more effective in the treatment of melasma than QSNYL alone.
4. b: Numerous studies suggest that use of triple combination cream prior to and following laser therapy is associated with better improvement in melasma than laser therapy alone. There is no increased risk of adverse events with the combination of laser and TCCs; in fact, the rate of PIH appears to be slightly reduced. Hydroquinone 4% is also considered to be a good adjuvant to laser therapy, but over-the-counter brightening agents have not been adequately studied.
5. a: Fractional resurfacing with Er:glass laser has been reported to cause sunburn-like erythema in 99% of subjects. Burning sensation and mild edema immediately after laser treatment are also commonly observed and self-resolve within a few hours to days after treatment. A retrospective review of 362 patients treated with non-ablative fractional thermolysis for any reason demonstrated prolonged erythema (1.8%), post-inflammatory hyperpigmentation (1.1%), aggravation of melasma (0.9%), herpes simplex outbreak (0.6%), and acneiform eruptions (0.2%).

54 Postinflammatory Hyperpigmentation

Renee C. Sheinin, Henry W. Lim, and David M. Ozog

Abstract

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis due to overproduction of melanin from cutaneous inflammation or injury. PIH can occur in all skin types and can be very difficult to treat. Treatment can be medical or procedural. Medical therapies include topical depigmenting agents such as hydroquinone, azelaic acid, kojic acid, and licorice extract, as well as topical retinoids, vitamin C, and sunscreens. Procedures that may be used to treat PIH include chemical peels, blue light photodynamic therapy (PDT), and various lasers including but not limited to the Q-switched ruby laser, the Q-switched Nd:YAG laser, and the fractional laser. The data available in the literature is limited to scarce case reports and case series. More studies need to be carried out to determine the overall effectiveness of each of the laser treatments described above.

Keywords

Postinflammatory · Hyperpigmentation · PIH Procedural therapy · Lasers · Q-switched ruby laser · Q-switched Nd:YAG laser

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Epidemiology

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis due to the overproduction of melanin resulting from cutaneous inflammation or injury (level 5) [1]. Inflammatory mediators including leukotrienes (LT-C4 and LT-D4), prostaglandins (PG-E2 and PG-D2), thromboxane-2, interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-alpha, epidermal growth factor, reactive oxygen species, and nitric oxide have been shown to stimulate melanocyte activity (level 1a, 5, 5) [2–5]. Ongoing inflammation and additional ultraviolet light exposure can worsen PIH (level 5) [6].

PIH affects all age groups and can occur anywhere on the body (level 4) [7]. The affected areas are determined by the location of underlying causative dermatoses. It shows no gender predilection; however, it is more common in darker Fitzpatrick skin types. The lesions are irregularly shaped macules and patches and can vary in color from light brown to bluish gray depending on the level of deposition of pigment in the skin (level 3a) [8]. PIH can be localized in the epidermis, the dermis, or both. Epidermal PIH involves increased production of melanin and its transfer to keratinocytes; it is characterized by tan to dark brown macules or patches in the same distribution as that of the preceding inflammatory process [2]. Dermal PIH involves melanin that transgresses a damaged basement membrane,

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which is then phagocytosed by macrophages, or macrophages that transgress the basement membrane to phagocytose melanin and then regress to the dermis (level 5) [9]; the pigment appears gray-blue or gray-brown (level 5) [9, 10].

Common instigators include acne, pseudofolliculitis barbae, insect bites, atopic dermatitis, contact dermatitis, psoriasis, pityriasis rosea, lichen planus, lichenoid drug reactions, lupus erythematosus, herpes zoster, fixed drug eruptions, irritants, burns, trauma, or cosmetic procedures including laser treatments (level 2c) [2, 3, 8, 11, 12]. PIH of the epidermis resolves spontaneously in most patients within months to years without therapy [2]; however, dermal PIH is persistent and can be recalcitrant to therapy (level 3a) [2, 13].

PIH can occur in all skin types; however, there is a higher frequency and severity in people of skin of color (skin types IV, V, VI (level 3a) [14]) compared to Caucasians (level 2c, 2b) [15, 16] such as in African Americans, Hispanics/Latinos, Asians (level 2c) [17], Native Americans, Pacific Islanders, and those of Middle Eastern descent (level 3a, 2c, 1b) [2, 15–25]. Furthermore, the degree of an individual's constitutive pigmentation may indicate a higher propensity for PIH [17]. The exact incidence of PIH is unknown. There is a reported prevalence of PIH of 5.8% for children of Middle Eastern descent (level 2c) [26]. The prevalence of pigmentary disorders in the United States ranges from 9% to 19.9% for blacks [16], 0% to 1.7% for whites, 6% to 7.5% for Hispanics/Latinos, and 56.4% to 55.9% for Arab Americans [15, 16, 23, 25]. The prevalence of pigmentary disorders outside of the United States has been reported to be 0.7–15.3% for blacks [19, 21, 24], 0.1% for whites [21], 0.42% for Arabs [19], 26.8% for Middle Eastern descent [26], 1.8% for Chinese [17], 2.7% for Malay [17], 0.3–2.3% for Indian [17], and 0.5% for mixed race [17]; no data were available for Hispanics/Latinos outside the United States.

Treatment Overview

PIH can be very difficult to treat. Treatment can be medical or procedural. Medical therapies include topical depigmenting agents such as hydroquinone, azelaic acid, kojic acid, and licorice extract, as well as topical retinoids and vitamin C [8]. These agents can be used alone or in combination with other therapies and work best for epidermal PIH [6]. Additionally, photoprotection including application of a broad-spectrum sunscreen with sun protection factor (SPF) greater or equal to 30, sun avoidance, and the use of photoprotective clothing should be recommended to all patients to prevent worsening of PIH [18].

Procedures that may be used to treat PIH include chemical peels, blue light photodynamic therapy (PDT), and various lasers. Importantly, all of these procedures used to treat PIH also have the probability to worsen it if they produce excessive inflammation. Chemical peels including salicylic acid peels and glycolic acid peels have been shown to be effective for the treatment of PIH in darker skin types. In a study of five patients with skin types V and VI, Grimes demonstrated that superficial salicylic acid peels are safe and effective in the treatment of PIH (level 4) [27]. In a randomized controlled trial, Burns et al. showed that serial glycolic acid peels in addition to a topical regimen consisting of 2% hydroquinone/10% glycolic acid gel twice daily and 0.05% tretinoin cream at night was more effective in treating PIH in skin types IV, V, and VI than the topical regimen alone. Both treatment groups had improvement in PIH, but the peel group had a faster and greater improvement as well as increased lightening of the normal skin (level 1b) [28]. Blue light PDT is an established treatment for acne vulgaris. One case report of a black female with acne vulgaris treated with blue light PDT described an improvement of not only her acne lesions but also her PIH, thereby proposing blue light PDT as an effective treatment for PIH (level 4) [29].

Lasers are another therapeutic modality used in the treatment of PIH. They need to be used with caution as they can exacerbate PIH inadvertently. It is important to note that efficacy data for using lasers to treat PIH are limited to case reports and small case series. The lasers used to treat PIH that have been described in the literature include the Q-switched ruby laser (QSRL), the Q-switched Nd:YAG laser, and the fractional laser (both erbium:YAG and CO_2 lasers).

The Q-switched ruby laser has been shown to have variable results. Taylor et al. showed no improvement in eight patients with either melasma or PIH treated with the Q-switched ruby laser with the following settings: 694 nm wavelength, 40 ns pulse duration, and fluences of 15–7.5 J/cm^2 (level 4) [30]. However, Tafazzoli et al. reported an improvement of 75–100% in 58% of patients with post-sclerotherapy hyperpigmentation who were treated with the Q-switched ruby laser (level 4) [31].

The Q-switched Nd:YAG laser has been demonstrated to be an effective treatment for PIH. Cho et al. reported a series of three patients with PIH who were successfully treated with five sessions of Q-switched Nd:YAG laser at fluences of 1.9–2.6 J/cm^2 (level 4) [32]. These treatments required minimal downtime, and there was no posttreatment bleeding or crusting. The authors postulated that the longer 1064 nm wavelength leads to less risk of developing PIH after the laser treatment due to its depth of penetration [32]. Another study that evaluated 20 patients with acne and PIH showed a greater than 50% statistically significant improvement in PIH after treatment with the 1064 nm Q-switched Nd:YAG laser (level 1b) [33]. Further studies are necessary to determine the efficacy and safety of the Q-switched ND:YAG laser for the treatment of PIH.

Fractional lasers have had mixed results in treating PIH. Katz et al. described a case of one patient with post-traumatic hyperpigmentation who was successfully treated with the 1550 nm erbium-doped Fraxel laser. The patient achieved near-complete resolution with three treatment sessions using a density of 880–1100 MTZ/cm^2 [7]. Furthermore, the 1927 nm fractionated thulium laser was described to achieve near-complete resolution of post-inflammatory hyperpigmentation caused by cupping in a 26-year-old female (level 4) [34]. Rokhsar et al. reported a case of one patient with PIH induced by CO_2 nonablative laser resurfacing who was treated with the 1550 nm Fraxel laser at densities of 2000–3000 MTZ/cm^2. They described an improvement of 50–75% after five sessions over a 2-month period with no adverse events (level 4) [35]. Another case depicted successful treatment with complete resolution of refractory PIH with two sessions, each 1 month apart, of fractional CO_2 laser in a 24-year-old female with skin type III (level 4) [36]. However, Kroon et al. reported that fractional laser was not effective for PIH as evidenced by a series of six patients, who each had a total of five treatments (level 4) [37].

Effectiveness of Treatments

The data available in the literature is limited to scarce case reports and case series. More studies need to be carried out to determine the overall effectiveness of each of the laser treatments described above as well as whether or not the effectiveness varies based on demographics such as age, gender, and ethnicity. It is unknown whether the effectiveness has changed over time and how long the results will last. Longitudinal studies have yet to be performed. The degree of improvement reported ranges from 50% to 100% in the case series and case reports mentioned above.

Comparative Effectiveness of Common Treatments

There is a paucity of data comparing the effectiveness of one treatment modality against another. One study evaluated the treatment of pigmented lesions with the Q-switched ruby laser and the frequency-doubled Q-switched Nd:YAG laser. The authors measured clinical lightening of the lesion 1 month after a single treatment. At least 30% of lightening was achieved in all 20 patients with either the Q-switched ruby laser or the Q-switched Nd:YAG laser. The Q-switched ruby laser had a slightly better outcome than the Q-switched Nd:YAG laser. Neither treatment modality caused side effects of scarring or textural change of the skin. Patients reported more pain during the treatment with the Q-switched ruby laser; however, they reported more posttreatment discomfort with the Q-switched Nd:YAG laser (level 4) [38].

To our knowledge, there were no other studies in the literature examining relative effectiveness, combination treatments, or prognosis. There is

likely some variability of outcome based on patient demographics, as well as condition-specific factors such as severity, type, or anatomic location. However, more studies need to be carried out to evaluate whether or not these factors will play a role in the effectiveness of treatment.

Most treatment paradigms begin with hydroquinone, photoprotection, and avoidance of the initial inflammatory process if possible. This is commonly done, although there is a lack of clinical trials demonstrating efficacy. Chemical peels are most commonly added at this point with salicylic acid, which is particularly useful for skin types IV–VI in a setting of inflammatory acne as a causative factor. Much less common is the use of lasers due to mixed results in a small number of case series studies, higher cost compared to medical therapies and chemical peels, and limited availability of devices in practice.

Preoperative Evaluation and Patient Selection

The preoperative evaluation is very important in selecting the right treatment for an individual patient. One such tool that can aid in determining what kind of PIH the patient has is the Wood's lamp. It can be a useful tool to differentiate between primary epidermal melanosis and primary dermal melanosis. This is most helpful in patients with skin types I–IV. Primary epidermal melanosis under Wood's lamp appears as well-circumscribed pigmentation with accentuated borders, whereas primary dermal melanosis is poorly circumscribed and is not accentuated under Wood's lamp illumination [13]. Based on the location of the pigment, the treatment plan can be tailored for optimal results.

PIH tends to improve slowly over time. Therefore, treatment is not necessary for all patients. Medical therapy and/or procedural therapy can be limited to patients who desire accelerated resolution of hyperpigmentation. Procedural therapy can also be considered for those patients whose PIH is refractory to medical treatments.

There are many factors that can influence the outcome of treatment. The location of the increased pigment within the skin is one example. Medical therapies work better for epidermal pigment than they do for dermal pigment. They reduce the production or distribution of epidermal pigment. Patients with increased melanin within the dermal macrophages are less likely to respond well to medical treatment [6]. Laser treatments can be used for either epidermal or dermal hyperpigmentation.

Impact of Patient Preference

A patient's propensity to choose to proceed with any given procedure depends on many factors including cost, discomfort during and after the procedure, adverse events, number of treatments required, and likelihood of improvement or resolution of their condition. The procedures described above vary considerably with regard to postoperative care and expected side effects. Superficial chemical peels require minimal immediate postoperative care. A thin coat of petroleum jelly or Aquaphor ointment is applied after most peels. If the patient has a more robust reaction, a topical steroid can be used. Additionally, in patients with skin type IV or greater, a topical steroid may reduce the risk of developing PIH from the procedure itself. Patients can expect their newly peeled skin to develop mild-to-moderate erythema in the first few days and superficial desquamation in the subsequent few days. The patient should be instructed to cleanse the peeled skin twice daily with gentle soap and water and to resume his or her normal skincare routine once the skin is back to baseline. This can take anywhere from 1 day to 1 week depending on the depth of the peel. If the patient has a history of facial herpes simplex outbreaks, it is best to prescribe prophylactic antiviral therapy. Photoprotection is of utmost importance in the post-procedural period, and broad-spectrum sunscreen with SPF $\geq$30 should be applied as soon as the skin can tolerate it [39].

Laser therapy requires immediate postoperative cooling with ice packs. This can reduce post-procedure perifollicular edema, which typically lasts for up to 48 h, and erythema, which can

persist up to 1 week, as well as reduce postoperative discomfort. If erythema persists beyond 10 days, a low- to mid-potency topical steroid can be applied. Some patients can develop an urticarial reaction, which is best managed with oral antihistamines. Crusting can develop and last from 7 to 10 days. This can be treated with twice-daily application of petroleum jelly or Aquaphor ointment. Patients should avoid picking or scratching the area. Similar to superficial peels, photoprotection and the use of sunscreen is highly recommended after the procedure. Analgesics are typically not required as long as the appropriate cooling measures are in place before, during, and after the laser treatment [39].

The fractional ablative lasers have a slightly longer downtime as compared to other lasers and superficial chemical peels and require more extensive wound care in the post-procedural period. The fractional Er:YAG resurfacing laser can cause erythema and swelling that lasts for an average of 3 days, whereas the fractional CO_2 laser has a downtime period of about 1 week on average and includes hemorrhagic crusting, swelling, and erythema. Wound care for proper re-epithelialization includes an occlusive dressing placed on the treated area for the first few days. The patient should cleanse the affected area daily. Alternatively, lukewarm water soaks can be performed to minimize crusting. As in the other procedures, liberal use of emollients such as petroleum jelly is necessary. It is important to note that erythema can persist even after re-epithelialization and the patient should be advised accordingly [39].

Given the variable efficacy for all of the procedures and medical treatments described above, patients select a treatment plan based on the combined variables of personal distress with their situation and available time and financial resources for the treatments.

Typical Treatment Plan

A 47-year-old female with skin type III presents to the clinic with facial PIH secondary to acne vulgaris. Her acne is under good control and her face is clear with the exception of the PIH that remains. She is interested in pursuing treatment for PIH. The gold standard for the treatment of this patient is topical hydroquinone. The data are limited for PIH, but hydroquinone has been extensively studied in patients with melasma. Second-line treatment options include topical retinoids, Tri-Luma (compounded topical retinoid, topical steroid, and hydroquinone), azelaic acid, and superficial chemical peels. There are insufficient data to determine their relative efficacy and how they compare to hydroquinone. The efficacy data of peels was described above; salicylic acid peel would be the next step of treatment for this patient.

For refractory PIH, lasers should be considered. Anesthesia is typically not required. Most patients describe the discomfort as being analogous to a rubber band snapping the skin surface. If a patient is particularly sensitive, a topical lidocaine 5% cream or an EMLA cream can be applied prior to treatment. Immediately after the laser treatment, the patient may experience sensations of pain or stinging. Postoperative cooling and occlusive dressings can help mitigate these symptoms. When using a Q-switched laser, the clinical endpoint is immediate skin whitening. This will typically resolve within 20–30 min. The treated area can become temporarily hyperpigmented and crusts can form. Daily application of petroleum jelly or other occlusive ointments and daily cleansing with a gentle soap and water will help promote healing of the treated area; crusts will usually fall off within 7–10 days. Photoprotection including the use of sunscreen is strongly recommended.

Novel Treatments

Although oral tranexamic acid has been reported as a successful treatment for melasma, it was not effective as prophylaxis for laser-induced PIH. The study included 32 patients who underwent QSRL treatment of lentigines, and all patients were divided into two groups: one that received oral tranexamic acid 750 mg daily and one that did not. The PIH appeared on average

about 4 weeks after the laser treatment in both groups. There was no difference observed among the two groups showing that oral tranexamic acid did not prevent induction of PIH (level 1b) [40]. Although the results of this study did not support the use of oral tranexamic acid in the treatment of PIH, it is important to appreciate this innovative approach by using oral therapies in expanding out-treatment armamentarium of PIH.

Safety

In general, lasers have an overall favorable safety profile when operated correctly. The most severe but rare adverse effect is retinal injury and ultimately blindness. This can be avoided with the use of the proper eye protection. The laser operator and everyone in the treatment room must wear safety goggles that are specific to the wavelength of that laser. The patient should be instructed to close his or her eyes and to wear external goggles that are not transparent. If the periocular area is being treated, metal eye shields should be inserted into the eye for protection. Other more common, less severe adverse events include blistering, bruising, dyspigmentation, and scarring. Both lasers and chemical peels may cause worsening of the PIH if an undetermined threshold of injury is reached resulting in undefined "excessive" inflammation.

Postoperative Care and Follow-Up

Often, one treatment is not sufficient to produce desirable results. Both chemical peels and laser treatments are performed as often as every 4–6 weeks, but this is an arbitrary timeframe. It is difficult to predict how many treatments an individual patient will need given the lack of evidence available in the literature. One important factor to consider when determining a treatment schedule is skin type. Patients with darker skin types should have longer intervals between treatments to help minimize adverse events. Some patients have been reported to have complete resolution of their PIH with the treatments described above. Others showed significant improvement but were unable to achieve complete clearance of their PIH.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Procedural therapy can be considered for those patients whose PIH is refractory to medical treatments	C
All of the procedures used to treat PIH, including chemical peels, blue light photodynamic therapy (PDT), and various lasers, have the capacity to worsen PIH if they produce excessive inflammation	C
Chemical peels including salicylic acid peels and glycolic acid peels have been shown to be effective for the treatment of PIH in darker skin types	B
The Q-switched ruby laser has been shown to have variable results in the treatment of PIH	C
The Q-switched Nd:YAG laser has been demonstrated to be an effective treatment for PIH	C
Fractional lasers (including erbium, thulium, and CO_2) have had mixed results in treating PIH	C
Oral tranexamic acid is not recommended as prophylaxis for laser-induced PIH	B

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Self-Assessment Questions

1. Which of the following is true regarding PIH?
   (a) PIH is more common in the elderly
   (b) PIH is more common in females
   (c) PIH is more common in darker Fitzpatrick skin types
   (d) PIH is localized to the epidermis only
   (e) PIH is more common on the forearms
2. All of the following have been used to treat PIH except:
   (a) Topical depigmenting agents such as hydroquinone
   (b) Red light photodynamic therapy
   (c) Chemical peels
   (d) Q-switched Nd:YAG laser
   (e) Fractional CO_2 laser
3. Which of the following is false?
   (a) Medical therapies work better for dermal pigment than they do for epidermal pigment
   (b) PIH tends to improve slowly over time
   (c) Laser treatments can be used for either epidermal or dermal hyperpigmentation
   (d) Epidermal melanosis under Wood's lamp appears as well-circumscribed pigmentation with accentuated borders
   (e) Dermal melanosis is poorly circumscribed and is not accentuated under Wood's lamp illumination
4. All of the following can be observed in the postoperative period after a laser treatment for PIH except
   (a) Perifollicular edema
   (b) Perifollicular erythema
   (c) Urticarial reaction
   (d) Crusting
   (e) All are correct
5. Which of the following is the most severe albeit rare adverse effect of laser therapy?
   (a) Blistering
   (b) Bruising
   (c) Dyspigmentation
   (d) Retinal injury
   (e) Scarring

Correct Answers

1. c: PIH affects all age groups. It shows no gender predilection. PIH can be localized in the epidermis, the dermis, or both. It can occur anywhere on the body. The affected areas are determined by the location of underlying causative dermatoses.
2. b: All of the above have been used in the treatment of PIH except B. Blue (not red) light PDT is another effective treatment for PIH.
3. a: All of the above statements are correct except A. Medical therapies work better for epidermal pigment than they do for dermal pigment. They reduce the production or distribution of epidermal pigment. Patients with increased melanin within the dermal macrophages are less likely to respond well to medical treatment.
4. e: All of the above can be seen in the postoperative period after a laser treatment.
5. d: All of the answer choices listed are possible adverse effects of laser therapy. However, answer D, retinal injury, is the most severe adverse effect as it can lead to blindness. This is a very rare adverse effect but a very important one that the clinician must be aware of.

Vitiligo

55

Jorge A. Hinojosa, Andrea Tovar-Garza, and Amit G. Pandya

Abstract

Vitiligo is a chronic autoimmune disorder of the skin in which melanocytes are destroyed resulting in patchy areas of skin depigmentation. This disease occurs in approximately 1% of the world's population without predilection for sex, race, or ethnicity (5) (Ezzedine et al., Lancet 386:74e84, 2015). Vitiligo can be classified into three major categories: segmental vitiligo, which has a unilateral distribution, non-segmental or generalized vitiligo, and mixed vitiligo, which is a combination of the former two (Ezzedine et al., Lancet 386:74e84, 2015). Approximately half of those affected with vitiligo develop their first lesion before the age of 20 (Ezzedine et al., Lancet 386:74e84, 2015). Vitiligo can be disfiguring, especially in dark-skinned individuals, and can have a significant psychological and social impact with major consequences on the quality of life for those affected (4) (Kostopoulou et al., Br J Dermatol 161:128–133, 2009). Other autoimmune disorders, including thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, and alopecia areata, have been associated with vitiligo (2c) (Alkhateeb et al., Pigment Cell Res 16(3):208–214, 2003).

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Repigmentation · Punch · Patient · Grafting · Vitiligo · Lesions · Transplantation

Introduction

Epidemiology

Vitiligo is a chronic autoimmune disorder of the skin in which melanocytes are destroyed resulting in patchy areas of skin depigmentation. This disease occurs in approximately 1% of the world's population without predilection for sex, race, or ethnicity (5) [1]. Vitiligo can be classified into three major categories: segmental vitiligo, which has a unilateral distribution, non-segmental or generalized vitiligo, and mixed vitiligo, which is a combination of the former two [1]. Approximately half of those affected with vitiligo develop their first lesion before the age of 20 [1]. Vitiligo can be disfiguring, especially in dark-skinned individuals, and can have a significant psychological and social impact with major consequences on the quality of life for those affected (4) [2]. Other autoimmune disorders, including thyroid disease, pernicious anemia, Addison's disease, systemic lupus erythematosus, and alopecia areata, have been associated with vitiligo (2c) [3].

Treatment Overview

Unfortunately, there are currently no FDA-approved therapies for repigmentation of vitiligo lesions. Off-label therapies that are often used alone or in combination include topical and systemic corticosteroids, topical immunomodulators, and phototherapies such as PUVA and NBUVB. While these treatments can result in complete repigmentation of lesions in some patients, rates of repigmentation are variable and usually do not result in complete repigmentation of all affected areas (2a) [4]. Patients with recalcitrant lesions that have been stable for 1–2 years after failed medical therapy may benefit from surgical methods of repigmentation (5) [5]. These surgical techniques can be divided into two groups: tissue grafting and cellular grafting. Autologous tissue grafting methods include suction blister epidermal grafts (SBEG), split-thickness grafts (STSG), and punch grafts (PG), also called mini-grafts. Cellular grafting techniques include non-cultured epidermal suspension (NCES) grafts, also called the melanocyte-keratinocyte transplantation procedure (MKTP), and cultured melanocyte transplantation (CMT). Other surgical methods that are less commonly used in the surgical treatment of vitiligo and will not be discussed in this review are microneedling, laser ablation as monotherapy, and hair follicle/outer root sheath transplantation. Regardless of the surgical approach, the aim of all of these methods is the same – to introduce melanocytes from non-affected melanocyte-rich tissue into a vitiligo lesion devoid of melanocytes. Because there is a risk of destruction of the transplanted cells due to inflammation at the recipient site, the most important factor for successful transplantation is to ensure disease stability or quiescence prior to undergoing any of the aforementioned procedures [5]. While there is no consensus on the definition of disease stability, the Vitiligo Global Issues Consensus Conference has stated that a 12-month period of photographically assessed stability is necessary for the purposes of surgical treatment (5) [6]. Contraindications to vitiligo surgery include a personal history of keloid diathesis and presence of the Koebner phenomenon (5) [5, 7]. Each technique has its own advantages and disadvantages, and thus the most appropriate surgical approach depends heavily on the size and location of the lesion(s) being treated, physician preference and experience, patient preference, and affordability and availability of required materials (Table 55.1).

Effectiveness of Treatments

Blister Grafting

Suction blister epidermal grafting (SBEG), or, simply, blister grafting, was first described by Falabella in 1971 (4) [8]. Since then, various modifications have been made to the original technique but the basic design remains the same; autologous epidermal blister roofs from a non-affected donor sites are transplanted onto de-epithelialized vitiligo lesions. To harvest the epidermal graft tissue, a negative pressure device is placed at the donor site (most commonly the thigh, abdomen, or arm) and set to −200 to −400 mmHg. This results in separation at the dermo-epidermal junction after 1–2 h (4) [9]. Heating the donor site to 42 °C can hasten the process and result in blister formation after just 45–60 min) (4) [10, 11]. Many negative pressure devices ranging from simple syringes to custom-made suction devices can be used, depending on availability, affordability, and physician preference. Once formed, the blister roofs are cut off at the edges, and the graft is placed onto the de-epithelialized recipient site which is typically first denuded by either dermabrasion, laser ablation, freezing with liquid nitrogen, suction blistering, or PUVA (5) [12].

Like other methods of melanocyte transplantation, successful repigmentation using blister grafting depends mostly on patient selection and vitiligo subtype. Indeed, patients with segmental or focal vitiligo have been shown to have higher rates of successful repigmentation than those with non-segmental vitiligo using SBEG (4) [13]. In addition, success rates are higher in patients younger than 20 years compared to older patients [13]. Nonetheless, repigmentation efficacy using SBEG is generally good. In a systematic review

Table 55.1 Summary

	Minigraft	Blister graft	Split-thickness graft	Cultured cellular transplant	Non-cultured cellular grafting
Melanocyte source	Punch biopsy graft	Suction blister	Thin dermo-epidermal sheets	Shave biopsy	Shave biopsy Suction blister
Size of lesions treated	0–50 cm	<20 cm	100–250 cm	100–500 cm^2	100–500 cm
Repigmentation area extension	6–12 mm	10–25 mm	n/a	n/a	n/a
Duration of procedure	45 m to 2 h	2–3 h	2–4 h	>24 h	45 m to 4 h
Immobilization/ dressing period (days)	7–14	7–14	7–14	7	7
Advantages	Easy and least expensive	Easy, inexpensive, excellent cosmetic results	Highest percentage of repigmentation	Large amount of cells from small sample	– Large areas treated by using a small donor area – Reduces cell preparation time and need for laboratory – One-day procedure
Disadvantages	Time-consuming in large areas	– Time-consuming – Color mismatch		– Expensive – Requires two visits – Specialized laboratory	– High cost – Higher level of training required – Specialized instruments
Side effects	Cobblestoning Polka-dot appearance Milia Scarring Color mismatch	Color mismatch	Color mismatch Milia Scarring Hematoma	Color mismatch Safety concerns of culture media	Color mismatch

of ten case-series studies using blister grafting, 301 out of 347 (87%) [95% CI 83–90%] of patients showed >75% repigmentation (4) [14]. In a retrospective review of 1100 patients by Li et al., 227 (20%) patients achieved complete repigmentation, while 568 (52%) achieved >50% repigmentation of lesions (4). Only 43 (3.9%) showed no repigmentation after treatment. Of the 227 patients with complete repigmentation, 16 (7%) patients developed depigmentation at the site of the transplants after 1–5 years. Most of these patients had generalized or acrofacial vitiligo. There was no recurrence of vitiligo in patients with segmental vitiligo. Success rates (defined as >50% repigmentation) for segmental (89.7%) and focal (76.5%) subtypes were significantly higher than in those with acrofacial (52.4%) or generalized (52.1%) subtypes. Lesions on the face, neck, and limbs showed higher success rates than other locations, while the scalp and hands had the lowest success rates (4) [15].

Survival of suction blister grafting using SBEG is considered high when in hands of an experienced physician. Success rate of up to 86.8% have been reported (4) [16]. As mentioned for other procedures, graft survival correlates indirectly with age; patients younger than 20 years have an excellent (100%) survival rate compared to a lower (75–78%) rate in patients older than 40 years. Regarding recipient sites, the face and neck have been shown to have the highest degree of pigment spread, doubling the size of the original graft [16].

Mini-punch Grafting

Mini-punch and punch grafting are similar techniques that differ only in the size of punch instrument used. Mini-punch grafts are 1 mm in diameter, while punch grafting refers to grafts that are 1.5–2 mm in diameter. Before performing extensive punch grafting procedures, all patients should first undergo a punch grafting test or trial [5]. This is done by implanting four mini-punch grafts in a depigmented lesion. If spreading of the pigment occurs within 8 weeks, then the patient could undergo the final, more extensive punch grafting procedure (4) [17].

When performing the procedure, the donor and recipient areas are both infiltrated with 1% lidocaine/epinephrine. The preferred donor site is typically a non-affected pigmented area of the thigh, hip, or buttocks. Donor skin using mini-punch biopsies reaching into the papillary dermis is obtained from the donor site and transplanted onto the recipient site. The recipient site should be prepared by removing skin with a punch biopsy instrument of the same diameter down to the subcutaneous fat [5, 17]. The recommended distance between each defect at the recipient site is 5–8 mm, at a depth of 2–3 mm [5]. Grafts can be spaced further apart in patients with darker skin types, since pigment spread is usually more robust in these patients. After placing the mini-punch grafts in the recipient area, hemostasis is achieved by applying pressure with saline-soaked gauze over the area. Both donor and recipient sites are then covered with small strips of tape (Steri-Strips®) [17].

Approximately 57% of patients achieve repigmentation which can be first observed between 14 and 32 days (mean 20.6 days) post-transplant. The repigmentation may continue to spread to maximum of 12 mm in diameter, but the average spread is 6.5 mm (4) [18]. Fifty-one percent of patients have good to excellent repigmentation (>65% repigmentation). Patients with segmental vitiligo typically demonstrate even better repigmentation overall with 89% of patients having good to excellent repigmentation [17]. *Malakar et al.*, found that 65.6% of patients with stable and recalcitrant vitiligo achieved repigmentation rates of 90–100% (4) [19]. Maximal repigmentation is observed at 3 months on the face and 2 months in other sites. Disease duration has not been shown to affect the repigmentation response (4) [20].

Higher rates of repigmentation of up to 86.7% are seen when NB-UVB is started immediately after the removal of the dressing at approximately 7 days post-surgery [20]. Other adjuvant phototherapies such as PUVASOL have shown repigmentation of up to 10 mm in diameter (4) [21]. Because of its lower cumulative dose, Excimer laser may be preferred in children or those with history of UV-induced phototoxicity. Nonetheless, NB-UVB is still the preferred choice as it is more feasible, less time-consuming, and more effective than other forms of phototherapy (4) [22].

The graft survival rate varies, depending on patient selection and surgical expertise and experience of the physician. Mini-punch grafting is an effective and easy to perform procedure, with an 87% graft survival rate. As we have mentioned, age and body site are important predictive factors for outcome, and patients younger than 20 years and grafts performed on the neck and trunk achieve better repigmentation. Additionally, inappropriate immobilization of acral regions and joints account for a poor outcome in these body sites (4) [23]. Other negative prognostic factors include active disease and presence of the Koebner phenomenon. Indeed, patients with stable disease show significantly higher rates of repigmentation (77–88%) compared to those with active disease (39–48%) ($p < 0.05$) (4) [17, 24]. Other factors such as acral distribution, extensive disease, and other types of leukodermas (such as nevus depigmentosus, herpes-induced lip leukoderma) are usually nonresponsive to mini-punch grafting [18]. Overall, the best results in patients undergoing mini-punch grafting occur in those with segmental and focal vitiligo and those younger than 20 years old [20].

Split-Thickness Grafts

In this method, grafts containing epidermis and papillary dermis are harvested from a non-affected site (typically the lateral thigh or gluteal region) using a dermatome or shaving blade and then transplanted onto an abraded recipient site

which has been previously prepared. The graft is then held in place using pressure and an appropriate dressing [5]. *Al-Mutairi et al*. performed this procedure on 17 patients with focal and segmental vitiligo who were clinically stable for at least 1 year. The size of the treated lesions ranged from 2 to 55 cm^2. The grafted area was then treated with excimer laser twice per week. At 16 weeks post-surgery (after 32 sessions of excimer), 12 out of the 17 patients had an excellent outcome, and the remaining 5 patients had good outcome. At 1-year follow-up, all 17 patients exhibited excellent repigmentation which remained for up to 4 years (4) [25]. Similarly, in a case series of 32 lesions in 21 patients, *Agrawal et al*. found that 100% repigmentation was achieved in 68% of lesions and 90–95% repigmentation was achieved in the remaining lesions. Importantly, satisfactory color match was not seen until 3–9 months (Average = 6.3 months) (4) [26].

In a systematic review by Njoo et al. which evaluated the results of 13 studies on split-thickness grafting, successful repigmentation (>75% repigmentation) was achieved in 87% [95% CI, 82–91%] of patients [14]. This was the highest rate of repigmentation among surgical techniques evaluated. Likewise, a systematic review by *Mulekar and Isedeh* found split-thickness grafting to have the highest repigmentation rates among the various grafting techniques (4) [27].

Cultured Melanocyte Transplant

The method of obtaining the donor tissue for cultured melanocyte grafts is similar to other methods. Typically, either a Silver skin grafting knife or suction blisters are used to obtain donor skin in non-cosmetically important areas like the thighs, buttocks, or waist (4)(4) [28, 29]. The skin graft is immediately transferred to a melanocyte culture laboratory for isolation of cells; the optimum time for successful culturing takes 1–3 weeks. After 3 weeks, the cell count is raised 50–100-fold after primary culture and subcultures are performed (4) [30].

The melanocyte-keratinocyte culture medium (MK medium) used most often in this form of grafting contains basic fibroblast growth factor, bovine pituitary extract, 10% fetal bovine serum, and penicillin-streptomycin, among others (4) [28, 29, 31]. The surgical procedure to graft the cultured cells onto the recipient site is similar to that described in non-cultured epidermal suspension grafting (4) [30–32].

This entire procedure requires a well-equipped laboratory and skilled technicians, which increases the patient's cost. There are also long-term safety concerns due to the use of bovine supplements, growth factors, and antibiotics during the cell culture process. In addition, the transplant procedure takes much longer than other forms of grafting due to an initial visit for harvesting donor cells and a second one approximately 3 weeks later for the actual melanocyte transplant procedure.

NCES/MKTP Grafting

Non-cultured epidermal suspension transplantation (NCES) was first described by *Gauthier et al.* in 1991. First, donor graft tissue was obtained from the scalp through superficial shaving with a dermatome and then immersed in a solution containing 0.25% trypsin for 18 h resulting in separation at the dermo-epidermal junction. At the same time, the recipient site was prepared by inducing blister formation with liquid nitrogen. Once the incubation of the donor graft tissue was complete, the epidermal side of the graft tissue was isolated by mechanical separation in order to obtain a cellular suspension consisting of a higher proportion of basal layer cells. This suspension was then injected directly into the blisters at the recipient site. The roof of the intact blister served as a natural dressing, holding the transplanted cells in place (4) [33]. In 1998, *Olsson et al*. modified the technique by using the gluteal region as the donor area, reducing trypsinization time to 50 min by incubating the donor tissue at 37 °C, and preparing the recipient site with dermabrasion (4) [34].

Modifications of this procedure continue to be made. For example, the fixation of the liquid suspension at the recipient area was thought to be a problem; therefore, hyaluronic acid was added as a carrier to increase the viscosity (4) [35]. Other methods of recipient site preparation have been adapted such as erbium/YAG or carbon dioxide

(CO_2) laser (4) [36]. Additionally, epidermal suction blisters have also been used to obtain donor cells (4) [37]. The benefits of this method include no need to separate epidermis from the dermis since the grafts are made of pure epidermis, a more cosmetically acceptable scar at the donor site and the use of blister fluid as a natural trypsin inhibitor [37]. The preferred technique will depend on the choice of the surgeon.

A double-blind placebo controlled study established that repigmentation was in fact induced by the transplanted melanocyte suspension and not simply a result of dermabrasion (3b) [38]. In an open-label, single-center study comparing dermabrasion and CO_2 laser to prepare the recipient site, both techniques resulted in similar rates of repigmentation; however there was a higher risk of temporary hyperpigmentation in recipient sites prepared with CO_2 laser (39% vs. 18%) (3b) [39]. *Silpa-Archa et al*. also compared the use of collagen dressing to petrolatum gauze for wound dressing and found there to be a slightly greater but insignificant improvement in repigmentation in the collagen dressing group [39]. Indeed, collagen dressing is preferred by most authors, as it provides an optimal environment for cellular growth and vascularization and holds transplanted cells in place (4) [40].

Like other methods of transplantation, the best results are observed in patients with stable segmental vitiligo and piebaldism which show repigmentation rates of 85% and 90%, respectively. Mean repigmentation rates in the treatment of halo nevi and generalized vitiligo are 91% and 70%, respectively. Patients with mixed vitiligo have shown the lowest rates of repigmentation (37%), causing them to be inappropriate candidates for NCES. Patients with stable disease have mean repigmentation rate of 88.6% (95% CI 83.2–94%) compared to 48.4% (95% CI 27–59.7%) in patients with active disease. Additionally, patients with Koebner phenomenon show lower rates of repigmentation (17%) compared to patients without this sign ($p = 0.015$) (4) [41].

The location of the recipient site can also influence successful repigmentation. The face and neck tend to have the highest success rates with 19% of lesions exhibiting excellent repigmentation (≥95% repigmentation) and 50% exhibiting good repigmentation (65–94% repigmentation). The extremities (excluding elbows and knees) show the second highest rates of repigmentation with 13% of lesions exhibiting excellent repigmentation and 25% exhibiting good repigmentation. Repigmentation rate in the trunk is highly variable, as 20% of lesions show excellent repigmentation but 80% of lesions show poor repigmentation (0–24% repigmentation). Lesions on the joints show a significantly lower response rate compared to the trunk and extremities ($p = 0.017$, $p = 0.0091$) [41]. Fingertips and distal toes do not improve with NCES. While a small number of patients may show initial improvement in these areas, they tend to relapse quickly. Large lesions (1000 cm^2) and multiple smaller lesions distributed on different anatomic locations may also have a poor prognosis (5) [42]. Transplantation of the lips is not encouraged due to the difficulty of appropriate dermabrasion and the constant trauma this area undergoes after grafting [40].

In children, focal and segmental vitiligo subtypes have shown better repigmentation rates than non-segmental vitiligo. In a retrospective, long-term follow-up study (9–54 months), 75% of focal vitiligo patients had excellent repigmentation (≥95% repigmentation). Sixty-two percent of those with segmental vitiligo had excellent repigmentation, 15% had good repigmentation (65–95% repigmentation), and only 8% had fair repigmentation (25–64% repigmentation) (4) [43]. Lastly, patients with lip and finger and toe tip involvement have been associated with poorer surgical outcomes; therefore, other treatment options should be pursued for these patients (4) [44].

As with other transplant procedures, adding phototherapy post-NCES grafting increases the repigmentation rate when compared to NCES alone and nontreatment. The median percent reduction of depigmentation in excimer and NCES in combination was 41.9% compared to 15.9% for NCES alone and 0.1% in untreated patches (3b) [45].

Importantly, studies have shown that repigmentation occurs for an average of 10 months after NCES transplantation (range 0–72 months). Therefore, reevaluation for repeating the proce-

dure should not occur until 1 year post-transplant (4) [41]. A 5-year follow-up study showed that repigmentation was sustained in those with stable disease [40].

Comparative Effectiveness of Common Treatments

Blister Grafting Versus NCES and CMP grafting

Budania et al. compared SBEG to NCES in a randomized study of 41 patients with 54 stable vitiligo lesions. Twenty-one patients with 28 lesions were treated with NCES and 20 patients with 26 lesions were treated with SBEG. At 16 weeks postsurgery, excellent repigmentation (90–100%) was observed in 20 of 28 (71%) of lesions treated with NCES compared to only 7 of 28 (27%) of lesions treated with SBEG (p = 0.002). Good repigmentation (≥75%) was achieved in 25 of 28 (89%) lesions in the NCES group compare to 25 of 26 (85%) lesions in the SBEG group (p = 0.61). Importantly, while Dermatology Life Quality Index (DLQI) [46] scores improved in both groups, there was a greater improvement in those who received NCES grafting compared to those who received SBEG (p = 0.045). Both groups showed excellent color match (2b) [47].

Czajkowski compared the effectiveness of cultured autologous melanocytes plus PUVA (CMP), SBEG plus PUVA (SBP), cryotherapy plus PUVA (CP), and PUVA alone (OP) in 20 patients with focal or acrofacial vitiligo of the dorsum of the hands and lower limbs. No significant difference was found between the number of successful transplants (100% repigmentation) between CMP and SBP. CP and OP methods were found to be ineffective (4) [48].

Suction Blister Grafting Versus Punch Grafts

Gupta et al. compared epidermal suction blister grafting to punch skin grafting in 49 patients. After 4–7 months, successful repigmentation (>75% repigmentation) occurred in 67% of the lesions in the punch graft group and in 82% of the lesions in the epidermal suction blister group. While the difference between groups was not significant, the group that received SBEG achieved cosmetically better results due to lower frequency of adverse effects such as cobblestoning and superficial scarring (4) [49].

Babu et al. compared the efficacies of punch grafting and suction blister epidermal grafting in patients with stable vitiligo of the lip. A total of 18 patients were included, of whom 8 (44.4%) patients had focal lip vitiligo, 9 (50%) patients had lip-tip vitiligo, and only 1 (5.6%) patient had generalized vitiligo. Punch grafting was done using a 1.5 mm instrument and each graft was placed 3–4 mm apart. Suction blister grafting was performed by obtaining 2 cm blisters after which the recipient site was prepared by manual dermabrasion until punctate bleeding was achieved. Blisters were placed 3–4 mm apart from each other. Of the punch grafting group, six (75%) of the patients achieved good to excellent (>50%) repigmentation compared to six (60%) patients in the suction blister grafting group. The color match was significantly better in the punch grafting group when compared to the suction blister grafting group (p = 0.02). Focal lip vitiligo patients had better outcome when compared to lip-tip vitiligo patients. The most common side effect in the recipient sites was cobblestoning in the punch graft group, whereas hyperpigmentation and thickening of grafts was the most common adverse effect in the suction blister group. There was no significant difference in repigmentation outcome in regard to age, sex, type of vitiligo, and disease duration. The authors concluded the preferred surgical treatment for stable lip vitiligo is punch grafting due to higher repigmentation, milder side effects, and better color match (4) [50].

NCES Grafting Versus CMT Grafting

In a study by *Verma et al.,* similar lesions on the same patient were transplanted with either NCES or CMT. Two target patches were grafted with 1500 cells/mm^2 with NCES and equal number of cells with CMT. The recipient site was prepared by dermabrasion until the appearance of pinpoint bleeding was achieved for both techniques. Repigmentation was evaluated by three-dimensional

analysis (3-D), transparent graph paper, and two-dimensional (2-D) computerized analysis. Excellent repigmentation (>75%) was observed in significantly higher number of lesions treated with CMT as compared to NCES as early as 8 weeks post-surgery. At the end of the 12-week period, four (100%) patients with segmental vitiligo achieved more than 90% repigmentation with CMT compared to 40% repigmentation with NCES. Overall 66% of lesions showed >70% repigmentation with CMT. A possible explanation for a better response could be due to the fact that pure melanocytes are transplanted in CMT allowing faster and better repigmentation compared to melanocytes from NCES, in which the number of melanocytes is lower (1 melanocyte:10–36 keratinocytes) (4) [51].

Cultured Melanocyte Grafting Versus Split-Thickness Grafting Versus NCES Grafting

In a retrospective case series of 124 patients with vitiligo, *Olsson and Juhlin* compared the long-term (1–7 years post-transplant) efficacy of autologous cultured melanocyte transplantation, split-thickness grafting, and NCES grafting. Of the 15 patients with segmental vitiligo, 5 were treated with cultured melanocytes, one was treated with split-thickness grafting, and 8 were treated with NCES grafting. All but one patient showed 95–100% repigmentation of their lesions. The remaining patient, who was treated with cultured melanocyte transplantation, had 85% repigmentation. Two patients with focal vitiligo treated with NCES grafting showed 100% repigmentation. In the 107 patients (369 anatomical sites treated) with non-segmental vitiligo, those who underwent cultured melanocyte transplantation (277 anatomical regions) achieved mean 42% repigmentation; those who underwent split-thickness grafting (40 anatomical regions) achieved mean 59% repigmentation; and those who underwent NCSE (52 anatomical regions) achieved mean 49% repigmentation. In the non-segmental group, patients with shorter disease duration, smaller affected areas, and younger age tended to response best to transplantation. The authors concluded that split-thickness grafting was the method which achieved better overall repigmentation but was also associated with worst outcome on the knees and elbows (4) [52].

Preoperative Evaluation and Patient Selection

The single and most important prerequisite prior to considering surgical intervention for vitiligo is to ensure disease stability. While there is no consensus regarding the minimum period of stability, the absence of new lesions, lack of progression of old lesions, and lack of signs of activity, such as the Koebner phenomenon, over the last year is the most commonly accepted definition of stability (4) [7, 53]. Some authors recommend test grafting in order to ensure disease stability [5]. While likely unnecessary in all cases, this method should be considered when there is doubt about stability or the patient's history is not entirely reliable. This method consists of placing four to eight mini-punch grafts and then observing the treated area for 12 weeks; if repigmentation is observed beyond 1 mm from the border of the graft, the test is positive and is considered a marker of disease stability (4) [54]. The Vitiligo Disease Stability Activity Score (VIDA) is another subjective method of establishing disease stability that relies heavily on patient recall. Surgery is recommended only in patients with VIDA scores of −1 or 0 (stable for at least 1 year and/or presence of spontaneous repigmentation) (4) [55].

While some studies suggest better surgical outcomes in younger patients, there is no consensus regarding the minimum age for surgery (4) [43]. Therefore, this decision should be left to the physician's judgment, taking all aspects of the disease and its impact on the patient and family into consideration. Lastly, the need for concomitant medical therapy, especially NB-UVB phototherapy, should be emphasized to the patient, as this can help repigmentation postoperatively.

Impact of Patient Preference

The choice of surgical intervention should be individualized. It is important to consider the type of vitiligo, location/size of depigmented

patches, downtime, and cost-effectiveness of the procedure. Small depigmented areas may achieve successful repigmentation with mini-punch grafting and blister grafting. Punch grafting is considered to be the easiest, fastest, and least expensive treatment modality. Mini-punch and blister grafting are the fastest procedures, whereas non-cultured cellular grafting takes up to 4 h. This should be explained to the patient when discussing the different treatment options. In large recipient areas, interventions like split-thickness grafting and cellular grafting should be considered. Split-thickness grafting might leave a less cosmetically acceptable scar in the donor area, compared to cellular grafting performed with blisters. Donor areas will usually have post-inflammatory hyperpigmentation, which usually resolves in a matter of months to 1 year. All cellular grafting comes with higher cost, therefore, cost of therapy should be discussed when proposing different surgical interventions to the patient (4) [56].

Typical Treatment Plan

A 23-year-old South Asian female presents to your clinic with a 16-year history of segmental vitiligo of her right chin and neck. The patient has been treating the areas with topical tacrolimus 0.1% twice daily and NBUVB phototherapy three times per week for over 1 year without any noticeable improvement. She would like further evaluation and management and would like to pursue surgical treatment options. There is no family history of vitiligo and no personal history of keloid diathesis.

Physical exam reveals a depigmented patch on her right chin extending to the right anterior neck approximately 5 × 10 cm in area, and leukotrichia is present throughout most of the lesion. There are no signs of repigmentation or signs of disease activity such as confetti-like depigmentation, trichrome depigmentation, or Koebner phenomenon. There are no other lesions on other areas of the body.

Segmental vitiligo is highly responsive to surgical therapies and should be considered when a patient has recalcitrant vitiligo despite 1 year of nonsurgical therapies. Given the size of the lesion in this case, the most appropriate surgical options to consider are autologous cultured transplant procedures and non-cultured epidermal suspension grafting. The patient is informed of the costs, possible risks, and efficacy of both procedures and elects to undergo NCES grafting, as she prefers to only miss 1 day of work. The patient is scheduled to undergo NCES grafting in 2 weeks and is told to continue NBUVB up until the day of procedure. Because the patient has a history of multiple herpes labialis outbreaks per year, she is prescribed oral valacyclovir 500 mg PO twice daily to be initiated 1 day prior to the procedure.

On the day of the procedure, the patient is consented for treatment, and the possible risks are explained, such as infection, scarring, incomplete repigmentation, and hypo-/hyperpigmentation. The steps of the procedure are explained to the patient and all remaining questions are addressed. The lesion to be treated is outlined using a 1 cm transparent grid paper, and the number of blisters necessary to cover a 50 cm^2 recipient area is calculated. The donor site is properly cleansed and suction blistering is initiated on her left lateral thigh with a negative pressure system. While the blisters are forming, the recipient area is prepared by first anesthetizing with lidocaine and then denuded using erbium/YAG laser with enough passes to produce pinpoint bleeding at the recipient site. Once formed, the blisters are prepared for suspension with trypsin and centrifugation and then transplanted onto the recipient site.

The recipient and donor sites are dressed appropriately, and the patient is instructed to leave the recipient site dressing in place for 7 days. She is also instructed to re-initiate NBUVB phototherapy thrice weekly the day after removal of the dressing. The patient is told to follow-up in clinic in 3 months, with the expectation that 25% repigmentation would be seen at this time. At her 2-month follow-up appointment, only 20% repigmentation is seen; however, the patient admits to inconsistent phototherapy adherence. The patient is informed of the importance of phototherapy post-transplantation and is encouraged to increase adherence as final repigmentation results are not seen until approxi-

mately 1-year post-transplantation. At her 1-year follow-up, 75% repigmentation is observed. Further surgical options, such as further NCES grafting, SBEG, and mini-punch grafting, are offered to the patient in order to cover any residual depigmentation; however, the patient is satisfied with her current progress and does not desire any further intervention.

Safety

Blister Grafts

Suction blistering is a relatively safe procedure without any serious adverse events reported in the literature [13]. Hyperpigmentation of both the donor and recipient sites is the most common adverse event using this technique. Rates of hyperpigmentation at the recipient site vary between 16.5% and 38% [13]. Hyperpigmentation of the donor site can be expected in most patients as a result of post-inflammatory hyperpigmentation, but this typically resolves 6 months post-surgery (4) [57]. Other less common side effects and their reported frequency include Koebner phenomenon of the donor site (2%) [95% CI 1–4%], imperfect color match (4%) [95% CI 4–10%], infection (1%) [95% CI 0–3%], and scar/keloid formation (1%) [95% CI 0–3%] [14]. Importantly, suction blistering has been safely and successfully used to treat adolescents (4) [58].

Split-Thickness

Milia and partial loss of grafts are the two most common adverse effects with split-thickness grafting, occurring in 13% [95% CI, 8–18%] and 11% [95% CI, 7–15%] of patients, respectively. Scar formation at the donor site occurs in approximately 12% [95% CI, 34–47%] of patients. Hyperpigmentation at the donor site can also be seen [14].

Punch Graft Safety

Complications of this procedure are most likely to be cobblestone-like appearance, which occurs in 27–31.8% of treated lesions. This side effect can be ameliorated by using smaller grafts (1–1.2 mm) [17, 18]. Polka dot appearance and color mismatch can be seen in 43% and 34%, respectively [19]. Hemostasis is essential, since graft protrusion caused by excessive bleeding often leads to milia formation [20].

It is important to consider that the smaller the punch graft, the better the cosmetic result and the faster the repigmentation rate; while the bigger the punch, the longer the repigmentation time and the greater the risk of cobblestone-like scarring (4) [59]. Fortunately, 87% of patients feel the transplant has had a positive impact on their quality of life [24].

Autologous Cultured Melanocyte Transplantation

The risk of infection at the donor and recipient site is relatively low, ranging from 7.4% to 11%. This procedure usually does not cause milia or scarring [30]. The presence of the Koebner phenomenon has been reported after CMT in 4% of patients. Safety concerns of culture media and supplements used to cultivate the melanocytes is a main concern. High concentrations of mitogenic factors that are used for melanocyte culture accelerate the growth cycle, potentially increasing the risk of carcinogenesis of transplanted cells. However, studies using different concentrations of culture media have not shown gene mutations in specific signaling pathways. Long-term follow-up studies are needed to assess this risk (4) [60].

NCES/MKTP Grafting

Common side effects seen in a retrospective study were color mismatch (hypo-/hyperpigmentation) in 80%; however, this was found to be non-concerning in 79% of treated patients. Furthermore color mismatch tends to improve improves after sun exposure ($p = 0.012$). Only 7% experienced some loss of pigment at follow-up, all with generalized vitiligo [41]. Less common side effects include mild scarring in 3% [44].

Postoperative Care and Follow-Up

Once post-transplant would healing has occurred, patients should be seen at regular 3–4-month intervals for up to a year after transplantation to ensure they have not had recurrence of disease

and to ensure adherence of any postoperative treatments (e.g., phototherapy). Final results of the transplantation procedure are not seen until after about 1-year post-transplantation in most cases. At this point, patients should be reevaluated and considered for an additional transplantation procedure if necessary.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
General	
Disease stability of over 1 year is associated with higher success rates for vitiligo grafting procedures	C
Test grafting with mini-punch grafts should be considered when the status of disease stability is unclear	C
Patients with focal and segmental vitiligo have better outcomes compared to those with generalized vitiligo	C
Distal extremities have a poorer outcome compared to the head, neck, and trunk	C
Younger patients tend to have better results compared to older patients	C
Postoperative phototherapy is associated with higher rates of repigmentation	C
Continued repigmentation of the recipient site is seen for up to a year after transplantation in some cases	C
Repeat procedures or combination of procedures may be required in order to obtain complete repigmentation	C
SBEG	
The majority of patients have over 50% repigmentation of treated lesions	C
Regarding recipient sites, the neck and face have been shown to have the highest degree of pigment spread	C
SBEG has been safely and successfully used to treat adolescents	C
Mini-punch grafting	
The majority of treated patients have good to excellent repigmentation of treated lesions	C
Patients with darker skin types tend to have larger areas of recipient site graft spread	C
Smaller punch grafts are associated with better cosmetic results	C
Split-thickness skin grafts	
Success rate is high with split-thickness skin grafts	C
Side effects include scarring and color mismatch	C
Cultured melanocyte transplants	
While usually successful, CMT requires a well-equipped lab and 1–3 weeks to prepare the cells prior to transplantation	C
Long-term safety concerns may be present due to additives in the culture medium	C
NCES/MKTP grafting	
The majority of treated patients have good to excellent repigmentation of treated lesions	C
Maximum repigmentation occurs at a mean of 10 months after surgery	C
Relative efficacy of procedures	
NCES grafting is more efficacious than SBEG grafting	C
SBEG grafting has lower risk of adverse effects compared to punch-grafting	C
Punch grafting is more efficacious than SBEG for lip vitiligo	C

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Self-Assessment Questions

1. True or False: PUVASOL and NB-UVB phototherapy are contraindicated in patients after undergoing mini-punch and epidermal blister grafting, due to a lower graft survival rate.
2. All of the following patients are good candidates for surgical procedures, EXCEPT:
   (a) A 10-year-old South Asian female, with segmental vitiligo in her left trunk diagnosed at age 5, who has tried topical steroids, tacrolimus, and NB-UVB phototherapy for 3 years.
   (b) A 30-year-old Hispanic male, with a depigmented 5 cm patch on his jawline, who has tried NB-UVB phototherapy for 3 years, which has resulted in 75% repigmentation.
   (c) An 18-year-old Caucasian male, with depigmented macules and patches on his face, chest, knees, and arms, which have responded to topical steroid and phototherapy achieving a 50–75% repigmentation in 14 months. He is interested in a surgical procedure only his forehead and cheek since those lesions are more visible.
   (d) A 29-year-old Caucasian female, with depigmented patches on her face and trunk; she has treated the areas with NB-UVB phototherapy and tacrolimus for 2 years and is very compliant with treatment. She denies any new lesions. On physical exam she has generalized vitiligo, with 4% BSA involvement, trichrome, and confetti-like lesions.
   (e) A 40-year-old African-American female with a depigmented patch on her left forehead since age 10. She states she tried phototherapy for 1 year but she did not see any repigmentation over 3 years ago. On physical exam you observe leukotrichia.
3. The appropriate depth that should be reached when preparing the recipient defect for punch grafts to minimize adverse effects is:
   (a) papillary dermis
   (b) upper reticular dermis
   (c) lower reticular dermis
   (d) subcutaneous tissue
   (e) none of the above
4. Punch grafting testing is a good method to determine disease stability when there is uncertainty. Patients are considered "stable" if there is a 1 mm spread of pigment at ____ post-transplant.
   (a) 6 weeks
   (b) 12 weeks
   (c) 20 weeks
   (d) 30 weeks
   (e) 40 weeks
5. You perform a non-cultured epidermal suspension graft in a 30-year-old South Asian female who presented to your clinic for segmental vitiligo on the chest. At her 6-month follow-up visit, you observe she has 40% repigmentation. The patient is very anxious. What would be your next approach?
   (a) Schedule her for a second NCES grafting on your next available date
   (b) Suggest performing a mini-punch grafting in the rest of the area, since it has been shown to have higher success rates than NCES grafting
   (c) Encourage the patient to continue her phototherapy and reassure her that improvement is usually until 1 year after the procedure is performed
   (d) Discuss with the patient she will not be a candidate for any surgical procedure at any point
   (e) Discuss with the patient the transplant was a failure since we except at a least 90% repigmentation by 6 months

Answers

1. False: Phototherapy post-transplantation have been shown to increase the repigmentation rate in patients with vitiligo compared to the surgical procedure alone.
2. d: The patient has active disease, due to the presence of trichrome and confetti-like lesions; therefore she is not a candidate for any surgical procedure.
3. b: The donor punch should reach the subcutaneous tissue to avoid a cobblestone effect postsurgery.
4. d: When in doubt regarding the presence of active disease, test grafting can be performed. The test is positive and considered a marker of disease stability if after placing four to eight punch grafts, repigmentation beyond 1 mm from the border of the graft at 12 weeks is observed.
5. c: Studies have shown that repigmentation occurs up to 10 months after NCES grafting. A second procedure could be considered and discussed with the patient after 1 year post-transplantation.

Morphea and Scleroderma

56

Rachel Kyllo and Martha Laurin Council

Abstract

Morphea and scleroderma are a spectrum of autoimmune connective tissue disorders hallmarked by tissue fibrosis. Morphea is localized to the skin, subcutaneous tissues, and occasionally, deeper, directly underlying structures such as muscle and bone. In contrast, scleroderma is characterized by systemic involvement, including the vasculature and internal organs (1a) (Fett, Clin Dermatol 31:432–437, 2013). Treatment largely depends upon the extent of disease, with minor cases of morphea requiring observation and systemic sclerosis requiring potent immunosuppressive medications. Although an exhaustive discussion of medical therapies for this spectrum of diseases is beyond the scope of this chapter, surgeries and laser therapy are important components of comprehensive care of these patients. The cosmetic and functional sequelae of morphea and scleroderma can be extensive, and the procedural dermatologist is in a unique position to reverse some of the manifestations of these debilitating diseases.

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Keywords

Morphea · En coup de sabre · Hemifacial atrophy · Scleroderma · Raynaud's Calcinosis · Telangiectasias

Introduction and Epidemiology

Morphea and scleroderma are a spectrum of autoimmune connective tissue disorders hallmarked by tissue fibrosis. Morphea is localized to the skin, subcutaneous tissues, and occasionally, deeper, directly underlying structures such as muscle and bone. In contrast, scleroderma is characterized by systemic involvement, including the vasculature and internal organs (1a) [1]. Treatment largely depends upon the extent of disease, with minor cases of morphea requiring observation and systemic sclerosis requiring potent immunosuppressive medications. Although an exhaustive discussion of medical therapies for this spectrum of diseases is beyond the scope of this chapter, surgeries and laser therapy are important components of comprehensive care of these patients. The cosmetic and functional sequelae of morphea and scleroderma can be extensive, and the procedural dermatologist is in a unique position to reverse some of the manifestations of these debilitating diseases.

Morphea is a distinct clinical entity characterized by sclerosis of the dermis and subcutaneous fat. Rarely, deeper tissues such as fascia,

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muscle, tendon, or bone, directly beneath the involved skin and subcutaneous tissue, may also be involved. Several clinical variants of morphea exist (2a) [2, 3]. The most common type is plaque-type morphea, featuring an erythematous, indurated plaque that becomes sclerotic over time, often with resulting post-inflammatory hyperpigmentation. Guttate morphea is characterized by smaller, more numerous lesions, otherwise similar in morphology to plaque morphea. Deep morphea has involvement of the deep dermis and subcutaneous fat, sometimes resulting in dystrophic calcification. Nodular morphea presents with keloidal papules and plaques. Linear morphea often involves the underlying fascia, tendons, and muscles, which can result in painful joint contractures and immobilization. Morphea *en coup de sabre* is a variant of linear morphea involving the forehead (Fig. 56.1); Parry-Romberg syndrome is a severe variant that results in hemifacial atrophy and significant cosmetic disfigurement.

The estimated prevalence of morphea in the United States is 2.7 per 100,000 population (2b) [4]. There is a female predominance of approximately 3:1 (2a, 2b) [3, 5]. Children and adults are affected at equal frequencies; the most common variant in adults is plaque-type morphea, while linear morphea is the most common presentation in children (2b) [4–7].

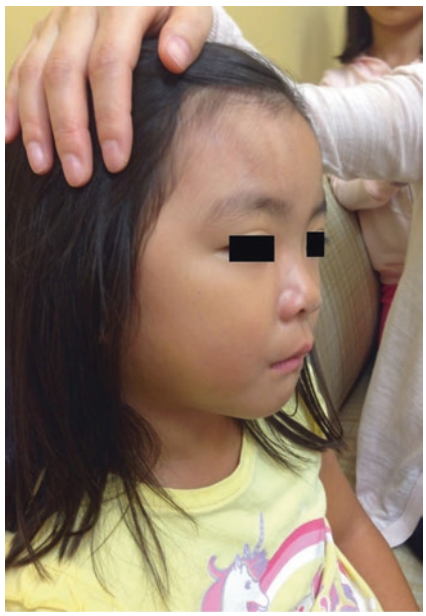

Fig. 56.1 En coup de sabre morphea. (Image courtesy of Dr. Lesley Lawley)

Scleroderma has a worldwide distribution and can affect all ages and races (2b, 1a) [8, 9]. The prevalence of scleroderma in North America is estimated at between 3 and 24 per 100,000 persons [9]. There is a strong predilection for the female gender; the incidence in women is approximately four times higher than in men (1a) [10]. The average age of onset is in the 4th–6th decades [9].

Scleroderma is divided into two clinical categories: limited systemic sclerosis, characterized by fibrosis limited to the face and peripheral extremities, and diffuse systemic sclerosis, in which fibrosis of the skin spreads to involve proximal extremities and the trunk (2a, 2b) [11, 12]. CREST syndrome is a variant of limited scleroderma characterized by calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (Fig. 56.2). Most patients with scleroderma (90%) will have a positive antinuclear antibody (ANA); other associated autoantibodies include the anti-centromere antibody, which is associated with CREST syndrome, and the anti-topoisomerase antibody, which is associated with diffuse scleroderma (1a, 1b, 1b) [13–15].

Scleroderma has numerous cutaneous manifestations (1a) [16–18]. As fibrosis of the peripheral extremity progresses, patients often develop painful digital ulcerations. Dyspigmentation is common, with both hyperpigmentation and hypopigmentation possible. Mat-like telangiectasias develop on the face, lips, and palms, which are cosmetically displeasing. Dystrophic calcification is possible, particularly on the digits. Scleroderma is one of the leading causes of secondary Raynaud's phenomenon, which can have a dramatic impact on patient quality of life (3a) [19].

Patients with scleroderma are best managed in conjunction with a multidisciplinary team of rheumatologists, pulmonologists, gastroenterologists, and nephrologists. The leading cause of mortality from systemic sclerosis is pulmonary disease [9]. Internal manifestations of sclero-

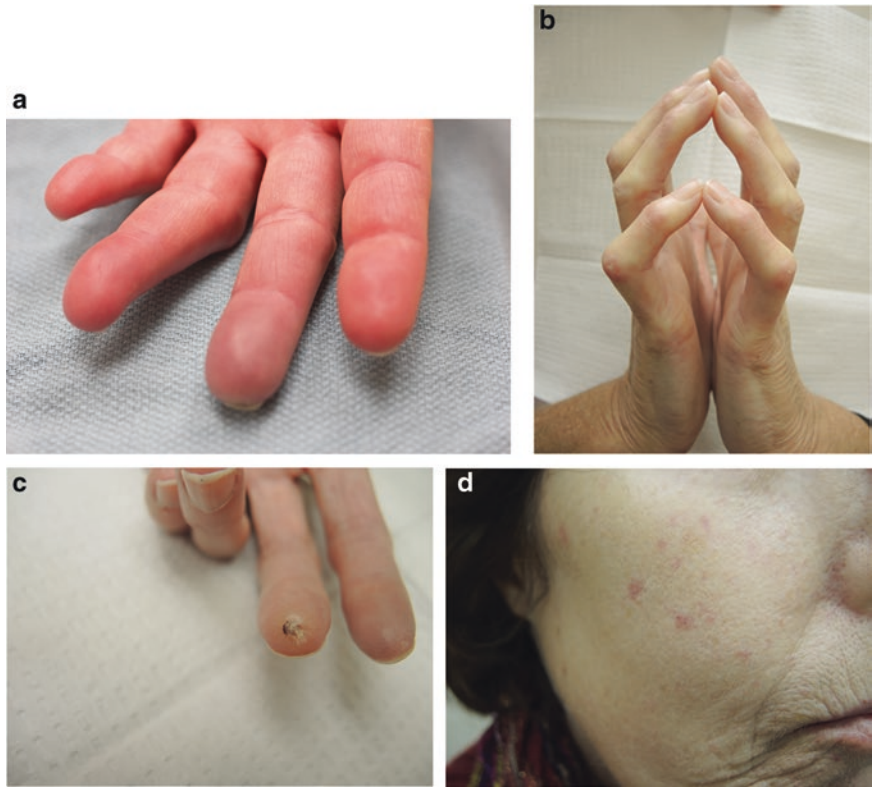

Fig. 56.2 Cutaneous manifestations of scleroderma. (**a**) Digital cyanosis upon exposure to cold, secondary to Raynaud's, (**b**) sclerodactyly, (**c**) digital calcinosis cutis, and (**d**) facial telangiectasias. (Image 2A courtesy of Dr. Eva Hurst. Images 2B-D courtesy of Dr. Caroline Mann)

derma are myriad and include pulmonary arterial hypertension, pulmonary interstitial fibrosis, esophageal dysmotility and reflux, scleroderma renal crisis, and congestive heart failure [16, 17]. Patients are often placed on immunosuppressive medications to prevent progression of internal organ involvement.

Treatment Considerations: Morphea

First-line treatments for plaque morphea include topical and intralesional corticosteroids, topical calcineurin inhibitors, and phototherapy (3a) [20]. Linear morphea tends to have an aggressive clinical course, and treatment with pulsed systemic corticosteroids as well as methotrexate appears to reduce the frequency of late-stage sequelae such as joint contractures, which lead to limited range of motion and functional disability. Importantly, variants of linear morphea that affect the face (morphea en coup de sabre and hemifacial atrophy) can dramatically affect facial symmetry. The resultant cosmetic defects can be pronounced, causing psychosocial distress to affected patients.

Morphea en coup de sabre affects the forehead or paramedian scalp, often leaving depressed linear scars. Various methods to cosmetically restore the resultant soft tissue deficit have been reported, including hyaluronic acid (HA) filler (4) [21, 22], polymethylmethacrylate (PMMA) (4) [23], polyacrylamide hydrogel (4) [24], and autologous fat transplantation (4) [25–27]. Progressive hemifacial atrophy (also known as Parry-Romberg syndrome) often involves the deeper soft tissues, cartilage, and bone, leading

to pronounced facial asymmetry. Surgical techniques that have been used to correct this asymmetry include autologous fat transplantation, bone and cartilage grafts, osteotomies with bone repositioning, pedicled and free flaps, and hair transplantation.

Practitioners must recognize the theoretical risk that injection of filler or other material into the area of a quiescent morphea plaque could result in reactivation of the patient's morphea. The typical time course of linear morphea involves a period of intense activity for 3–5 years, after which the disease typically becomes quiescent. However, the time course of the disease is variable, and reactivation has been reported decades after initial diagnosis (2b) [28]. Ideally, clinicians wait to perform any cosmetic restoration on patients with linear morphea until the disease has been quiescent (asymptomatic with no progression and no changes in size or color) for a period of at least 3–5 years. Regardless, patients should be counseled regarding the theoretical risks of reactivation of their underlying morphea prior to cosmetic restoration attempts.

Hyaluronic acid fillers are United States Food and Drug Administration (FDA) approved for the correction of facial rhytides and have been used for decades with an acceptable safety profile. Rare complications of hyaluronic acid filler injection include tissue necrosis or embolization due to inappropriate injection of filler into blood vessels, allergic reactions, and granuloma formation. Injection of hyaluronic acid has been utilized in multiple case reports to fill the atrophic defects left by morphea en coup de sabre and hemifacial atrophy (4) [21, 22, 29].

Notably, these procedures involve injection of hyaluronic acid into the forehead and medial cheek, where most clinicians have little experience injecting filler. One should be especially cautious not to inject in or near blood vessels which could result in tissue necrosis. In general, physicians performing hyaluronic acid filler injection in unfamiliar areas should aspirate before injecting to ensure appropriate needle positioning (outside of any blood vessels), and low volumes should be used (1.0 cc or less at a time) to avoid these complications. With these precautions, hyaluronic acid injection is a noninvasive option for replacing the soft tissue defects left by morphea en coup de sabre and hemifacial atrophy. Appropriate pretreatment counseling regarding the theoretical risk of reactivation of their underlying morphea is an absolute necessity. Patients should also be counseled regarding expected posttreatment bruising and edema and the probable need for repeat treatments as the hyaluronic acid is dissolved over time.

Alternatives to hyaluronic acid filler injection include permanent fillers such as polymethylacrylate and polyacrylamide hydrogel. Polyacrylamide and polymethylacrylate are permanent fillers that have primarily been used to treat Human Immunodeficiency Virus-associated lipoatrophy. Polyacrylamide filler has been used successfully in the treatment of progressive hemifacial atrophy in a single case report [24], while polymethylmethacrylate has been used successfully in the treatment of morphea en coup de sabre of the forehead in a single case report [23]. Only experienced injectors should consider use of permanent filler, as injection techniques must be impeccable to avoid overcorrection.

Autologous fat grafting is another procedure that has been used for the treatment of linear morphea (4, 4, 4, 4, 3b) [25–27, 30, 31]. The fat graft is typically harvested from an area with high adipocyte density (such as the abdomen, hip, or buttocks). The adipocytes can either be injected directly into the area of atrophy [26, 31] or the graft can be harvested en bloc and inserted into a pocket created by a linear incision along the atrophic defect [27, 31]. Overcorrection of the defect is recommended, as the graft will flatten naturally with resorption over time. Injected fat grafts tend to require multiple treatments over time to achieve an acceptable cosmetic result [25, 26, 31]. One study involving 20 patients with linear scleroderma of the face showed 51–75% long-term correction of forehead lesions after an average of 4.2 treatments [31].

Advantages of autologous fat grafting include the wide availability of donor tissue in most individuals, and the biocompatibility of the graft, with decreased risk of granulomatous or allergic reactions compared to injection of foreign materials. As with hyaluronic acid injection, rare reports of tissue necrosis or embolization of injected

material to cerebral or retinal vessels have been reported after autologous fat injection (3a) [32]. Patients should also be counseled regarding expected postoperative bruising, edema, scarring (if the en bloc technique is used), and risk for infection. Overall, autologous fat grafting appears to be an acceptable option for the restoration of atrophy associated with linear morphea of the face. Existing evidence for the procedure is limited to case reports and case series. No studies comparing hyaluronic acid filler with autologous fat grafting for this indication exist.

Patients with severe disfigurement due to progressive hemifacial atrophy or larger defects of morphea en coup de sabre may require more aggressive plastic surgery under general anesthesia for repair. Localized pedicled flaps or free flaps can be used to replace the soft tissue volume of the affected side of the face (4) [33–35]. A recent systematic review comparing free flaps, localized pedicled flaps, and structural autologous fat grafting found that free flaps were superior, with the lowest complication rate (8.4% compared to 12.4% for localized flaps) and reoperative rate (0.7% compared to 7.1% for fat grafting) (2a) [36].

Osteotomies with subsequent bone repositioning may be necessary in cases with significant involvement of the facial bones. Autologous bone grafts (4) [37], demineralized bone matrix [33], and calcium phosphate hydroxyapatite cement (4) [38] have been used when bony repositioning is insufficient to fill the defect. Defects of the nasal ala may be repaired using composite grafts, and scalp grafts can be used to replace the hair of the eyebrow [37]. In general, preoperative imaging with a computerized tomography (CT) scan of the face to delineate the extent of bone and muscle involvement is prudent.

Often, extensive plastic surgery is carried out over the course of multiple operations, with less invasive techniques such as filler or autologous fat grafting used to perfect the final cosmetic result only after the patient has fully healed from the operation. As expected, major facial plastic surgeries have increased risks compared to noninvasive techniques. Patients should be counseled regarding the possibilities for postoperative bleeding or hematoma, wound infection, flap necrosis or atrophy, nerve damage, and hardware failure. A recent report including 43 patients who underwent plastic surgery for progressive hemifacial atrophy reported a 6% complication rate (3b) [39].

Treatment Considerations: Scleroderma

Raynaud's Phenomenon

Raynaud's phenomenon is a painful condition in which vasoconstriction leads to reduced blood flow to the distal fingers or toes, causing characteristic color changes from pallor (white), to cyanosis (blue), to rubor (red) as the episode resolves. Scleroderma is the leading cause of secondary Raynaud's phenomenon, and more than 95% of scleroderma patients suffer from Raynaud's (1a, 1b, 1b) [40–42]. The pathophysiology of Raynaud's phenomenon is abnormal vascular thermoregulatory control related to hyperactivation of the sympathetic nervous system and endothelial cell dysfunction (1a) [43]. Raynaud's phenomenon is typically treated with cold avoidance and oral calcium channel blockers such as nifedipine (1a) [44]. Second-line therapies include phosphodiesterase type 5 inhibitors (1a) [45] and topical nitrates.

Surgical intervention can be considered for cases of treatment-resistant Raynaud's phenomenon with recalcitrant digital ulcers or digital ischemia. Chemical sympathectomy, achieved by injection of local anesthetic in the proximity of the affected sympathetic ganglia, can induce relief of symptoms (3b, 4, 4) [46–48]. Unfortunately, this may result in compensatory decreased blood flow on the contralateral side, and symptomatic relief is only temporary [48].

Endoscopic thoracic sympathectomy may be used to surgically disrupt the sympathetic chain between the T2 and T4 levels and reduce sympathetic hyperactivation to the hands. A 2011 meta-analysis of thoracic sympathectomy of 15 non-randomized trials found that thoracic sympathectomy resulted in long-term benefit for 58%

of patients with Raynaud's related to underlying scleroderma (2a) [49]. Digital ulcer healing occurred after thoracic sympathectomy in 81% of patients. There is substantial risk of postoperative compensatory sweating (between 45% and 99% reported risk) or ipsilateral Horner syndrome (up to 7% of patients). Overall, thoracic sympathectomy is an invasive surgical procedure with significant risks and should only be undertaken in refractory cases that have exhausted all other treatment options at significant risk for digit auto-amputation.

A less invasive approach is local digital sympathectomy, in which the nerves providing sympathetic innervation are stripped from the arteries providing blood flow to the affected digits. This procedure is not associated with risk for Horner syndrome or compensatory sweating (4) [50]. A retrospective review found that 32/38 (84%) of patients treated with digital sympathectomy for digital ulcers associated with scleroderma had ulcer healing after the procedure (2a) [51]. A 2015 clinical case series of 31 cases of digital sympathectomy found that 86% of patients experienced relief of ischemic pain, and 83% of patients had decreased incidence of digital ulceration after 5 years of postoperative follow-up (4) [52]. Digital sympathectomy is a less invasive procedure with fewer risks than thoracic sympathectomy, although 37% of patients have reported postoperative complications [50] (level 4, grade C).

Recently, several case reports and case series have shown encouraging results on the use of injected botulinum toxin-A (BTX-A) in Raynaud's phenomenon. BTX-A has been shown in animal studies to block sympathetic nerve conduction, providing a mechanistic explanation for its utility in reducing vasoconstriction in patients suffering from Raynaud's (5) [53]. Typically, 100 units of BTX-A is injected locally into the hand, with injections concentrated on neurovascular bundles of digits and the superficial palmar arch (3b) [54]. A 2016 review of 11 case series found that between 85% and 100% of patients reported decreased pain after BTX-A injection, with the majority of patients experiencing immediate relief (2a) [55]. The duration of treatment effect averaged to 4–6 months (3b, 2a, 4, 2b, 2b, 2b) [54, 56–59]. Healing of digital ulcers was noted in 48–100% of patients.

BTX-A has an excellent safety profile, with risk for allergy or anaphylaxis quite low. The main adverse event associated with BTX-A injection in these areas is weakness of the intrinsic muscles of the hand, which is typically transient and mild. Therefore, BTX-A may be a safe and effective second-line treatment for secondary Raynaud's phenomenon, with improved pain and healing of digital ulcerations with minimal side effects. BTX-A injection is less invasive than surgical sympathectomy, and its effects are transient. A blinded, randomized controlled trial on the efficacy of BTX-A injection in secondary Raynaud's is needed.

Calcinosis Cutis

Calcinosis cutis is characterized by dystrophic deposition of calcium in the soft tissues. Calcinosis is a frequent occurrence in patients with scleroderma and is associated with significant morbidity due to pain, overlying ulceration, and subsequent functional disability. In addition, the calcium deposits are often visible and may be cosmetically displeasing to some patients. Medical treatment options are disappointing. Treatment of calcinosis with low-dose warfarin, bisphosphonates, diltiazem, minocycline, and rituximab has been reported in the literature, but treatment effects are minimal, particularly for long-standing or larger lesions (4) [60, 61]. Surgical excision or curettage of calcinosis cutis is effective for both small and large lesions and is the treatment of choice for idiopathic calcinosis cutis [61]. Surgical excision has been used successfully in the treatment of calcinosis secondary to scleroderma (4) [62]. However, patients with scleroderma frequently have issues with prolonged wound healing, making surgical excision a less attractive option in these patients (2a) [63].

Carbon dioxide (CO_2) laser has also been used as an ablative therapy to vaporize calcinosis

cutis in scleroderma (4, 3b) [64, 65]. The largest case series reported at least moderate improvement in 17/21 (81%) lesions treated with CO_2 laser, with a recurrence rate of 10% after median follow-up of 20 months [65]. The main risk associated with CO_2 laser treatment is postoperative infection, and patients can be placed on prophylactic antibiotics posttreatment for prophylaxis if desired [64]. Scleroderma patients treated with ablative CO_2 laser may experience delayed wound healing as with other surgical treatments for calcinosis. CO_2 laser is likely an effective therapy for calcinosis cutis and can be considered for patients with calcinosis who prefer to avoid surgical excision or curettage of lesions.

Extracorporeal shock wave lithotripsy (ESWL), in which acoustic shock waves are used to break up calcium deposits, has also been reported as a treatment for calcinosis cutis in one case report and one small cohort (4, 2b) [66, 67]. In the largest case series reported, patients were treated with three 20-min sessions of ESWL to the affected areas of the skin. Pain reduction was seen in five of seven patients, and six of nine treated lesions showed reduced surface area after three treatment sessions, while no patients experienced an adverse effect [67]. Contraindications to ESWL include pregnancy, chronic renal insufficiency, and presence of a pacemaker. ESWL is more effective for calcinosis lesions that have already ulcerated [60]. ESWL appears to be associated with decreased pain compared to surgical procedures; however, it is likely less effective. Studies directly comparing ESWL to ablative therapies will need to be done before the procedure can be recommended routinely over surgical procedures.

Telangiectasias

The mat-like telangiectasias of scleroderma commonly affect cosmetically sensitive areas of the face, neck, upper trunk, and distal upper extremities. Many patients find the appearance of their telangiectasias cosmetically disfiguring. The 585 nm pulsed dye laser (PDL) was first reported as a treatment for the telangiectasias associated with scleroderma in 1996 (2b) [68]. PDL works by inducing selective photothermolysis of the ectatic vessels that make up the telangiectasia, as the oxyhemoglobin within the vessel wall preferentially absorbs that wavelength of light. In general, patients are treated with a 585 or 595 nm pulsed dye laser at fluences of 5.5–7 J/cm^2 with a 5–7 mm spot size. Each lesion is treated with 1–2 pulses to a treatment end point of mild purpura (3b) [69].

More recently, intense pulsed light (IPL) has been described as a treatment modality for telangiectasias associated with scleroderma. IPL emits noncoherent, broad-spectrum white light, which induces some degree of photothermolysis of vessels via absorption of the radiation throughout the entire depth of the vessel (2b) [70]. In general, patients treated with IPL receive 1–2 passes of intense pulsed light (550–1100 nm wavelength) at a fluence of 24–36 J/cm^2 after skin preparation with ultrasound gel to facilitate light-tissue coupling [70]. Fluence and pulse duration should be selected based on patient's skin type, with more conservative (lower fluence) values chosen for initial treatment in darker skin types. Both PDL and IPL have been reported as successful treatment modalities for telangiectasias associated with scleroderma (2b, 3b, 2b, 1b) [68–71].

Posttreatment purpura and edema are expected side effects after PDL treatment. Scarring is a very rare but cosmetically disfiguring complication. Intense pulsed light has fewer side effects but may be less effective. A within-subject randomized trial in which patients received IPL to one side of the face and PDL to the other demonstrated significant improvement with decreased number of telangiectasias bilaterally. PDL resulted in greater clinical improvement but with greater adverse effects (bruising) [71].

Histopathologic analysis of skin samples has shown that, relative to normal skin controls, the telangiectasias of scleroderma patients have

thicker vessel walls and collagen fibers. The telangiectasias associated with scleroderma have been shown to be more resistant to standard laser treatments used for essential telangiectasias, requiring an average of twofold the number of treatments to clearance of individual lesions [69]. Patients should therefore be counseled pretreatment regarding expectations and the likely need for repeat treatments. Overall, both PDL and IPL appear to be effective treatments for telangiectasias associated with scleroderma (level 2b, moderate). PDL appears to be more effective but with greater risk for adverse effects such as bruising and complications.

Conclusions

In summary, morphea and scleroderma encompass a wide spectrum of diseases with several dermatologic manifestations. Although some patients will be treated with observation, topical therapy, or systemic therapy, dermatologic surgery plays a role in managing the characteristic cutaneous signs of disease. The rare nature of these diseases and the continued advances in technology assure that new therapies will continue to emerge for these difficult conditions.

Evidence-based procedural correction of morphea and manifestations of systemic sclerosis

Dermatologic condition	Procedural treatment (quality of evidence)
Morphea	
En coup de sabre	HA filler (moderate evidence) PMMA (low evidence) Polyacrylamide hydrogel (low evidence) Autologous fat (moderate evidence)
Hemifacial atrophy	Surgery, including fat transfer, bone and cartilage grafts, hair transplant, and local tissue flaps (moderate evidence)
Systemic sclerosis	
Raynaud's	Chemical sympathectomy (low evidence) Endoscopic thoracic sympathectomy (low evidence) Local digital sympathectomy (low evidence) Botulinum toxin (moderate evidence)
Calcinosis cutis	Surgical excision or curettage (low evidence) CO_2 laser (low evidence) Extracorporeal shock-wave lithotripsy (low evidence)
Telangiectasias	Pulsed dye laser (moderate evidence) Intense pulsed light (moderate evidence)

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Self-Assessment Questions

1. A 50-year-old woman with scleroderma and secondary Raynaud's syndrome is considering botulinum toxin-A (BTX-A) injection for treatment of her Raynaud's. Which of the following regarding BTX-A treatment in this situation is not true?
   (a) BTX-A treatment will often speed healing of digital ulcers.
   (b) A typical treatment for Raynaud's of the hands involves injection of 100 units of BTX-A.
   (c) Repeated BTX-A injections are usually necessary to maintain treatment effect.
   (d) Animal studies have shown that BTX-A blocks parasympathetic nerve conduction, which provides a pathophysiological explanation for its use in Raynaud's.
   (e) Patients should be warned regarding possible weakness of hand intrinsic muscles after injection of BTX-A.

2. A 55-year-old woman with diffuse scleroderma presents with painful calcinosis cutis of the right third digit. The calcium deposit measures approximately 0.8 cm in size. She is interested in the simplest, most effective treatment option. Although you discuss various medical and surgical interventions with her, what procedure will you ultimately recommend for the treatment of this lesion?
   (a) Medical therapy with warfarin
   (b) CO_2 ablative laser
   (c) Simple excision
   (d) Extracorporeal shock wave lithotripsy

3. A 36-year-old woman with a 10-year history of CREST syndrome presents to your office. Physical examination is notable for scattered mat-like telangiectasias of the face, upper chest, and neck. She would like to discuss options for laser removal of these telangiectasias. She is interested in obtaining maximum clinical benefit with fewer treatments if possible and is not bothered by postoperative bruising. What is the best laser treatment option for her?
   (a) Intense pulsed light
   (b) 585 nm pulsed dye laser
   (c) CO_2 ablative laser
   (d) Erbium-YAG resurfacing laser

4. A 14-year-old boy with a 2-year history of morphea en coup de sabre affecting his left paramedian forehead presents for discussion of treatment options to fill the resultant atrophic defect. What treatment do you recommend at this point?
   (a) Medical treatment alone
   (b) Structural fat grafting
   (c) Hyaluronic acid filler injection
   (d) Local pedicled flap
   (e) Free flap

5. A 26-year-old woman with a 15-year history of progressive hemifacial atrophy presents to discuss treatment options. She has already undergone multiple facial plastic surgeries to correct the underlying bony deformities and is interested in discussing less invasive treatment options to smooth out her facial contours. She wants "a natural look," with no overcorrection, and does not mind coming in for repeat treatments. She does not want another procedure that would leave her with a scar. Which of the below treatments would you recommend?
   (a) Hyaluronic acid filler
   (b) Polymethylacrylate filler
   (c) En bloc autologous fat grafting
   (d) Local pedicled flap
   (e) Free flap
   (f) Observation

Answers

1. d: Botulinum toxin-A has been shown in animal studies to block sympathetic nerve conduction, not parasympathetic nerve conduction. The remaining answers are correct.
2. c: Simple excision remains the most appropriate treatment for a single, large lesion of calcinosis cutis. Medical therapies are not particularly effective for the treatment of calcinosis cutis. ESWL requires multiple treatments and is more effective for smaller lesions that have already ulcerated. CO_2 ablative laser could be considered in this situation but remains relatively untested for larger lesions of calcinosis cutis; also, this particular patient is interested in the simplest treatment option.
3. b: The 585 nm pulsed dye laser and intense pulsed light have both been reported as effective treatment options for the telangiectasias associated with scleroderma. PDL is slightly superior to IPL in efficacy, although PDL is associated with higher rates of postoperative edema and ecchymosis.
4. a: In general, patients undergoing elective repair of cosmetic defects for linear morphea of the face should have quiescent disease for at least 3 years prior to repair. This patient should have methotrexate +/− pulsed dose corticosteroids, pending a discussion with her rheumatologist and/or general dermatologist, and be re-evaluated 3–5 years after disease quiescence.
5. a: Hyaluronic acid filler is the best treatment option for this patient. Her desire to avoid overcorrections makes her a poor candidate for permanent filler such as polymethylacrylate, and her desire to avoid additional scars makes her a poor candidate for en bloc autologous fat grafting. Local pedicled or free flaps are invasive procedures that would be too aggressive for the subtle facial contouring that the patient is requesting. She is more than 5 years out from disease quiescence, and observation alone would be inappropriate.

Port-Wine Birthmark and Hemangioma

57

Leah K. Spring and Andrew C. Krakowski

Abstract

Port-wine birthmarks (PWB) and infantile hemangiomas (IH) typically present, respectively, at birth to within weeks of birth and represent two of the most common types of vascular anomalies in children. Without treatment, port-wine birthmarks follow an expected evolution of hypertrophic change and bleb development (usually around the third decade of life) with associated physical and psychosocial comorbidities. Conversely, infantile hemangiomas typically follow a process of predictable involution that begins at approximately 1 year of life; despite the overall positive clinical outcome of most infantile hemangiomas, permanent sequelae such as telangiectasia, atrophic wrinkling, and redundant skin with fibro-fatty residua may be observed in up to 50% of patients after "spontaneous resolution," a consideration that should be included in long-term prognosis and patient expectation discussions. Myriad medical and procedural treatment options exist for both PWB and IH and their associated complications, and patients may seek intervention at any age (i.e., infant to adult). It is therefore incumbent on all dermatologists and plastic surgeons to keep abreast of evolving treatment technologies and therapeutic approaches in order to deliver optimal clinical outcomes. This chapter reviews the published evidence regarding clinical evaluation and efficacy of available procedural interventions for PWB and IH and offers a practical approach based on that data.

Keywords

Port-wine birthmarks · Port-wine stain
Hemangioma · Laser · Pulsed dye · PDL
Nd:YAG · Alexandrite

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Introduction

Two major categories of vascular anomalies are recognized by the International Society for the Study of Vascular Anomalies: vascular malformations

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and vascular tumors. Cutaneous capillary malformations (commonly referred to as *port-wine stains* or, preferably from a patient advocacy perspective, as *port-wine birthmarks*) represent a relatively common pediatric type of vascular malformation. Infantile hemangiomas, quite distinctly, are the most common benign vascular tumor of infancy [1].

Port-Wine Birthmark

Port-wine birthmarks (PWB) are congenital low-flow vascular malformations caused by a somatic activating mutation in GNAQ, occurring in an estimated 0.3–0.5% of newborns [2, 3]. Males and females are affected equally, and there is no difference in prevalence between premature and full-term infants. The overwhelming majority of PWB are present at birth (i.e., congenital), occur on the head and neck, and grow proportionately with the child; very rarely, however, this type of vascular malformation can be acquired following trauma. Though facial PWB have been classically described as overlying the trigeminal nerve (ophthalmic, maxillary, and mandibular regions), recent evidence supports distribution following the embryonic vasculature of the face [2].

A rare and serious disorder associated with PWB—and associated with the same mutation in GNAQ—is Sturge-Weber syndrome (SWS), which may manifest clinically with seizures, mental retardation, glaucoma, hemianopsia, and hemiparesis [2, 3]. Forehead and eye involvement of a PWB confers risk of SWS. An ophthalmologic examination for any infant with eyelid involvement and neuroimaging (brain MRI with gadolinium contrast) for those with specific signs or symptoms or extensive bilateral, hemifacial, or median forehead PWB may be recommended [2, 4].

Other congenital syndromes associated with PWB, bony overgrowth, and soft tissue hypertrophy include Klippel-Trenaunay and Parkes-Weber. Cobb syndrome is described as PWB with underlying arteriovenous malformations of the spinal cord.

Left untreated, a PWB follows a predictable evolution attributable to chronic progressive vascular ectasia. Well-defined pink to red patches gradually darken to violaceous or deep purple. These lesions may be associated with the Meyerson phenomenon, an inflammatory component characterized by scaling, oozing, and crusting resembling an overlying eczematous dermatitis. More worrisome are the hypertrophic changes that include diffuse thickening and development of nodules or "blebs," most commonly in the V2 distribution; these findings typically begin to present around the third decade of life, eventually affecting 65–71% of all patients over the age of 50 [5] (Fig. 57.1). Early-onset hypertrophy (before the age of 15) has been reported and often accompanies soft tissue and bony overgrowth. In these individuals, the lips are the most frequently affected site, and odontologic problems (enlarge-

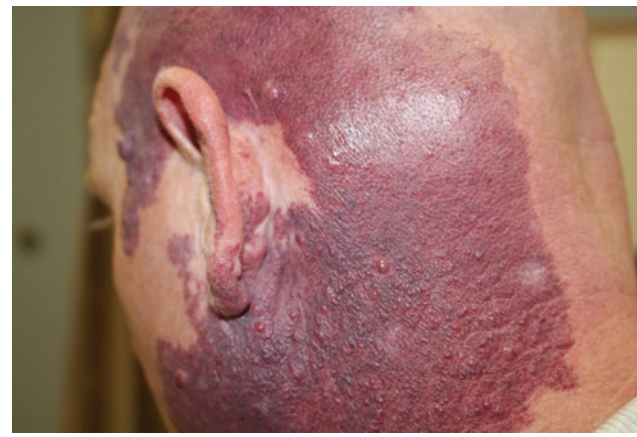

Fig. 57.1 Port-wine birthmark with blebs on the lateral scalp, neck, and face. Treatment with PDL 595 nm has begun (with mild lightening) on the upper posterior third of the lesion

ment of the maxilla causing open bite deformity) have been reported in 40% of the cases [6, 7].

Hypertrophic development in PWB is associated with disfigurement of normal tissue architecture, an increased risk of spontaneous bleeding, development of pyogenic granulomas and non-melanoma skin cancers, and functional impairment all leading to decreased quality of life. Given that most PWB are found on the head and neck, it is not surprising that they are often associated with psychosocial impairment. It is recommended by many experts that all patients with PWB receive early intervention to prevent morbidity and achieve optimal results [8].

Infantile Hemangioma

Infantile hemangiomas (IH) are benign proliferations of endothelial tissue occurring in 4–10% of infants and children [9, 10]. Increased incidence is seen in Caucasians (as many as 10% within their first year of life), females (three times that of males), premature infants (23% incidence in those weighing <1000 g at birth), and infants of mothers who underwent chorionic villus sampling (21% incidence) [11]. Hispanic infants with IH are more likely to have segmental lesions associated with "PHACES" (posterior fossa brain malformations, facial hemangiomas, arterial anomalies, cardiac anomalies, eye abnormalities, sternal clefting and/or supraumbilical raphae) syndrome as well as mucosal involvement [12] (Fig. 57.2).

Over 50% of IH occur on the head and neck (particularly along embryologic fusion lines), but the lesions may also be found on the trunk and extremities [12]. Large segmental hemangiomas should raise concern for "PHACES" or "LUMBAR" (lower body hemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies) syndromes [13–15]. Superficial or deep IH in the "beard distribution" (i.e., the lower lip, mandible, chin, and neck) may portend concomitant upper airway or subglottic involvement, which manifests as stridor, a hoarse cry, and increasingly "noisy" breathing [16] (Fig. 57.3). Potential complications of all hemangiomas include ulceration (5–13% of all IH), bleeding, pain, visual and airway compromise, as well as permanent disfigurement and scarring [12, 17].

Most infantile hemangiomas are recognized around 2 weeks of life and enter a rapid proliferative phase that peaks in velocity between 5.5 and 7.5 weeks [13, 18] and can continue for up to 18 months. Those relatively rare lesions that pose serious risks to patients are now treated, first-line, with systemic beta-blockers (e.g., oral propranolol) with tremendous success [19]. Left untreated, hemangiomas typically enter an involution phase that begins around 1 year of life and may last more than 2–6 years. Involution may be heralded by a color change from bright to dull red. A grey to white hue may also be noted centrally and expand peripherally. The surface flattens and softens, and the volume of the lesion

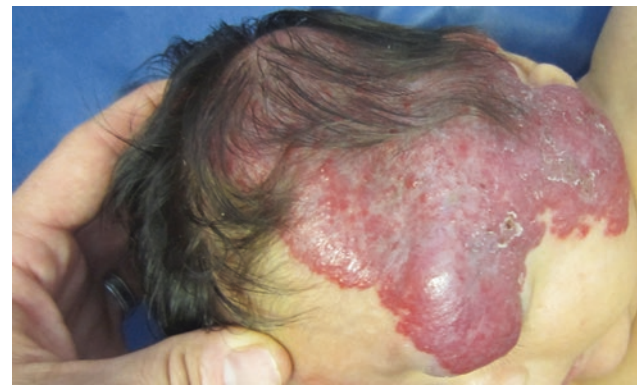

Fig. 57.2 Large segmental hemangioma associated with PHACES involving the entire left face including the orbit. Oral propranolol was initiated with tremendous success; pulsed dye laser was utilized as adjuvant treatment to help with areas of active and pending ulceration

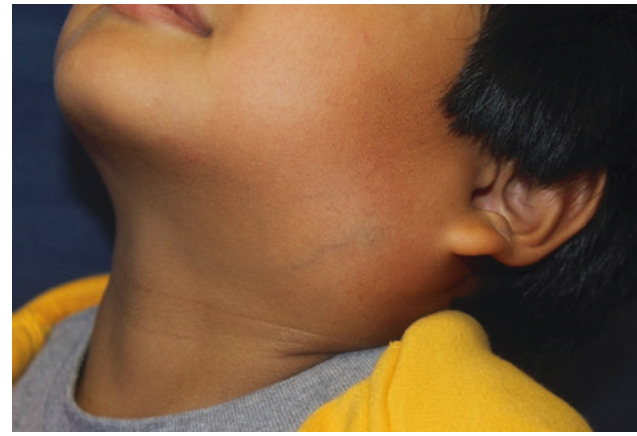

Fig. 57.3 Deep hemangioma in the "beard distribution" of a pediatric patient with skin of color. The lesion was most appreciable when the head was placed in the gravity-dependent position. This patient originally presented to his pediatrician as a young infant with stridor and increased work of breathing

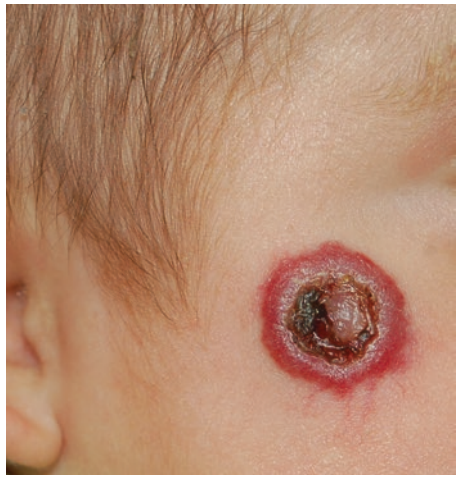

Fig. 57.4 Ulcerated hemangioma on the right cheek of an infant. This lesion will almost certainly leave a permanent scar in a cosmetically sensitive area. It is also at risk for infection

decreases. Gradually, fibro-fatty tissue deposits around the blood vessels.

It is estimated that about half of children with hemangiomas will have normal skin after involution of the lesion. Of course, the other way to consider this axiom is that "half may not," and, thus, up to 50% of children may have permanent sequelae such as telangiectasias, atrophic wrinkling, anetoderma, yellow or hypopigmented discoloration, alopecia, and redundant skin with fibro-fatty residua [20]. Ulceration, untreated infection, and bleeding are additional risk factors for permanent scarring (Fig. 57.4). Consequently, even in this modern era of systemic beta-blockers, some hemangiomas require treatment with interventional modalities. If the potential for permanent physical disfigurement, functional impairment, negative self-image, and lack of self-confidence are real concerns, then aggressive management of these lesions utilizing a full armamentarium (and the guiding principle of "do no harm") should be the goal.

Preoperative Evaluation of the Patient

The patient's Fitzpatrick skin type, age, location of anatomic involvement, functional compromise (present or future), associated symptoms (bleeding, infection, or pain), and a history of prior treatment must be documented. These features guide the treatment modalities that should be selected, as well as the specific parameters to be utilized.

A thorough physical examination of the lesions themselves is essential at every appointment. The long and short axis of each lesion should be measured and documented, and special attention should be paid to color and thickness, as well as the presence of blebs, ulceration, or scars. Standard photographs (to include both anterior-posterior and lateral angles) should be taken.

While most port-wine birthmarks and infantile hemangiomas are diagnosed by history and physical exam alone, some lesions may require

further evaluation by imaging or lab work. When possible, management of complex PWB or IH should be coordinated through a multidisciplinary team to help rule out any associated comorbidities and to optimize the short- and long-term treatment plans.

Imaging Studies

If an arterial, venous, or lymphatic anomaly is suspected, imaging may be performed to help distinguish "high-flow" (i.e., hemangiomas, arteriovenous malformations, and arteriovenous fistulas) from "low-flow" (i.e., venous, lymphatic, or capillary malformation) lesions. Both ultrasound (US) and magnetic resonance imaging (MRI) are superior to radiographs and computed tomography (CT) in the evaluation of vascular lesions [21].

US may be selected as an initial screening method as it is readily available, inexpensive, and safe. Sedation is generally not needed on patients able to hold (or be held) still, and there are no absolute contraindications to its use [22]. Ultrasound provides good soft tissue contrast and basic anatomy information, and, in expert hands, it can help determine vascularity and flow dynamics. This modality is best utilized for superficial vascular anomalies and is suboptimal in the evaluation of deeper vascular lesions particularly when muscle or bone involvement is suspected [21].

MRI can also help determine vascularity and flow dynamics, as well as provide superior spatial resolution and detailed superficial and deep soft tissue evaluation [23]. MRI, usually in conjunction with magnetic resonance angiography (MRA), is the preferred study if ultrasound has provided insufficient information, or it may be chosen as a first-line modality if deeper or more complicated vascular anatomy is suspected [21]. Contraindications to MRI include the presence of implanted devices (e.g., cardiac pacemakers, defibrillators, wires, or metal parts) or certain patient populations: pregnant, claustrophobic, morbidly obese, unstable, or those with renal failure [24, 25]. An important consideration for the pediatric patient undergoing MRI is that of sedation (and the potential inherent risks of anesthesia), as this study typically requires that patients remain still for prolonged periods of time in an enclosed space.

Ultimately, the decision to image a vascular anomaly should be reserved for those cases where the additional information would be helpful to confirm the diagnosis, rule out associated co-morbidities, or determine an optimal management strategy [21].

Specialty Consultation

Neuroimaging (brain MRI with gadolinium contrast) may be recommended for any symptomatic patient or infants with extensive bilateral, hemifacial, or median forehead PWB, keeping in mind that forehead and eyelid involvement confer the greatest risk for SWS [2, 4]. An ophthalmologic examination to rule out glaucoma is recommended for any infant with upper and lower eyelid involvement, bilateral PWB, episcleral hemangioma, iris heterochromia, or choroidal hemangioma [26, 27]. Referral to pediatric dermatology, cardiology, ophthalmology, and neurology for infants with large segmental hemangiomas may be indicated to rule out a diagnosis of PHACES [21]. If general anesthesia is required during planned procedural intervention, then the anesthesiologist must assess the patient prior to the procedure.

Setting the Standard

As this textbook is driven by evidence-based reporting, it must be mentioned that our ability to evaluate the relative efficacy of port-wine birthmark and infantile hemangioma interventions is complicated by several factors. At the bench, reliable animal models for both lesions are lacking, hampering in vivo research. Likewise, there are no universally accepted and validated assessment tools to grade clinical improvement of port-wine birthmarks or hemangiomas before and after intervention. There are also no universally

accepted "expert consensus" recommendations, policy papers, or definitive treatment guidelines, and long-term, rigorously controlled studies are nearly absent in the pediatric peer-reviewed literature.

Seeking Comparative Studies

It is interesting to try to explain the deficiency in the number of "head-to-head" interventional comparisons in the peer-reviewed literature. Practically speaking, we might start by acknowledging that, given the overall competitiveness of the laser surgery field and the reputations (and egos) involved, there may be a lack of incentive – and even a disincentive – to publish "negative" studies. There are also fundamental access issues to the numerous interventional modalities that could and should be considered. For example, a well-known laser surgeon may enjoy direct access to 30 or more lasers, each with a different wavelength representing a potentially different chromophore and different depth of penetration. The pediatric dermatologist, on the other hand, may have limited access to a pulsed dye laser and, if fortunate, one or two other devices. That same pediatric dermatologist, on the other hand, may enjoy the benefit of working within a tertiary or quaternary healthcare facility and may have access to pediatric anesthesia services and a multidisciplinary vascular lesions team; the private practice laser surgeon may be limited to in-office topical pain management and the plastic surgeon down the street. The concept of "use what you got" is a pervasive confounding factor in the real-world treatment (and assessment of treatment) of these skin lesions.

Seeking Consensus

Given the variations in clinical photographic technique and lighting, a standardized photography protocol for these lesions would better permit comparison of pre- and posttreatment images with one another and from one study to the next. A blue background should be adopted whenever possible, and photography without flash is recommended to help prevent color "washout" of the clinical images. As PWB and hemangioma are vascular (i.e., gravity-dependent) lesions, patient position must be consistent as well. Ambient temperature may also affect clinical photography, as a chilly operating room may be associated with more superficial vasoconstriction as compared to a warm patient exam room.

A validated visual grading scale for vascular lesions would be the next logical step to assist both clinicians and researchers alike. Likewise, expert consensus on timing of treatments, time interval between treatments, the total number of treatments performed, the type of anesthetic (topical and general) used, the definition of "long-term follow-up," Fitzpatrick skin type, the use of cooling, posttreatment wound care, and some attempt to capture patient (or, more likely, parent) satisfaction and cost-effectiveness would also be helpful.

Seeking More Objective Assessment

Attempts to quantify pre- and posttreatment changes using noninvasive technologies are evolving. For example, epidermal thickness and depth of PWB upper boundary have been associated with treatment outcomes [28]. These clinical characteristics likely play a key role in guiding therapy; however, they are difficult to accurately predict, even on multiple sites of the same patient. Consider the even greater inherent variability between different patients (e.g., age, skin type, etc.) and different lesions themselves (e.g., anatomic location, history of prior treatment, size of vessels, ratio of oxy- to deoxy- and methemoglobin, etc.) and the range in providers' proficiency with each device being compared; it becomes clear why a definitive review of the published evidence is so difficult.

Both reflectance spectrophotometry and colorimetry have proven useful for the objective

assessment of pre- and posttreatment erythema [29]. Sometimes utilizing more than 40 or more sensors, spectrophotometers provide highly accurate quantitative measurements of the color and intensity of reflected light at each wavelength over the visible and near-infrared portions of the electromagnetic spectrum. Less complex is colorimetry, which seeks to account for the wide variability inherent in human color perception by quantifying the three primary colors (red, green, and blue) for which the human eye possesses receptors. Colorimetry assumes that all colors are perceived as some mixture of these three primaries, the components of which are referred to as X-Y-Z coordinates. Typically, three photocells acting as receptors capture the red, green, and blue data and convert them to saturation and light intensity, representing the relative amounts of erythema and skin pigmentation, respectively [30]. Cross-polarized diffuse reflectance color imaging is another technique that is helpful for quantitatively assessing erythema and melanin in vascular lesions, especially when large areas are involved [31].

In terms of evaluation of PWB and hemangioma ultrastructure, reflectance confocal microscopy employs a low-power, near-infrared laser to noninvasively produce in vivo tissue images to a depth of 200–300 microns. Similarly, optical coherence tomography utilizes light to produce high-resolution, three-dimensional, in vivo images to a depth of up to 1 mm. Both techniques are highly user dependent and are limited by their depths of penetration. However, they offer tremendous potential for diagnosing and better characterizing vascular anomalies in vivo, a step toward the standardization of treatments of these lesions.

Perfusion through a lesion, measured in blood perfusion units, may be objectively and noninvasively quantified using laser Doppler flowmetry (LDF). Similarly, laser speckle imaging (LSI) can be used to detect the relative motion of red blood cells (i.e., the speckle pattern) through the lesion. Both techniques may prove useful for objectively quantifying the degree of photocoagulation pre- and post-laser treatment [32].

Pushing Forward

In short, a limited number of randomized controlled trials, a lack of general expert consensus, and limited objectively quantifiable data make head-to-head comparisons of one modality to the others extremely difficult. High-quality, long-term studies are required to evaluate relative efficacy, and physicians should be encouraged to adopt objective tools that decrease the subjectivity inherent in this topic. Doing so could, ultimately, allow for improved direct objective comparison of treatment options for these vascular lesions and help reduce the total number of treatments (and the number of costly, painful procedures) necessary for patients to optimize clinical outcomes.

Approach to Treatment

Because the interventional modalities used to manage both PWB and hemangiomas may themselves be associated with certain side effects and complications (e.g., pain, ulceration, skin dyspigmentation, scarring, etc.), treating physicians should approach their patients with humility and the guiding principle of “do no harm” in mind. Intervention should begin as early as possible, when the vascular lesions are smaller and typically more superficial; it is assumed (not proven) that these characteristics may lend themselves to improved response to intervention, thus decreasing the total number of treatments necessary and the likelihood of long-term complications.

Treatment of Port Wine Birthmark

Many procedural interventions have been utilized in the treatment of port-wine birthmarks, including myriad lasers (e.g., carbon dioxide, alexandrite, Nd:YAG, argon, copper vapor, etc.), intense pulsed light (IPL), photodynamic therapy (PDT), surgical excision, dermabrasion, cryotherapy, sclerotherapy, radium implants, X-ray therapy, electrocautery, tattooing, and cosmetic camouflage.

Laser Treatment

Numerous lasers have historically been used to treat PWB. The ruby laser was first, as pioneered by Dr. Leon Goldman, in 1963. The argon laser, with peak emissions around 488 and 514 nm (i.e., the blue-green section of the electromagnetic spectrum), also demonstrated a high absorption coefficient for hemoglobin. The continuous wave carbon dioxide laser, emitting at 10,600 nm, was utilized to non-selectively treat vascular lesions. However, these original devices were associated with pulse durations (i.e., continuous wave) that were longer than the thermal relaxation time of the targeted blood vessels. In the absence of epidermal cooling, their utility proved to be very user dependent, and even in expert hands these devices were associated with a high risk of scarring and dyspigmentation.

Pulsed Dye Laser (Table 57.1)

Laser treatment of vascular lesions was revolutionized by the development of the yellow light-emitting flashlamp-pumped pulsed dye laser (PDL). PDL was the first laser to be specifically developed with the principle of "selective photothermolysis" in mind. It was pioneered by Anderson and Parrish, who were driven to develop a laser for the treatment of pediatric port-wine birthmarks, in the 1980s [33]. First-generation PDL utilized yellow light emitting at wavelength 577 nm to target oxyhemoglobin (roughly 70% of total hemoglobin, the remainder being mostly deoxyhemoglobin and methemoglobin), a chromophore with absorption peaks located around 418, 542, and 577 nm. This wavelength laser caused selective thermal destruction of the abnormally dilated blood vessels with minimal to no

Table 57.1 Pulsed dye laser treatment of port-wine birthmark

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Smit et al. [34]	1a	71 prospective, objectively measured, and/or controlled studies	Varied	PDL is the most studied, most commonly used "gold standard" treatment for PWB
Faurschou et al. [35]	1a	5 RCT, 103 patients	Varied	PDL leads to clinically relevant clearance of PWB
Yung and Sheehan-Dare [36]	2b	18 with PWB	585 nm: 7 mm, 15 J/cm^2, 1.5 ms 595 nm: 7 mm, 15 J/cm^2, and 1.5 ms, 6 ms, or 20 ms	Efficacy of 585 nm = 595 nm
Greve and Raulin [37]	2b	15 with PWB	585 nm: 7 mm, 5.5 J/cm^2, 0.5 ms 595 nm: 7 mm, 5.5 J/cm^2, 0.5 ms; 7 mm, 13 J/cm^2, 20 ms	Efficacy of 585 nm > 595 nm, but with higher rate of side effects (purpura, pain, and crusting)
Chapas et al. [42]	2b	49 infants with PWB	595 nm: 7.75–9. 5 J/cm^2	88.6% average clearance after 1 year (best improvement along V1)
Reyes and Geronemus [44]	2b	73 (3 months to 14 years) with PWB	557 or 585 nm: MPD, 360 or 450 microseconds, 5 mm	53–95% lightening
Fitzpatrick et al. [45]	2b	133 with 140 PWB	585 nm: 5.5–7.5 J/cm^2	Positive clinical response: pink PWB, located on head and neck, patients <10 years old Negative clinical response: purple PWB, lesions on distal extremities, patients >50
Yu et al. [48]	2b	13 with PWB	595 nm: 12 J/cm^2, 1.5 ms, 7 mm	Lateral face blanching rate: 34.01% Central face blanching rate: 8.68%

collateral damage of surrounding cutaneous structures. Eventually, 585 nm and 595 nm wavelength devices were developed because they combined still-precise absorption with slightly deeper penetration through cutaneous tissue and enhanced dye life. The addition of surface cooling devices permitted improved treatment of darker skin and the use of higher fluences with larger spot sizes.

A literature review of 71 prospective, objectively measured, and/or controlled studies from 1993 to 2003 found the pulsed dye laser (PDL) to be the most studied, most commonly used, and widely considered "gold standard" for a variety of cutaneous vascular lesions, including PWB [34]. Similarly, a Cochrane review through 2010 identified five randomized clinical trials with 103 participants and concluded that PDL leads to clinically relevant clearance of PWB but that patients marginally preferred treatment with the 1064 nm Nd:YAG because of a shorter duration of posttreatment purpura [35].

Both the 585 nm and 595 nm wavelengths appear efficacious, without definitive published statistical advantage of one over the other [36, 37]. Lightening of PWB is directly related to the number of PDL treatments, with the majority of PWB requiring six or more laser sessions to achieve stable improvement [38]. Fluences of 6–12 J/cm^2 at 8-week intervals have been reported to result in an average of 12% lightening per treatment [34]. Spot sizes of 7 mm and 10 mm are ideal and result in similar therapeutic outcomes. The 10-mm spot is considered by some to be more efficacious, as the larger beam penetrates deeper into the skin, targeting larger vessels. Additionally, the 10-mm spot allows for lower radiant exposure (i.e., less joules) and reduced treatment time [39]. When using the 595 nm laser, clinical outcomes from pulse durations of 20 ms are comparable to 1.5 ms, and both were superior to 6 ms [36].

The most apparent side effect of PDL treatment of PWB is purpura, which should be used to determine if a therapeutic endpoint has been achieved. Purpura limited to the selected spot size should occur immediately following the typical PDL settings (7–10-mm spot size, 6–9 J/cm^2, 0.4–3 ms). Purpura reaches maximal intensity 1–2 days after treatment, and it gradually fades over the next 7–10 days [40]. Brauer et al. recently reported statistically significant improvement in ecchymosis by using subpurpuric PDL settings (10 mm, 7.5 J/cm^2, 6 ms) 48 h after treatment of PWB [41].

Pigmentary alterations have been reported in 3–24% of patients, most commonly in those with darker skin types [35]. Other reported complications include pain, crusting, blistering, and scarring, with most side effects resolving within several weeks [34, 35].

Treatment with PDL appears to be most successful when initiated within 3 months of birth, as the overall lesion is small, and vessels are smaller and more superficial [8, 42, 43]. Reyes et al. reported 55% lightening after a single treatment in patients 3 months to 6 years of age, which decreased to 48% in patients older than 7 years of age [44]. In another study, 90% of children 0–10 years of age experienced "good to excellent" responses, whereas only 67% of patients older than 50 had the same clinical response [45]. Early treatment of PWB also prevents hypertrophic evolution of the lesion, which in its natural history occurs in 20% of patients at a median age of onset of 31 years [46].

PWB located on the lateral face and neck responds more favorably to treatment with PDL than to central facial lesions [47]. Histologic investigation suggests that variations in vessel location and diameter (more superficial vessels are found in lateral PWB) are responsible for this treatment response [48].

Treatment of PDL-Resistant or Hypertrophic PWB (Table 57.2)

Though most PWB lighten with PDL treatment (the "gold standard"), only 40% of patients achieve "good" lesional clearance. Suboptimal clearance has been reported in 20–46% of patients, and 14–40% of patients are considered "PDL resistant" [49]. Additionally, PWB can recur following treatment with PDL via angiogenesis, with reported recurrence rates of 11% after "sev-

Table 57.2 Treatment of PDL-resistant PWB or hypertrophic PWB

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Tierney and Hanke [58]	1b	8 with PDL-resistant PWB	755 nm: 8–12 mm, 40–60 J/cm^2, 3 ms, 60/40 DCD	56.3% improvement of color, 60% improvement in skin texture, and 59.4% improvement in overall cosmetic outcome
Izikson et al. [28]	2b	20 with hypertrophic or PDL-resistant PWB	755 nm: 8–12 mm, 35–100 J/cm^2, 3 ms, 60/40 DCD 755 nm (as above) + concurrent or alternating sessions of PDL	Hypertrophic PWB: Significant lightening (3/3 patients). No complications except expected posttreatment purpura, edema, erythema, and discomfort Resistant PWB: Significant lightening (1/17 patients), moderate lightening (12/17), mild lightening (3/17), no response (1/17). 2 patients with scars after blistering, 1 patient with hypopigmentation
Grillo et al. [59]	1b	21 with PDL-resistant PWB	755 nm: 10 mm, 35–55 J/cm^2, 3 ms	Mean global improvement 2.28. Mean patient satisfaction 8.5. Minimal scarring & blistering in 1 patient
Carlsen et al. [60]	1b	16 with PDL-resistant PWB	755: 8 mm, fluence titrated to effect, 3–10 ms	3 ms pulse duration superior in both clearance and safety
McGill et al. [56]	1b	18 with PDL-resistant capillary malformation	755, KTP, and Nd:YAG IPL & PDL as control	Alexandrite induced largest mean improvement in color, but with highest risk of hyperpigmentation and scarring (4 patients) KTP and Nd:YAG were least effective
Li et al. [57]	1b	11 with PWB	755 nm vs PDL	PDL most appropriate for flat, pink PWB Hypertrophic, purple PWB respond best to 755 nm
Yang et al. [52]	1b	17, split lesion study	1064 nm: 5 & 7 mm, Fluence determined by MPD (widely varied), 3–15 ms PDL 595 nm: 7 mm, 8 J/cm^2, 1.5 ms	PDL resulted in >75% clearance (3 patients), 51–75% clearance (6 patients) Nd:YAG @ 1 MPD resulted in >75% clearance (1 patient), 51–75% clearance (5 patients) Hyperpigmentation, hypertrophic scar, and pyogenic granuloma reported
Van Drooge et al. [62]	2b	32 with PWB	1064 nm	Majority of patients with good or excellent improvement, with > 60% improvement in color. Hypertrophic responded more favorably than color. Mild to moderate scars in seven patients, hypopigmentation in one
Kono et al. [63]	1b	10 with hypertrophic PWB on lips	1064 nm	80% with good to excellent improvement without complications
Chang et al. [64]	4	4 with blebbed PWB	1064 nm: 5–6 mm, 120–150 J/cm^2, 30 ms	80–100% improvement of blebs
Alster and Tanzi [65]	1b	25 with recalcitrant PWB treated with dual wavelength laser	595 nm: 10 mm, 6.5–9 J/cm^2, 6 or 10 ms 1064 nm: 10 mm, 30–50 J/cm^2, 10–20 ms	25–50% improvement in 48%. Mild purpura. No PIPA or scarring
Wang et al. [66]	1b	61 with PWB treated with dual wavelength laser	595 PDL: 10 mm vs 595 + 1064 DWL: 10 mm	No treatment advantage, higher rate of scarring with DWL than PDL
Kwiek et al. [69]	2b	44 with facial CM	532 nm: 5–10 mm, 8–11.5 J/cm^2, 5–9 ms	At least 25% improvement: All patients At least 50% improvement: 77.3% At least 75% improvement: 38.6% At least 90% improvement: 13.64%

Table 57.2 (continued)

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Al-Dhalimi et al. [68]	1b	14 with facial PWB	1064 vs 532 (split-lesion comparative study)	532: 57.2% with moderate to good improvement; 28.6% with excellent improvement. 1064: 7.1% with moderate to good improvement; 0% with excellent improvement No scarring or hyperpigmentation after 3 months of the last session
Al-Janabi et al. [70]	1b	16 with PWB	532 nm	Mild improvement = 6.25% Moderate improvement = 12.5% Good improvement = 31.25% Excellent improvement = 50%
Reddy et al. [55]	1b	5 with PWB, lesion split into 4 quadrants	532 nm: 6–10 mm, 4.8–9 J/cm^2, 3–6 ms	12/20 quadrants: 1–25% improvement 3/20 quadrants: 26–50% improvement 5/20 quadrants: 51–75% improvement
Latkowski et al. [71]	1b	155 with PWB	532 nm	Fair improvement: 23% Good improvement: 27% Excellent improvement: 31% Trunk and limb PWS most resistant to treatment. No scarring or persistent PIPA
Pence et al. [72]	1b	89 with PWB	532 nm: 2–6 mm, 9.5–20 J/cm^2, 15–50 ms	50–74% improvement: 44% 75–90% improvement = 38% >95% improvement = 13% Transient hyperpigmentation (2.25%), hypopigmentation (1.12%), and "hypotrophic" scarring (1.12%)

eral years" [50], 16% after at least 1 year [51], and up to 50% 5 years after treatment [52].

The limited success of PDL is attributed to incomplete photocoagulation of the target vessels. PDL's yellow light penetrates 1–2 mm deep into a lesion than can extend 3–5 mm into the skin, targeting vessels between 55 and 150 μm. Larger and deeper vessels remain patent [49, 53]. In addition to vessel depth and diameter, variable vessel density, anatomic location of the lesion, and high epidermal melanin content make uniform and predictable treatment outcomes a therapeutic challenge.

PDL-resistant PWB or hypertrophic PWB in adults may respond to the 755 nm alexandrite and the 1064 nm neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers, which are preferentially absorbed by deoxyhemoglobin over oxyhemoglobin (HbO_2). Additionally, these lasers are less absorbed by melanin than the yellow wavelengths and penetrate 50–75% deeper into the skin. Both the 755 nm and 1064 nm lasers require higher fluences to achieve sufficient photocoagulation, which is associated with a higher risk of scarring and permanent pigmentary change [49, 54]. Alternatively, the frequency-doubled 532 nm Nd:YAG laser can also be used in select cases to reduce both vessel number and size, with penetrating depths of 0.35–4 mm into the skin [55].

Alexandrite Laser (755 nm)

The 755 nm wavelength provides two theoretical advantages over the 1064 nm laser: a greater absorption coefficient of deoxyhemoglobin over HbO_2 (preferentially damaging veins more than arteries) and a less pronounced effect of methemoglobin (an oxidized species that appears during laser-induced heating of blood vessels; methemoglobin has a much stronger absorption than either deoxyhemoglobin or HbO_2 at 1064 nm, producing an "all or nothing" fluence-response relationship) [54].

The 755 nm laser was the most effective treatment modality, with the highest associated risk (hyperpigmentation and scarring), in a direct comparison study of 18 patients with PDL-resistant capillary malformations treated with either the 755 nm alexandrite, 532 nm KTP, 1064 nm Nd:YAG lasers, or intense pulsed light (IPL). The KTP and Nd:YAG lasers were least effective in this study [56]. Another comparative study of 11 patients treated with either the 755 nm alexandrite or PDL suggested that the PDL was most appropriate for flat, pink PWB whereas hypertrophic, purple PWB responded best to 755 nm [57].

Three case series detailing a total of 49 patients with PDL-resistant PWB treated with the 755 nm alexandrite laser demonstrated "moderate to significant" lightening in 80% of patients [54] and 50–60% improvement of color, skin texture, and overall cosmetic appearance [58], and both mean global improvements and good patient satisfaction [59]. In addition to the expected post-laser effects (purpura, edema, erythema, and discomfort) experienced by all patients, more serious sequelae (blistering, scarring, and hypopigmentation) were also noted. All authors cautioned that the potential risk for adverse effects and very narrow therapeutic index mandate conservative parameters and close observation of the treated tissue [54, 58, 59].

A study of 16 patients (14 of whom had failed PDL treatment) treated with the alexandrite 755 nm laser at 8 mm and fluence titrated to effect revealed that a 3 ms pulse duration was superior to both 5 ms (*P* 0.016) and 10 ms (*P* 0.004) in both clearance and safety. The authors concluded this treatment modality is best suited for patients with purple, hypertrophic PWB and should be "restricted to experienced personnel due to particularly narrow therapeutic window" [60].

Treatment Pearls for the 755 nm Alexandrite Laser

- Best suited for purple, hypertrophic PWB or PDL-resistant PWB;
- Treatment should be performed by only experienced laser physicians because of the narrow therapeutic window and risk for scarring;
- Treat the darkest part of the PWB first and closely monitor for the desired endpoint: A subtle grey-blue darkening that transitions over several minutes to lasting purpura [54];
- If no response, increase fluence by 5–10 J/cm2 and treat the unresponsive areas [54]; and
- Complete treatment with one pass (no double pulses), minimal to no overlap.

Neodymium-Doped Yttrium-Aluminum-Garnet Laser (1064 nm)

As with the 755 nm alexandrite laser, the 1064 nm Nd:YAG laser penetrates more deeply into the skin than PDL, causing complete constriction and immediate blood vessel disappearance in up to 60.6% of vessels ranging in diameter from 30 to 300 μm [61]. Higher fluences are required to achieve this desired response, and nonselective bulk heating can occur. Significant scarring can result when fluences greater than 1.2 times the minimal purpura dose (MPD) are used, making treatment of the anatomically heterogeneous PWB lesion challenging [53]. Short pulse durations (<10 ms) should be utilized to minimize collateral tissue damage [61]. Ultimately, however, the Nd:YAG should only be used by experienced clinicians who can successfully navigate its narrow therapeutic window.

Multiple studies have demonstrated good to excellent (50–75%) improvement of PWB, PWB blebs, and hypertrophic PWB, with risks of pigmentary alteration and mild to moderate scarring reported in up to 20% of patients [53, 62–64]. Hypertrophy appears to respond more favorably than color. What is most impressive, however, is the wide variability of MPD elicited by the Nd:YAG as reported by Yang et al., demonstrated in Table 57.3.

Disparate reports of the dual-wavelength laser (DWL) (595 nm PDL + 1064 nm Nd:YAG) have found this treatment modality to be both effective and without adverse effects [65], as well as demonstrating no advantage in efficacy over the PDL but associated with a significantly higher rate of scarring [66]. Post-DWL biopsies have demonstrated maximum vessel wall damage and epidermal sparing when the 10-mm spot size is used, PDL pulses are shorter than 10 ms, and a second pass with PDL only is performed [67].

Table 57.3 Minimal purpura dose in patients treated with the Nd:YAG [53]

PWS color	Fluence	Pulse duration	Spot size
Pink	90–250 J/cm^2	6–15 ms	7 mm (<100 J/cm^2) 5 mm (>100 J/cm^2)
Red	50–130 J/cm^2	4–8 ms	7 mm (<100 J/cm^2) 5 mm (>100 J/cm^2)
Purple	40–60 J/cm^2	4 ms	7 mm

Treatment Pearls for the 1064 nm Nd:YAG Laser

- Best suited for purple, hypertrophic PWB or PDL-resistant PWB.
- Treatment should be performed by only experienced laser physicians because of the narrow therapeutic window and risk for scarring.
- Determine the MPD: Perform test pulses in rows of three pulses, starting at 30 J/cm^2; fluence is increased by 20% increments until a subtle darkening (purpura) lasting beyond 15 min is appreciated [53].
- Complete treatment with one pass (no double pulses), minimal to no overlap.

Frequency-Doubled Neodymium-Doped Yttrium-Aluminum-Garnet Laser (532 nm)

A split-lesion, randomized study comparing the long-pulsed Nd:YAG 532 nm and 1064 nm laser in the treatment of 14 patients with facial PWB showed an overwhelming greater therapeutic efficacy with the 532 nm laser ($P = 0.001$). Over 50% of patients treated with 532 nm laser experienced moderate to good improvement compared to 7.1% of patients treated with the 1064 nm laser. No patients developed scarring, and the solitary incidence of hyperpigmentation resolved with hydroquinone cream [68].

Multiple studies confirm the safety and efficacy of the 532 nm laser in the treatment of PWB, reporting an average of 50–75% improvement in the 380 patients treated [55, 69–73]. PWB on the face responded most favorably, whereas lesions on the trunk and extremities were often recalcitrant to treatment [71]. Post-inflammatory hyperpigmentation was reported in patients with Fitzpatrick skin types III to IV but was a rare occurrence in lighter-skinned individuals [68, 72, 73]. "Hypotrophic scarring" was reported only in one study (1.12%) [72].

Treatment of PWB in Skin of Color (Table 57.4)

The treatment of vascular anomalies (specifically PWB) on over 1500 patients with skin types III–V has been reported to be moderately effective and generally well tolerated.

Chinese patients (Fitzpatrick skin types III–IV) with PWB treated with the 585 nm laser, 595 nm laser, Nd:YAG 532 nm laser, or both 585 nm and 532 nm laser demonstrated moderate efficacy (more than 60% with 25% clearance) [73], a "favorable response" (69.9%) [74], or "excellent" improvement (62%) [75], irrespective of the laser system used. Post-procedural hyperpigmentation was most commonly reported at rates of 13% [73], 4% [74], or 6% [75], and it typically resolved in 3–6 months. Less common side effects included focal textural changes (1.6%), hypopigmentation (2.2%), and hypertrophic scarring (one patient) [75].

Patients under 1 year of age experienced the best results (93.9% responded, 18.2% with complete resolution), and those over 50 were noted to have the least response (25% responded, 0% with complete resolution) [74].

Indian patients (Fitzpatrick skin types IV and V) with PWB demonstrated 25–75% lightening when treated with the 585 nm PDL [76] and 54% mean lightening of flat PWB and 40% mean lightening of hypertrophic PWB when treated with the 595 nm PDL [77]. Children experienced a superior and faster response (61–80% improvement was noted in 70% of children compared to 50% of adults after 8–10 sessions). The poorest response was noted in adult patients with thick, non-blanching PWB and PWB located on the upper cutaneous lip [78]. A greater therapeutic effect was demonstrated after ten sessions (58.6%) than four sessions (41.8%). Post-procedural hyperpigmentation occurred in

Table 57.4 PDL treatment of vascular lesions in patients with skin of color

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Liu et al. [75]	1b	184 (Chinese) with PWB of face, neck, trunk, limbs	595 nm: Variable	62% with "excellent" improvement, 20% with "good" improvement Prominent hyperpigmentation (6%), hypopigmentation (2.2%), focal textural changes (1.6%), hypertrophic scarring (1 patient)
Woo SH et al. [80]	2b	237 (Korean, skin types III to V) with nevus flammeus, telangiectasia, hemangioma	595 nm: variable, depending on lesion type	Nevus Flammeus: 48% with good to excellent results Telangiectasias: 78% with good to excellent results Hemangiomas: 54.1% with good to excellent results Transient hyperpigmentation (21.3%), hypopigmentation (3.3%), cutaneous atrophy (1.7%), hypertrophic scarring (0.8%)
Shi et al. [74]	2b	848 (Chinese, skin types II–IV) with PDL-resistant PWB	595 nm: 8–12 J/cm^2, 1.5–10 ms	69.9% favorable response, with patients under 1 year of age experiencing the best results (93.9% responded), those over 50 with least response (25% responded) Hyperpigmentation (4%), resolved in 3 months
Khandpur and Sharma [77]	2b	98 (Indian, skin types IV and V) with PWB	Flat PWB: 595 nm: 7 mm, 8–10 J/cm^2, 1.5–3 ms Hypertrophic PWB: 595 nm: 7 mm, 8–12 J/cm^2, 1.5–6 ms	Mean lightening: 54% (flat), 40% (hypertrophic) Hyperpigmentation (40.5% of flat PWB, 29.2% of hypertrophic PWB), post-laser burning (13%), pain (25%), honeycombing (8.1%), erythema, blistering, hypopigmentation, and atrophy
Sharma and Khandpur [76]	4	27 (Indian, type IV and V) with PWB	585 nm: 7 mm, 5–7.5 J/cm^2, 0.45 ms	60% with 25–75% lightening Hyperpigmentation (26%), hypopigmentation (3%). No textural change or scarring
Bae et al. [79]	4	2 (African American) with PWB	595 nm: 10 mm, 7–8.25 J/cm^2, 1.5 ms	Resolution of PWB, no side effects
Ho et al. [73]	2b	107 (Chinese) with PWB	585 nm 532 nm 585 nm + 532 nm	More than 60% of patients experienced >25% clearance 13% with complications (most commonly pigmentary changes)
Thajudheen et al. [78]	1b	75 (Indian) with PWB	595 nm: 7–10 mm, 6–12 J/cm^2, 0.45–10 ms x 10 sessions @ 4 week intervals	70% of children with 61–80% improvement 50% of adults with 61–80% improvement Hyperpigmentation (30%), superficial scarring attributed to pulse stacking

26% [76], 30% [78], and 40% [77] of patients. Strict photoprotection (all patients), hydroquinone (select patients), and time (6–8 weeks [78] up to 6–9 months [77]) resolved all undesired pigmentary alteration. Other side effects included pain (25%), honeycombing (8.1%), transient hypopigmentation (3%), erythema, and blistering [77]. No textural change or scarring was appreciated except in an isolated case of pulse stacking [78]. No significant benefit or difference in side effect profile was seen between the two PDL wavelengths [76, 77].

Two African American pediatric patients (Fitzpatrick skin types IV and V; age 1 month

and 4 years) experienced resolution of their PWB without complication when treated with 595 nm PDL [79].

Nevus flammeus, telangiectasias, and hemangiomas on Korean patients with skin types III to V have also responded favorably to PDL. Over 50% achieved good to excellent improvement of their vascular skin lesions. Transient hyperpigmentation occurred in 21% of patients. Others experienced hypopigmentation (3.3%), cutaneous atrophy (1.7%), and hypertrophic scarring (0.8%) [80].

Sufficient evidence has demonstrated that darker-skinned patients with PWB and other vascular neoplasms can benefit from laser intervention. These patients generally require more treatment sessions to achieve the desired result. Post-inflammatory hyperpigmentation is the most common reported sequelae of treatment, and it generally resolves in weeks to 9 months with strict sun protection. A detailed informed consent discussion regarding expectations of a moderate response and associated risks (emphasizing pigmentary alteration) is necessary prior to treatment.

Treatment Pearls for Patients with Skin of Color

- Start with conservative settings.
- Single pulses with minimal to no overlap (avoid pulse stacking).
- 6–8-week intervals between treatments.
- Delay additional treatment until any post-inflammatory hyperpigmentation has resolved.
- Strict photoprotection for at least 3–4 weeks following each treatment.

Emerging/Experimental Treatments for PWB

Photodynamic therapy (PDT) has emerged as a potential alternative to laser treatment, and today it is most commonly performed in China. Targeted destruction of PWB blood vessels occurs when a photosensitizer (photocarcinorin, hemoporfin, benzoporphyrin derivative monoacid ring A, or talaporfin sodium) within the blood vessel is excited, generating cytotoxic singlet oxygen that causes direct endothelial cell damage, thrombosis, and vascular collapse [49, 81]. Similar to laser (where efficacy is dependent upon selection of the correct wavelength, fluence, pulse duration, and spot size), PDT's success depends on a variety of factors such as choice of photosensitizer, wavelength and light intensity, and exposure time [49]. Efficacy appears similar or even superior to PDL, and fewer treatments are necessary to achieve clearance (on average 1–4) [82–86]. Patients 5–20 years old have been observed to have the greatest response to PDT treatment (in contrast to PDL which is most effective in younger patients) [84]. Side effects can include blistering, swelling, severe pruritus, pigmentary alteration, scarring, photoallergy, and photo-thermal injury. Strict sun avoidance is necessary for 2–4 weeks after treatment [82–86]. Clinical trials are ongoing; however, researchers postulate that PDT could potentially be used in the future either as a solitary or synergistic treatment modality for PWB [87].

Intense pulsed light (IPL) is an option when non-purpuric treatment is desired or when access to PDL is limited. IPL produces broadband, non-coherent light between 390 nm and 1200 nm using a xenon flashlamp. Filters are available to adjust the wavelength range that is delivered to the PWB, conferring a wider "target" range. Limitations include pigmentary changes (hypo- and hyper-pigmentation) that may result and an overall reduced efficacy in comparison to PDL.

Treatment of Infantile Hemangioma (Table 57.5)

As most hemangiomas pose no threat to life or function, a viable treatment strategy may be to simply adopt a "wait and see" approach. For those relatively rare lesions that do pose serious risks to patients, first-line treatment with systemic beta-blockers (e.g., oral propranolol) has produced tremendous results and volumes of well-controlled published studies. A plethora of procedural interventions—the focus of this chapter—have been utilized to treat hemangiomas and

Table 57.5 Treatment of infantile hemangioma

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Admani et al. [88]	4	5	585/595 nm PDL: 7–12-mm spot; 5–10 J/cm^2; 0.45–1.5 ms pulse duration; dynamic cooling 30/10–30 ms; treatments repeated 2–8 weeks until desired effect	No adverse events reported
Chinnadurai et al. [89]	1a	29 studies (4 RCT, 8 retrospective cohort, 17 case series)	PDL, Nd:YAG, CO_2 were included; specific parameters varied across studies	Long-pulse PDL, at 585/595 nm, with epidermal cooling was most commonly utilized device; variations in treatment protocols and parameters did not allow for identification of a single method's clinical superiority
Kwon et al. [90]	2b	40 children (age 9.6 at initiation of treatment and 18 at completion); 47 hemangiomas (32 superficial, 15 mixed)	595 nm PDL with dynamic cooling: 10-mm spot; 7–10 J/cm^2; pulse duration 3–6 ms; dynamic cooling 30/10; treatments repeated at 1–4 week intervals	Mean number treatments 4.6; treatment was more effective in superficial lesions than mixed; hyperpigmentation was reported as an adverse event
Chen et al. [91]	2b	43 patients with infantile hemangiomas on the hand	595 nm PDL: 7-mm spot; 10–13 J/cm^2; pulse duration 20–40 ms; epidermal cooling 20/40	Hemangiomas were treated effectively; confounding factor was that the mean age of patients at initial treatment was 8.92 months, coinciding temporally with the expected natural transition to involution
Zhong et al. [93]	2b	794 Chinese patients (900 hemangiomas); mean age 3.6 months	Long-pulse Nd:YAG with contact cooling copper plate for up to five treatments: superficial and mixed lesions treated with 3–5-mm spot; 120–235 J/cm^2; 10–30 ms pulse duration Deep lesions treated with 7-mm spot; 65–120 J/cm^2; 20–30 ms pulse duration	Most superficial lesions responded in 1–2 treatments; mixed and deeper lesion response was poor until propranolol was added. Adverse events include blistering (82%), change in skin (8.4%), hyperpigmentation (4.3%), atrophic scarring (2%), postoperative secondary ulcer (0.5%), hypopigmentation (0.1%)
Batta et al. [94]	1b	60 superficial early hemangiomas	585 nm PDL: 3–5-mm spot; 6–7.5 J/cm^2; 0.45 ms pulse duration	25 patients had complete clearance or minimum residual signs. Adverse events include ulceration (7%), painful ulceration (5%), bleeding (3%), infection (3%), and need for oral steroid (2%)
David et al. [89]	2b	78 children with ulcerated hemangiomas (147 lesions total; mean size 21 cm^2)	585 PDL: 5–7-mm spot; 5–6.8 J/cm^2; 3–4 week treatment intervals (average two treatments)	71 patients showed good response with no adverse events reported
Cerrati et al. [96]	4	20 patients (average age 2.69 years) with residual telangiectasia following hemangioma involution	532 nm diode laser: 0.7–2-mm spot; 10.2–25 J/cm^2; 36–44 ms pulse duration; pulse frequency 3–5 Hz	Complete response (73%), near-complete response (23%) in patients

Table 57.5 (continued)

Author	Level of evidence	# Patients	Laser parameters	Clinical outcome
Alcántara González et al. [97]	2b	12 patients with atrophic scar or fibro-fatty residua	2790 nm ablative fractional yttrium-scandium-gallium-garnet: 300-μm spot; 120–200 mJ; density level 3; 600-μm pulse width. Treatment with 595 nm PDL or combined sequential 595 nm PDL and 1064 nm Nd:YAG applied if telangiectasias or residual vascular component present	Mean parent satisfaction was 6.75 (scale from 0 to 10); mean improvement was 1.58 based on 3 dermatologists rating photographs on scale of 0–4; "discrete punctate pattern" noted in e patients as long-term adverse event
Brightman et al. [98]	4	5 patients (age 4.5–13 years at initial treatment)	Ablative fractional CO_2: 20–40 mJ; 0.29–80 kJ total energy; 20–40% coverage; 2–13 treatments; 2–10 month average treatment interval	On average, patients experienced 50%–75% improvement in color, texture, and overall appearance
Feng et al. [99]	4	1 patient (age 2 years; Fitzpatrick skin type IV)	755 nm alexandrite laser: 15-mm spot; 25–30 J/cm^2; 3 ms pulse duration; cryogen spray cooling with spurt duration of 40 ms; pulses stacked (3–5 per area) at approximately 1 pulse delivered every 3–4 s to minimize epidermal damage	"Vessel darkening" was obtained and clinical outcome was excellent
Daramola et al. [100]	2B	92 patients (average age 36 months) with 94 hemangiomas (mostly head/neck with mean surface area 7.75 cm^2)	Surgery	Head and neck lesions were more statistically likely to require multiple modality treatment

their sequelae. Laser surgery, surgical excision, intralesional therapy, cryotherapy, electrocautery, and embolization are all modalities that have been used with reported effect.

Laser Treatment

Laser treatment has been demonstrated to be both safe and effective in the management of infantile hemangiomas. Small, thin, superficial lesions are the best candidates when specific complications (or the risk of complications) are not driving the clinical decision to laser. Patients who are excluded from utilizing systemic beta-blockers or those patients who cannot tolerate beta-blockers may also benefit from laser surgery. Several studies comparing laser with systemic beta-blockers or in combination with beta-blockers tend to report greater clinical improvements in combination arms versus beta-blockers alone; these additive effects suggest that laser treatment should retain an important role in the management of refractory hemangiomas [88].

A 2016 systematic review of multiple databases including MEDLINE® and EMBASE, from 1982 to June 2015, identified 29 studies addressing the use of lasers for infantile hemangiomas. A total of 4 randomized controlled trials, 8 retrospective cohort studies, and 17 case series were identified by two investigators working independently to assess risk of bias and strength of evidence. Parameters varied widely across studies in terms of laser type, pulse width, or cooling materials. Overall, the long-pulse PDL, at 585 nm or 595 nm, with epidermal cooling was

the most commonly utilized device. These lasers allow for a depth of penetration of approximately 1–2 mm into the target vasculature. However, variations in treatment protocols and parameters did not allow for identification of a single method's clinical superiority [89].

At least one retrospective study of 40 children with 47 hemangiomas reported early intervention with PDL (average age at initiation of treatment was 9.6 weeks) to be effective in helping to prevent further hemangioma growth, as well as utility in accelerating the transition to "plateau" or "involution" phase [90].

PDL may also be used on areas specifically at risk for significant functional or psychological impact. A complication of some hand hemangiomas, for example, is the increased risk for overlying skin maceration secondary to "infant sucking." For the same reason, hand hemangiomas may inadvertently transform a topical medication into a systemic one, making management strategies in this anatomic location difficult. In these cases, laser offers an alternative approach. A 2014 retrospective review of 43 patients with infantile hemangiomas on the hand supported the role of PDL (595 nm) with fluence 10–13 J/cm^2, pulse duration 20–40 ms, 7-mm spot, and epidermal cooling 20/40 to treat hand hemangiomas effectively. However, a confounding factor was that the mean age of patients at initial treatment was 8.92 months, coinciding temporally with the expected natural transition to involution [91].

A 2014 retrospective interdisciplinary study involving 77 hemangiomas reported that combination treatment with pulsed dye laser (595 nm) and Nd:YAG laser (1064 nm) was also an effective management strategy. The study utilized ultrasound to more objectively assess hemangioma thickness. Overall, parents reported that treatment results were "good" or "very good" in most lesions. Transient blistering was the main side effect noted [92].

With its depth of penetration to around 4–6 mm, the long-pulsed Nd:YAG (1064 nm) laser has also shown promising results for the treatment of hemangiomas. A 5-year study involving 794 Chinese patients demonstrated greatest efficacy in superficial lesions and older patients (as would be expected by the natural course of infantile hemangiomas). Interestingly, efficacy did not depend on anatomic location of the lesions themselves [93].

Ulceration and pain are specific indications for consideration of laser, though physicians are reminded that laser treatment itself may worsen ulceration, particularly when treating deep or combined superficial and deep lesions. Large, rapidly growing hemangiomas, especially segmental ones on the head and neck, are more likely to ulcerate. Anatomic location (e.g., scalp, lip, and perineum) may also help predict ulceration risk. Rapid reepithelialization—sometimes as early as a few days after initial treatment—has been reported after PDL treatment. Recommended treatment intervals have been based largely on anecdotal reports and range from "weekly" to "every two weeks" [94]. A larger retrospective review of 78 children with ulcerated hemangiomas requiring treatment (mean size of 21 cm^2) followed a protocol using PDL at mean energy 6.6 J at 3–4-week intervals until healing occurred. Seventy-one of the 78 patients responded to PDL alone (mean number of 2 treatments; mean number of 173 pulses per treatment) [95].

Recently, a great deal of attention has been paid to utilizing laser for "hemangioma residua." This refers to the telangiectasias, erythema, and fibro-fatty textural changes that may be left behind after hemangiomas involute. PDL has been demonstrated to be effective in helping to clear residual telangiectasias. Similarly, a 2015 case series involving 20 patients (average age 2.69 years) suggested that treatment with a 532 nm diode laser was effective, with more than half of patients showing a complete response [96].

For fibro-fatty residua, specifically, a 2012 retrospective study of 12 patients with atrophic scar or fibro-fatty tissue demonstrated that ablative fractional yttrium-scandium-gallium-garnet laser could treat these sequelae of involuted hemangiomas with mixed results [97]. A separate observational study suggested that patients could experience at least 50–75% improvement in color, texture, and overall appearance following ablative laser resurfacing [98]. Most likely,

a multimodal approach will prove best, as it often does in the world of pediatrics. Supporting this belief is a single case report, published in 2017, that demonstrated successful treatment of hemangioma residua utilizing a combination of 755 nm alexandrite laser and ablative fractional laser resurfacing with a carbon dioxide laser. Interestingly, the pediatric patient was Fitzpatrick skin type IV who had been previously treated with 6 months of oral propranolol. The protocol utilized the following parameters: 755 nm alexandrite laser at 15-mm spot, fluence 25–30 J/cm^2, 3 ms pulse duration, and cryogen spray cooling with spurt duration of 40 ms. Crucially, pulses were stacked (3–5 per area) at approximately 1 pulse delivered every 3–4 s to minimize epidermal damage. The clinical endpoint was "vessel darkening." A single ablative fractional laser resurfacing treatment was also performed, and the overall clinical outcome was excellent [99].

Surgery

The role of surgery in the management of infantile hemangiomas has been greatly reduced since the advent of beta-blockers as systemic and topical therapeutic options. Rapidly proliferating hemangiomas at risk for hemorrhage, ulceration, functional impairment, and disfigurement remain lesions for which surgery may be an option. Likewise, surgery could be considered in any nonhealing, recalcitrant hemangioma in which case a scar may be a reasonable option to replace the primary lesion. Surgery may also be helpful in repairing the cutaneous defects associated with involuted hemangiomas. In one large retrospective review performed at a tertiary pediatric hospital, a subset of 92 patients (average age of 36 months) underwent surgery for a total of 94 infantile hemangiomas. Most lesions were located on the head and neck, and the mean surface area was 7.75 cm^2. These head and neck lesions were more statistically likely to require multiple modality treatment, reaffirming that a multidisciplinary approach that includes a skilled surgeon may prove beneficial [100].

Intralesional Therapies

The use of intralesional treatment for hemangiomas was much more common in the era preceding systemic beta-blockers; however, interest has recurred with the discovery of laser-assisted delivery of medications. Corticosteroids, propranolol, bleomycin, and bleomycin A5 (pingyangmycin) have all been utilized intralesionally. Many providers prior to the era of systemic beta-blockers utilized intralesional corticosteroid for complicated hemangiomas, especially intraocular lesions. This technique, while effective, may be associated with systemic side effects including adrenal suppression, as several case series have reported [101, 102].

At least one retrospective study of 18 patients (average age 8.6 years) found bleomycin A5 to be "not safe" for infantile hemangiomas because of the medication's association with soft tissue atrophy [103].

Repeated injection with intralesional propranolol was found to be safe but not effective in treating small, noncomplicated hemangiomas in areas of cosmetic concern [104].

In 2014, a prospective feasibility study evaluated the use of fractional carbon dioxide laser-assisted drug delivery of topical timolol in deep hemangiomas. Nine patients, ages 1–6 months, underwent fractional ablative laser resurfacing at 1-week intervals, after which topical timolol maleate 0.5% ophthalmic solution was applied under occlusion for 30 min, four to five times per day for an average of 11.6 laser treatments over an average of 14.2 weeks. Plasma timolol levels were not detected after the first administration of topical timolol, and eight out of nine patients showed good or excellent regression. The authors report that small sample size, lack of a control group, and lack of ultrasonographic assessment of the change in size of hemangiomas after treatment severely limit the general applicability of this study; however, the novelty of the delivery is commendable [105].

Other Treatments Modalities

Electrocautery has historically been utilized for treatment of hemangiomas, especially for superfi-

cial lesions; however, its association with scarring makes it less than ideal in this modern treatment era. Likewise, cryosurgery was utilized as an option for superficial lesions in the 1960s; however, the complications of scarring scars, dyspigmentation, and milia have limited its use. Some renewed interest in cryotherapy developed after a case series of 19 young patients with 24 hemangiomas treated with a device with a constant applicator tip temperature of −32 °C was published in 2000 [106]. Sclerotherapy consists of injecting a sclerosing substance, such as polidocanol, sodium tetradecyl sulfate, or ethyl alcohol, directly into the lesion. Radiation and radioisotope therapy has been used rarely for cases where hemangiomas imminently threaten life or function. Further rigorously controlled studies are needed to better evaluate these treatment modalities and compare them directly to the now-accepted first-line use of systemic beta-blockers.

Treatment Pearls for Infantile Hemangiomas

- Systemic beta-blockers are first-line therapy for complicated lesions;
- Early treatment with laser, either concurrently with beta-blockers or alone, may help prevent rapid growth;
- Ulcerated hemangiomas may benefit from laser;
- Lasers are useful in the treatment of hemangioma residua (telangiectasias, erythema, and fibro-fatty textural changes);
- Surgery has a diminished role in management but remains useful for complicated hemangiomas in specific anatomic locations; and.
- A multidisciplinary approach, when possible, may lead to better clinical outcomes.

Safety and Sequelae Mitigation

When using lasers, wavelength-specific eye protection must be worn by the physician, patient, and all medical personnel in the room. Ocular risks (corneal burns or retinal pigment loss) are devastating but a very controllable risk when diligent safety procedures are practiced [107]. Standard goggles usually suffice for adults but frequently do not fit infants and small children. In these cases, white gauze may be used to ensure that the entire periorbital area is completely covered. If laser surgery is planned in proximity to the eye, then metal corneal shields are necessary. Even then, metal eye shields may not offer complete protection (i.e., they may be incorrectly fitted or placed), and there is at least one report of ocular damage from unexpected heating of the metal eye shield itself after treatment of an eyelid hemangioma with a long-pulsed 1064 nm Nd:YAG laser [108].

Flammability is a concern whenever lasers are utilized near or around a source of supplemental oxygen (i.e., the operating room). Wetting hairs with a water-based lubricant or protecting areas with water-soaked draping may help reduce the risk of combustion.

The most common cutaneous side effects of laser treatment of hemangiomas and PWB are transient and, typically, include pain, erythema, edema, and purpura. The pulse of the lasers has been described as feeling like the "snap of a rubber band." In the authors' opinions, this is a gross underestimate. Nevertheless, procedural discomfort is generally tolerable for teens and adults and, if it is not, these patients are physically capable of saying so. Pediatric patients are a more vulnerable population and may require the use of general anesthesia to facilitate a safe, well-tolerated, controlled laser treatment by minimizing discomfort, emotional stress, and unexpected movement.

Post-laser erythema and edema typically resolve over hours, but may occasionally persist up to days or weeks. If permissible for the procedure, ice and patient positioning (propping the head up with an additional pillow at bedtime) may help to dramatically reduce these symptoms.

Purpura is an expected (and often desired) immediate post-laser finding, as PWB and infantile hemangiomas are typically treated at settings that induce bruising for more effective results. Patients can be reassured that most purpuras typically fade over 1–2 weeks. Lasing without cooling, double-pulsing, or overlapping pulses can lead to blistering and crusting, which should be treated with application of petrolatum ointment at least thrice daily until healed [107].

Permanent side effects are rare and include hyperpigmentation and hypopigmentation (either

from post-inflammatory pigmentary alteration and/or damage to melanosomes) or hypertrophic or atrophic scarring (reported risk of less than 1%) [109, 110]. These risks can be mitigated by selecting the appropriate laser wavelength matched to the patient's Fitzpatrick skin type and thickness of the targeted lesion, the use of epidermal cooling (either cryogen or Zimmer forced air cooling), strict photoprotection prior to and after treatment, and the use of test spots for treatment-naïve individuals. Hair loss, either permanent or temporary, may also be observed after lasing in hair-bearing areas like the scalp or eyebrow.

Risks of General Anesthesia

A recent focus on the risks of neurocognitive deficits associated with prolonged or repeated exposure to general anesthesia has developed, based on findings from young animal studies [111–113]. While no firm conclusions have been demonstrated in human studies, several studies have been published that offer insight into this debate. A sibling-matched cohort study of 105 sibling pairs (one exposed to a single anesthetic episode at a mean age of 17.3 months, one unexposed) demonstrated no statistically significant difference in IQ scores in later childhood [114]. A much larger cohort (33,514 anesthesia-exposed children compared to 159,619 unexposed children) demonstrated that 0.41% and 0.97% of anesthesia-exposed children had lower school grades and lower IQs, respectively [115].

Three retrospective chart reviews inform our understanding of the risks of general anesthesia in the specific setting of laser-treated pediatric patients with vascular lesions. In 1997, Grevelink et al. published the outcomes of 179 patients, aged 5 weeks to 18 years old, who underwent a total of 745 treatments: 78% in office and 22% in the same-day surgical unit. No side effects were observed in 76% of patients. The two most common reported side effects—laryngospasm upon emergence from general anesthesia and nausea/vomiting—were experienced by 10% and 6% of patients, respectively. The overwhelming majority of patients reported a positive experience. Overall, general anesthesia was shown to be effective in minimizing pain and discomfort associated with laser treatment, and, moreover, more pulses per treatment could be performed [116].

A multicenter retrospective review of 881 procedures performed on 269 children revealed 90% of patients experienced no clinically relevant complications. Nausea was the most commonly reported side effect (4% of patients). The authors postulated that the low complication rate of general anesthesia in elective dermatologic cases was secondary to the good baseline health of their patients, short procedural duration, the elective nature of the procedures, and the use of pediatric anesthesiologists [117].

A recent retrospective study of 33 patients averaging 6.7 laser treatments under general anesthesia before the age of 4 found no increased risks of neurodevelopmental abnormalities. The prevalence rates of speech and language disorders, attention-deficit hyperactivity disorder, anxiety, behavior disorders, and motor disorders were similar to those reported in the US population [118].

Based on available evidence in humans, one-time use of general anesthesia for the laser treatment of pediatric patients appears to be safe with a low rate of complications. Less data exists for serial treatments under general anesthesia, and it is unclear if there is a critical point at which the risks outweigh the benefits. Long-term, rigorous studies are underway, the results of which should provide the laser surgeon with some much-needed guidance.

Patient Preference and Informed Consent

Treatment of vascular lesions often requires multiple sessions over months to years. A physician-patient-parent partnership founded in trust and understanding of the process, duration of treatment, expected outcomes, and risks is essential to ensuring compliance as well as good medico-legal outcomes. Discussing preferences of the patient and/or parents can help achieve this relationship and should be considered in any discussion concerning which treatment modality to use.

Any Informed consent discussion should emphasize the commitment to the treatment process and the risks and benefits associated with the specific modality being utilized. Patients and

parents of children with PWB and infantile hemangiomas should carefully consider the holy grail of "total resolution" against the very real risks of pigmentary alteration, ulceration, scarring, blistering, and textural abnormalities associated with laser therapy. It is even more important to consider these risks against the expected natural progression of the lesions themselves, specifically, a tendency for PWB to hypertrophy and bleb with time and an expectation for most infantile hemangiomas to involute at least to some degree with time. Patients and parents should also be aware of the possibility that treatment (particularly of deep or complicated hemangiomas) may not lead to any appreciable improvement at all and may only result in adverse events [119].

Cost of intervention should also be a consideration for patients, their families, and the health system at large. Though most insurance companies cover pulsed dye laser therapy of infantile hemangioma and PWB, variability does exist between carriers, and the determination of medical necessity is sometimes dependent on anatomic location (face and neck appear to be preferentially covered) and/or the presence of bleeding, infection, pain, ulceration, or documented functional impairment. Presence of any of these signs and symptoms should be well-documented to ensure a positive prior authorization review.

Conclusion

Myriad treatment options for port-wine birthmarks and infantile hemangiomas exist, with no universal consensus on what constitutes the safest and most efficacious treatment modalities. Even less is certain regarding the use of these interventions in the pediatric and adolescent populations due to a lack of controlled trials within these age groups. Nevertheless, much progress has been made in the last several years with multimodal therapy yielding tremendous clinical improvements and technological enhancements. The emergence of specific therapies that target specific molecular and cellular pathways—used alone or in combination with procedural interventions—represents a promising future in the management of these vascular lesions.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Treatment recommendations for PWB and hemangiomas

PWB treatment recommendations	**Level of evidence**
PDL (585 nm or 595 nm) is the preferred treatment of flat PWB for patients with all skin types. Best results are achieved when treatment is initiated early, ideally within the first year of the patient's life	B
755 nm alexandrite and 1064 nm Nd:YAG lasers are the preferred treatment for PDL-resistant and hypertrophic PWB. Treatment should be performed only by physicians with extensive laser experience	B
755 nm alexandrite, 1064 nm Nd:YAG, 532 nm Nd:YAG, and PDT can be considered as second-line treatment modalities for PWB. Treatment should be performed only by physicians with extensive laser experience	B
Hemangioma treatment recommendations	**Level of evidence**
Systemic beta-blockers are the preferred treatment for complicated hemangiomas	A
PDL can be considered for the following situations: Patients who cannot tolerate beta-blockers Small, thin, superficial lesions Lesions with ulceration and associated pain Hemangioma residua	B
Fractional ablative laser alone or in combination with 755 nm alexandrite laser can be used to improve color, texture, and overall appearance of hemangioma residua	C
Surgery can be considered as part of a multidisciplinary approach to complicated hemangiomas (lesions at risk for hemorrhage, ulceration, functional impairment, and disfigurement)	C

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Self-Assessment

1. Port-wine birthmarks and Sturge-Weber syndrome share a common mutation (GNAQ). What anatomic locations of PWB confer the highest risk for SWS?
   (a) Forehead
   (b) Eyelid
   (c) Temple
   (d) Cheek
   (e) A & B
2. What techniques can be used to limit post-inflammatory hyperpigmentation when using lasers to treat a patient with skin of color?
   (a) Double-pulsing with 20% overlap
   (b) Single-pulsing with minimal to no overlap
   (c) 4–6-week treatment interval
   (d) Strict photoprotection for 3–4 weeks after treatment
   (e) B & D
3. When counseling a patient with PWB and the family about pulsed dye laser, which of the following is **INCORRECT**?
   (a) Lightening of the PWB is directly related to the number of treatments. Most patients require six or more treatments.
   (b) One expected side effect is purpura, which reaches maximal intensity 1–2 days after treatment, and gradually fades over the next 7–10 days.
   (c) 50% improvement in color can be seen after the first treatment. On average, over 75% of patients will have complete resolution of their PWB.
   (d) Treatment is most successful when initiated within 3 months of life.
   (e) Central facial PWB tend to be more resistant to PDL treatment than lesions on the lateral face and neck.
4. Factors that may contribute to the lack of good comparative data for the evaluation of different modalities in the treatment of port-wine birthmarks and infantile hemangiomas include:
   (a) A lack of reliable animal models that has hampered in vivo research.
   (b) A lack of universally accepted, validated assessment tools that makes grading clinical improvement of port-wine birthmarks or hemangiomas before and after intervention difficult.
   (c) There are no universally accepted "expert consensus" recommendations or definitive treatment guidelines.
   (d) Authors may be disincentivized to publish "negative" results.
   (e) All of the above.
5. First-line treatment of a rapidly growing periocular hemangioma should include an assessment to initiate which therapy?
   (a) Radiation
   (b) Intralesional corticosteroid
   (c) Systemic beta-blockers (oral propranolol)
   (d) Oral corticosteroids
   (e) Nd:YAG (but only with metal eye shields in place)

Answers

1. e: Forehead and eye involvement of the PWB confer risk of SWS. An ophthalmologic examination is recommended for any infant with eyelid involvement and neuroimaging (brain MRI with gadolinium contrast) for those with extensive bilateral, hemifacial, or median forehead PWB.
2. e: Conservative settings administered via single pulses with minimal to no overlap, avoidance of pulse stacking, longer treatment intervals (6–8 weeks), strict post-laser photoprotection, and delaying additional treatment until any post-inflammatory hyperpigmentation has resolved are all essential components to minimize risk of hyperpigmentation when treating darker-skinned individuals.
3. c: On average, 12% improvement can be appreciated with each PDL treatment. Only 40% of patients achieve "good" lesional clearance, the rest experience suboptimal or even no improvement.
4. e: All of these stated factors may confound the ability to perform rigorous head-to-head comparisons of interventional modalities for port-wine birthmarks and infantile hemangiomas. There is much clinical and technological progress to be made!
5. c: Systemic beta-blockers (oral propranolol) are now the first-line therapy of choice for complicated hemangiomas. This rapidly growing lesion could compromise function, so a quick-acting, reliable therapy is necessary. If the lesion proves recalcitrant to systemic beta-blocker therapy, then additional modalities could also be considered.

Rosacea

58

Shlomit Halachmi

Abstract

Rosacea is a chronic inflammatory disorder of the skin that develops in adults and progresses with age. Treatment is guided for each subtype based on its major presenting clinical features: erythema, inflammation, and tissue hypertrophy. A 2015 Cochrane Database Review showed that most high-level evidence studies address topical and oral therapies used for papulopustular rosacea. This chapter surveys peer-reviewed studies of ten or more subjects reporting outcomes of energy-based, surgical, and injection procedures. The erythematous and papular components of rosacea respond well to light in the near-infrared range (532–1064 nm), with response rates of 55–96% after a series of sessions, but relapse is high. Studies comparing response to different light sources reveal minimal differences in their effectiveness. Phymatous changes respond to destructive and surgical modalities, including electrocautery, CO_2, and surgical debulking, with comparable outcomes. Photodynamic therapy has been proposed but does not provide significant benefit. Low-level evidence suggests possible effects of intradermal microdroplet botulinum toxin injections.

Keywords

Laser · Rosacea · Inflammation
Telangiectasia · Electrocautery · Rhinophyma

Epidemiology

Rosacea is a chronic inflammatory disorder of the skin that develops in adults and progresses with age. Epidemiological studies have shown rates of 2–22% prevalence of rosacea depending on the populations studied. The relatively wide range is likely attributable to regional variation in skin phototypes and environment, but most studies point to a prevalence of 10% in the United States and Europe. Risk factors include European or Celtic heritage and lighter skin types.

Rosacea can further be exacerbated in susceptible individuals by any element that can cause flushing:

- sun exposure
- heat
- consumption of spicy food, hot beverages, or alcohol
- physical exertion
- emotional flushing

The nearly ubiquitous Demodex mites, estimated to reside in the skin of 80–100% of adults, have also been suggested as an underlying factor in rosacea. This theory is supported

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Table 58.1 Rosacea subtypes

	Main clinical features	Targets for treatment
Erythematotelangiectatic rosacea (ETR)	Facial erythema, flushing, telangiectasia	Vascular structures
Papulopustular rosacea (PPR)	Central facial erythema, acneiform papules, and pustules	Inflammation
Phymatous	Hypertrophy and irregular cobblestoning of the nose	Hypertrophic tissue
Ocular	Blepharitis, Meibomian gland dysfunction	Inflammation

by several studies of Demodex prevalence in rosacea-affected skin and by the response, in some cases, to antiparasitic treatment.

To guide management, rosacea is classified into subtypes based on the major presenting clinical features (Table 58.1). These in turn drive the main treatment target.

As reported in a 2015 Cochrane Database Review of interventions for rosacea, most of the high-level evidence studies from randomized controlled studies (RCTs) address topical and oral therapies used for papulopustular rosacea (PPR) (1a) [1]. The Review concludes that laser- and light-based device studies are of low quality and summarizes a few. This chapter, in complement to the medical therapies review, addresses only manual interventions and includes procedures, whether energy-based, surgical, or injectable, of treating ETR, PPR, and phymatous rosacea. The studies are not amenable to pooling due to wide variation in methodology and lack of standardized core outcomes [2]. For this chapter, studies that include ten or more subjects are included regardless of methodology.

Treatment Overview: Energy-based Devices

Erythematotelangiectatic (ETR) and phymatous rosacea are most amenable to procedural interventions. Technologies that target hemoglobin-rich targets, including laser, intense pulsed light (IPL), and electrocoagulation (EC) can be used to treat either diffuse erythema or discrete telangiectasia. Phymatous changes of the nose can also be treated with debulking procedures for reduction of hypertrophy and improvement of texture. The favored technologies for treating ETR are primarily those that emit light in the visible and near-infrared range (532–1000 nm), while those used to treat phymatous rosacea are nonspecific long-wavelength ablative lasers.

The sources of energy reported in the treatment of rosacea include:

ETR and PPR

532 nm	Potassium titanyl phosphate laser (KTP)
585–595 nm	Pulsed dye laser (PDL)
1064 nm	Neodymium doped:yttrium-aluminum-garnet laser (Nd:YAG)
400–1200 nm	Intense pulsed light systems (IPL), with variable filters

Phymatous Rosacea

10,600 nm	Carbon dioxide laser (CO_2)
Electrodessication	

Rosacea commonly affects individuals whose skin has low background melanin levels and limited ability to generate melanin in response to ultraviolet light. In skin that tans easily, ultraviolet (UV)-induced damage triggers melanin production, protecting the skin from further UV-induced damage. In lighter skin types, the skin cannot mount this response and therefore is more susceptible to UV damage, manifested in part by inflammation and vasodilation, leading to redness. Further, in lighter skin the reedness is more visible because there is little melanin to mask the redness.

Treatment of redness in rosacea rests on targeting of hemoglobin in the superficial blood vessels. Since rosacea tends to develop in lighter skin phototypes, treatment with lasers is aided by the relatively higher ratio of hemoglobin to melanin. The higher density of the target chromophore, hemoglobin, and the relatively lower density of the competing chromophore, melanin, improve

the therapeutic window when lasers emitting visible light are used. Due to the wavelength-dependent penetration of light into skin, the use of shorter wavelengths, including those that are well absorbed by hemoglobin, can provide adequate vascular coagulation with lower energy doses. Therefore, it may be anticipated that visible light would have a wider therapeutic window than some of the longer-wavelength lasers or electrocoagulation, which penetrate more deeply and which may produce greater nonspecific tissue heating due to absorption in water.

Lastly, rosacea occurs on the central face, an area that is rich in sebaceous glands and is capable of rapid healing with lower risk of scarring than other sites. Therefore, aggressive debridement of hypertrophic tissue, as is seen in phymatous changes of the nose, is remarkably safe and effective on the nose, allowing the use of ablative lasers.

Effectiveness of Commonly Available Methods for Treating ETR and PPR

Vascular lasers used to treat the erythema or telangiectasia of ETR are effective, most often after a series of treatments. Larger spot size lasers or IPL are appropriate for treating diffuse erythema, while discrete vessels are targeted with small laser spot sizes. Pulse duration and power are selected based on provider and patient preferences of the desired immediate visible endpoint, which may be erythema or purpura. The relative effectiveness of purpuric vs. nonpurpuric treatment has been assessed in a few studies, but the choice is made ultimately by the patient's willingness to bear purpuric lesions on the face for 7–10 days.

Treatment is repeated after a variable interval until the desired response is achieved. As the erythema and telangiectasia improve, treatment parameters can be adjusted for the clinical presentation.

The signs of rosacea invariably recur because procedure-based treatments target the signs of rosacea but do not alter the underlying predilection. Avoidance of known triggers can delay recurrence. The time to recurrence may be months or years and is not routinely monitored in studies or in clinical practice. Additional treatments, if needed, can be performed at the time of recurrence.

Potassium Titanyl Phosphate Laser (KTP), 532 nm

Studies of KTP in the Treatment of Erythematotelangiectatic Rosacea (ETR)

Maxwell et al. assessed 14 patients with ETR in a prospective randomized blinded clinical trial (1c) [3]. One side of the face was treated with 532-nm laser. A subset of patients was also instructed to apply retinaldehyde to the face. Patients underwent six treatments over 3 months. Patients and five blinded evaluators scored digital images using a 5-point improvement scale to assess reduction of overall redness and of telangiectasia, difference between the treated and untreated hemiface, and skin texture improvement. All patients reported mild-to-moderate improvement. However, blinded evaluators could identify correctly the treated and untreated sides only 47% of the time. Due to the use of a topical treatment in a subset of subjects, it is not possible to pool all laser-treated hemifaces. Therefore, the number of subjects in each treatment group does not support statistical conclusions.

Insufficient data is available for rates of adverse events in treatment of rosacea with KTP. The expected adverse events include edema, purpura, blistering and scabbing, and pigmentary changes, and the risk is dose-dependent. Pigmentary changes might be less common due in rosacea than in other vascular lesion treatments due to the higher proportion of rosacea in lighter skin types. Scarring has been reported for KTP treatment of superficial vascular lesions, but accurate rates in rosacea are not available (4) [4].

Pulsed Dye Laser (PDL)

Studies of PDL in Erythematotelangiectatic Rosacea (ETR)

The largest portion of clinical studies evaluates the safety and effectiveness of PDL. The studies are not amenable to pooling, but all support PDL's effectiveness and safety. The primary outcome for most studies is degree of improvement,

largely assessed by subjective scales, and at times aided by device-based measurements of erythema. Some studies directly examine impact on quality of life (QoL).

Tan et al. published a retrospective study of 40 consecutive patients whose facial erythema was treated with PDL at purpuragenic parameters (585 nm, 0.45 ms, 5.4–6.5 J/cm^2, spot sizes 5 or 7 mm). Telangiectasia were treated with an additional pass using 3-mm spot and fluence 6.5–7.5 J/cm^2 (4) [5]. The average number of treatments was 2.4 [range 1–10] and the average follow-up time was 2 years [range 6 months to 4.5 years]. Subjects, family members, and 10 hospital staff rated improvement on a 5-point scale (1 = worse; 2 = no improvement; 3 = slight improvement; 4 = moderate improvement; 5 = marked improvement). Subjects and families rated improvement at 4.4 and 4.3, respectively, and the mean score of the judges was 3.7. During the treatment and follow-up, three patients experienced exacerbations requiring antibiotics; six developed post-inflammatory hyperpigmentation; and three developed recurrent erythema after 6, 16, and 52 months. Study limitations include the use of a nonsymmetric improvement scale (2/5 is the neutral score, with 1 score to assess worsening and 3 scores to assess improvement) and the pooling of all subjects despite wide variation in the number of treatments without a dose-response analysis correlating improvement and the number of treatments.

Jasim et al. assessed response to subpurpuragenic PDL in 12 subjects with rosacea-associated telangiectasia (4) [6]. A single treatment was performed at 595 nm, 6 ms, and fluence 7–9 J/cm^2 titrated to produce transient violaceous change. Pretreatment images were compared to images taken 6–8 weeks after treatment, and the percent reduction, in quartiles, was subjectively assessed. Two of the 12 subjects (17%) scored improvement of >75%, two subjects (17%) improved 50–75%, and five (42%) improved 25–50%. No subjects developed purpura or adverse events. These improvement rates are slightly lower than those reported in other PDL studies, perhaps reflecting the use of a single treatment session. However, the overall positive response to a single treatment combined with an absence of purpura generates a net positive benefit:risk ratio and supports offering this option to patients.

A similar study by Bernstein et al. in 2008 reported the response of 20 subjects with linear telangiectasia and diffuse facial erythema (4) [7]. Telangiectasia were treated with a 595-nm, long-pulse, elliptical spot, followed by full-face treatment with short-pulse circular spots. Parameters were adjusted for each patient. Severity was graded on a 0–6 scale before and 8 weeks after the last treatment. All subjects experienced some improvement, and no severe adverse events were reported. The mean severity score by blinded physician observers was 2.3 ± 1.3 at baseline and 1.4 ± 0.9. The mean per-patient change in score is not reported. The study is limited by the lack of untreated controls, partial blinding, and variable parameters. The low mean baseline score of 2.3/6 supports benefit of the approach for mild-to-moderate rosacea; the response of more severe rosacea is not addressed.

Studies of PDL in Papulopustular Rosacea (PPR)

Lowe et al. assessed the effects on PPR in 27 patients who had been treated for telangiectasia and erythema with 585-nm flash lamp-pumped dye laser (FPDL) (4) [8]. Of the 27 patients, 24 had improved erythema after one to three treatments. Papular and pustular activity decreased in 59.2% of the patients, and those with severe pre-treatment PPR exhibited the greatest degree of improvement.

In a similar study, Berg et al. treated ten subjects with erythema and telangiectasia using FPDL and then followed them for change in papulopustular activity (4) [9]. Ten months after treatment, five subjects had fewer lesions of PPR, three were unchanged, and two had more lesions.

The outcomes reported in these studies are similar: 50–59% of subjects treated for the vascular component had additional benefit in the papulopustular component. However, the authors summarize their findings differently: Lowe et al. propose that the response to FPDL is significant, while Berg et al. state that FPDL is of limited

value. A fair conclusion may be that FPDL is best suited for ETR and that some patients (approximately half) may also experience reduction in PPR.

Neodymium Doped:Yttrium-Aluminum-Garnet Laser (Nd:YAG)

Studies of Nd:YAG for Papulopustular Rosacea (PPR)

Lee et al. treated 30 Korean subjects with PPR using long-pulsed Nd:YAG (4) [10]. Group A (22 patients with mild-to-moderate PPR) were treated with laser only, and Group B (8 patients with severe PPR) were treated with laser and doxycycline 100 mg BID. Three treatments were provided (1064 nm, 10 mm, 50 ms, 40–50 J/cm^2, with dynamic cooling) at 4-week intervals. Three dermatologists assessed blinded photographs after 4 weeks using a 4-point severity scale. Laser alone yielded good improvement in 17 of 22 subjects (77%), while laser and doxycycline yielded good response in 7 of 8 (88%). All tolerated treatment well. Due to the small number of subjects in group B, and the inclusion of severe PPR only in group B, the two groups cannot be compared. The study suggests that long-pulse Nd:YAG is safe and effective, though no conclusions can be drawn regarding added benefit or risk of cotreatment with doxycycline.

Intense Pulsed Light (IPL)

Studies of IPL for ETR and PPR

Taub et al. report a study of 32 adults with facial erythema refractory to medical management who underwent treatments with IPL (2.4/4.0 ms double pulse with 20 ms delay, 32–36 J/cm^2 at 570-nm filter or 27–32 J/cm^2 at 560-nm filter) (4) [11]. Twenty-eight subjects completed the study, with a mean of 3.6 treatments per patient and mean follow up of 3.7 months. Three subjects experienced adverse events (purpura, peeling, or post-inflammatory hyperpigmentation). Most patients reported improved redness (83%), improvement in flushing (75%), and reduction of acneiform lesions (64%). Two subjects reported no benefits.

Kawana et al. treated 12 adults (6 with ETR and 6 with PPR) with rosacea using IPL (550–670 nm) for a total of 3 sessions at 4-week intervals (4) [12]. Spectrophotometer measurements showed that skin color approached those of unaffected skin in 6/6 ETR and 5/6 PPR subjects (total response rate 91.6%), with greater mean reduction in erythema in ETR.

Taub and Devita treated 21 patients with moderate-to-severe rosacea with either three or five monthly full-face treatments using IPL 470–980 nm combined with radiofrequency (4) [13]. Patient- and physician-reported improvements in flushing, erythema telangiectasia, and global severity indicated improvement after three treatments, with marginal additional improvement after five treatments. The study does not compare results with IPL alone, at comparable light dosing. The treatment was well-tolerated, but the greater penetration depth of RF than of visible light could lead to heating in deeper, nontarget tissues.

Kassir et al. evaluated the effects of IPL fluence, pulse duration, and pulse stacking on treatment response (4) [14]. IPL was used to treat 102 patients with mild-to-severe rosacea using 2.5/5 ms pulses, with one, two, three, or four stacked pulses delivered with 20–30 ms delay. ETR was treated with 530-nm filter and fluence 10–30 J/cm^2, while PPR was treated with 420 nm filter and fluence 10–20 J/cm^2. Patients underwent a mean of 7.2 treatments at 1–3-week intervals. Digital analysis of images showed that 80% of patients had reduced erythema. In patient-reported outcomes, 78% reported reduced flushing and 72% reported reduced papular lesions. The authors conclude that the parameters used describe optimal settings. Considering the multiple permutations (two wavelengths, variable fluence, and 1–4 pulses stacked) and the application to two patient types, the study does not provide sufficient power for any single parameter set to determine that its outcome defines the ideal protocol. The data do, however, support effectiveness and safety of IPL for treatment of ETR and PPR.

Liu et al. compared the effectiveness of IPL (540–950 nm) in treating different elements

of erythema associated with rosacea (3b) [15]. Sixteen patients with ETR and 16 with PPR underwent three treatments at 3-week intervals. Improvement in erythema was assessed by two dermatologists using a quartile grading scale [0, ≤25% improvement; 1, 26–50% improvement; 2, 51–75% improvement; 3, 76–100% improvement]. Patients reported satisfaction with treatment outcomes using a 10-point scale. All 30 subjects completing the study improved, with the PPR subjects showing higher mean improvement scores (2.1 ± 0.7 vs. ETR group, 1.4 ± 0.5; $p = 0.003$) and >75% improvement in 5/15 PPR subjects vs. 0/5 ETR subjects ($p = 0.026$). Patient satisfaction was higher (6.9 ± 1.5 PPR vs. ETR group, 5.6 ± 1.5; $p = 0.026$). It should be noted that for PPR the improvement cited was in perilesional erythema, and not in the number of papules or pustules. Therefore, this study may be assessing the response of discrete (and transient) erythematous lesions in PPR to that of more global erythema and telangiectasia of ETR.

Combination Treatments

Studies of Combination Treatments for Erythematotelangiectatic Rosacea (ETR)

Kim et al. sought to increase the available chromophore in rosacea by pretreating the face with topical niacin to induce flushing (3b) [16]. Eighteen subjects underwent split-face treatment with 585-nm PDL after application of niacin to one side. Both sides of the face were treated with the same PDL parameters using subpurpuragenic setting for three sessions at 3-week intervals. Erythema was assessed by polarization color imaging, as well as by three blinded dermatologists and by the subjects. Subjects and blinded evaluators rated improvement as better on the niacin-treated hemiface ($p = 0.007$ and 0.0050), but imaging measurements showed no significant difference between the two sides. The reasons for this discrepancy are not clear. A limitation of the study is that the treatments were performed on flushed vs. non-flushed hemifaces, but the evaluation was done in the absence of the same stimulated flushing. It is possible that niacin leads to dilation of smaller capillaries that are not visible in the absence of a flushing trigger, but has a lesser effect on already dilated pathological vessels that are visible "at rest." In such a case, the niacin treatment could increase laser absorption in the "triggerable" background vessels, resulting in reduced flushing upon stimulation. Such effects may not be visible at rest. Perhaps this explains the perception of patients, who experience less flushing on the niacin-treated side, but the absence of objective differences in static erythema at rest.

Karsai et al. assessed the benefits of combined treatment with PDL and Nd:YAG, on the premise that 595-nm exposure leads to temporary conversion to methemoglobin, which has particular affinity for 1064-nm light (3b) [17]. The split-face study assessed the application of sequential dual wavelengths (595 nm then 1064 nm) versus 595-nm PDL or 1064-nm Nd:YAG alone in 20 subjects. Telangiectasias on one side of the nose were treated with PDL (595 nm, 7 mm, 10 ms, 10 J/cm^2) followed immediately (100 ms delay) by Nd:YAG (1064 nm, 7 mm, 15 ms, 70 J/cm^2). The other side of the nose was treated with either PDL or Nd:YAG. Four weeks after a single treatment, blinded assessment of before and after photos showed greater improvement after dual laser than after 595 nm or 1064 nm alone ($p < 0.05$). There was no significant difference between 595 nm and 1064 nm alone. The authors conclude that sequential delivery of 595-nm and 1064-nm laser can provide a synergistic approach to treatment. Study limitations include lack of controls for total light dose (total power delivered) and for evaluation of additive vs. synergistic effects of 595 nm and 1064 nm. The former limitation could be assessed in part with a control study arm in which hemifaces were treated with dual-pulse 595 nm/595 nm or 1064 nm/1064 nm at the parameters of the sub-pulses in the active arm. The latter could be assessed by reversing the order in which 1064-nm and 595-nm light were delivered or by delivering 595 nm/1064 nm with ultrashort interpulse delay vs. long interpulse delay; either approach would reveal whether pre-exposure to 595 nm immediately prior to 1064 nm provides increased benefit to other combinations in the treatment of rosacea.

Other Procedures

Photodynamic Therapy (PDT)

A consensus panel statement published in 2006 provided recommended light sources for use with 5-aminolevulenic acid (ALA) in photodynamic treatment of rosacea, based on the experience of the panel members (5) [18]. The consensus report recommends the use of ALA with PDL using pulse stacking, or with visible light sources (blue, green, yellow, red). A recommended protocol is two treatment sessions at 2–5-week intervals, with increased ALA incubation times in the second treatment.

Calzavara-Pinton et al. assessed the response to PDT with methyl aminolevulinate (MAL) in a retrospective chart review of 20 hospitals in Italy who used the procedure for off-label indications (4) [19]. Although acne responded well, rosacea was less responsive and PDT did not appear to be a viable treatment.

Botulinum Toxins

Dayan et al. treated 13 patients with intralesional microdroplet injections (0.05 cc) of onabotulinumtoxinA, reconstituted as 100 units in 7 cc saline (4) [20]. Intradermal injections totaling 8–12 units per cheek resulted in reduced erythema after 1 week, sustained for 3 months.

Bloom et al. enrolled 25 subjects with ETR, injecting 15–45 units of abobotulinumtoxinA into the dermis over the nasal tip, ridge, and alae (4) [21]. Fifteen subjects completed the study. The treatment resulted in reduced mean erythema severity scores at 1, 2, and 3 months after treatment ($p < 0.05$, $p < 0.001$, and $p < 0.05$, respectively). Pairwise comparison of 3-month erythema score to baseline showed statistically significant reduction at all time points.

Effectiveness of Commonly Available Methods for Treating Phymatous Rosacea (Rhinophyma)

Abundant literature is available for procedures used to treat rhinophyma. However, most reports include small case series, and all are retrospective, non-blinded, and non-controlled. Reports that include ten or more patients are summarized below.

Carbon Dioxide Laser (CO_2)

Karim et al. report their experience from 1983 to 1993 in treating 18 patients with good results and safety and durability of response which they defined as "curative" (4) [22]. El-Azhary et al. report 30 patients treated by CO_2 ablation from 1986 to 1989 (4) [23]. If rhinophyma was severe, CO_2 excision was used for debulking prior to vaporization. Treatments were generally well tolerated, with infrequent hypopigmentation, scarring, and a single case of alar lift.

Madan et al. review their experience with 124 cases of treating rhinophyma with CO_2 under local anesthetic (4) [24]. The approach applied CO_2 in continuous mode to debulk, followed by reshaping the contours using either defocused 2–3 mm beam or resurfacing mode (scanner) with 4–7 mm spot. Most patients (118) experienced good outcomes with no serious adverse events. Six patients had scarring, hypopigmentation, or dilated pores.

Corradino describe their results in 14 men treated with a similar approach, the "downward steps" technique, in which high-power CO_2 is used for initial debulking, followed by progressive reduction of power for coagulation and finer shaping in a single procedure (4) [25].

Electrosurgery

Clark and Hanke report the use of electrosurgery to treat 13 patients with severe rhinophyma (4) [26]. The technique was particularly well suited for patients with lobular rhinophyma. In contrast, patients with generalized hypertrophy of the nasal tissue had poorer outcome and higher risk of scarring. The authors cite the lower cost of equipment as a significant benefit over laser treatment.

Relative Effectiveness of Procedures

Few comparative studies evaluate the benefits of one energy-based device over another. Due to the variability of treatment settings and baseline severity, there is insufficient evidence to render a clear distinction between the available devices.

ETR: PDL Versus Nd:YAG

Alam et al. compare the effectiveness of nonpurpuragenic 595-nm PDL with 1064-nm Nd:YAG for diffuse facial erythema in a split-face, double-blind randomized controlled trial (1b) [27]. Cheeks were treated with either PDL or Nd:YAG monthly for four treatments. In 14 evaluable subjects, spectrophotometer readings showed PDL led to greater improvement than Nd:YAG (8.9% vs. 2.5%), correlating with better subject-reported improvements with PDL than Nd:YAG (52% vs. Nd:YAG 34%). Both treatments were safe, though PDL was perceived as more painful than Nd:YAG. The authors suggest that Nd:YAG may have a relative benefit in darker-skinned patients, particularly due to less pain.

Similarly, Salem et al. reported a split-face study comparing the response to PDL and Nd:YAG in 15 patients with ETR (1c) [28]. After three monthly sessions, 73% of Nd:YAG-treated patients had significant reduction in erythema and telangiectasia vs. 53.3% of PDL-treated patients. Substance P staining in skin biopsies showed lower substance density after Nd:YAG than PDL, correlating with clinical response. This study was performed in Egypt, where sun exposure and skin phototype effects may have affected parameters' selection for each device. This appears to be in agreement with the suggestion posed by Alam et al. that Nd:YAG may have an advantage in darker phototypes [27].

ETR: PDL Versus IPL

Neuhaus et al. report a randomized, controlled, single-blind, split-face trial comparing nonpurpuragenic PDL treatment, IPL, and untreated control (1b) [29]. Twenty-nine subjects underwent 3 monthly treatment sessions (PDL, 10 mm, 6 ms, 7 J/cm^2, with cryogen cooling; IPL, 560-nm filter, 2.4/6.0 ms pulse train with 15 ms delay, 25 J/cm^2). Evaluation measures included spectrophotometric erythema scores, blinded investigator grading, and patient assessment of severity and associated symptoms. Both nonpurpuragenic PDL and IPL reduced erythema and telangiectasia in spectrophotometric analyses and blinded evaluations, with equivalent safety and effectiveness.

Rhinophyma: Scalpel Versus CO_2

In 1993, Har-el et al. retrospectively review the charts of 23 patients treated surgically for rhinophyma: 16 had undergone CO_2 laser ablation, and 7 had sharp blade excision (4) [30]. No differences were identified in the length of surgery, preservation of normal tissue, pain, outcome, or adverse events, although the laser procedure was easier for the providers and support staff.

In 2013, Lazzeri et al. reported their long-term results in 67 patients treated by either tangential scalpel excision (N = 45) or CO_2 (N = 22) (4) [31]. Outcomes were comparable. They conclude that the accuracy and precision of the lasers are not justified by cost of the device.

Preoperative Evaluation and Patient Selection

Papulopustular rosacea (PPR) is generally managed by medical therapies, including topical and oral antibiotics, often with good outcomes. Procedures are not first-line therapies for PPR. As described above, laser-based procedures targeted at ETR may offer some benefit to PPR in addition, but patients should be advised that the treatments are not intended to reduce the papular/pustular activity.

The flushing, fixed erythema, and telangiectasia of ETR are the visible sequelae of vascular pathology. Unlike PPR, the changes visible in ETR are anatomic and do not respond to medical therapies. Vascular lasers can coagulate the structures visible in ETR with excellent results. However, the underlying causes of the vascular change are not affected by the procedure. Consequently, erythema nearly always recurs.

Rhinophyma is best treated with ablative modalities. Mild or early cases, particularly in younger adults, are best treated by mild ablative means ("vaporization"), whereas larger, lobular hypertrophic areas require excision, either by ablative laser or scalpel. Few larger studies are available to compare scalpel and CO_2 excision. Two summarized above conclude that there are not significant differences in patient outcomes, though the laser approach may be preferable to providers.

Impact of Patient Preference

Patients being treated for ETR may be able to choose among IPL, purpuragenic PDL, non-purpuragenic PDL, and Nd:YAG. The literature summarized above suggests that results are comparable for effectiveness overall, though Nd:YAG may be a better option for darker phototypes due to reduced absorption by melanin at 1064 nm. Patients may have a strong preference, however, between purpuric and nonpurpuric PDL, given the profound visual appearance of PDL-induced purpura on the face.

Due to variable treatment parameters in the studies, there is no data regarding a correlation between the choice of device and recurrence rates. However, all procedures share a common goal of reducing the density of vascularity in the skin, and treatment is concluded when that endpoint is achieved. It is reasonable to predict, then that the visible reductions in erythema are accurate measures of vascular reduction at an anatomic level and that regardless of the means for achieving the reduction in vascularity, the rate at which future erythema will develop is more closely dependent on the substrate (the patient's genetics and environment) than on the technical energy parameters used.

Typical Treatment Plan

Patients referred with a diagnosis of rosacea should be evaluated first to confirm the diagnosis and identify the subtype. Typically, rosacea affects adults, particularly those with Fitzpatrick skin types I–III. Rosacea affects primarily the midface but can also include the chin and lateral cheeks, particularly over the malar eminences. Involvement that spares the midface, or which is primarily located in the periphery of the face and jawlines, may suggest other acneiform disorders. Rosacea, in contrast to acne vulgaris, does not exhibit comedones. Upon history, patients may confirm family history of rosacea, symptoms of flushing, and gradual worsening over time.

Papules and pustules point to PPR. This is best treated with topical or oral prescription medications. More severe cases may require treatment with isotretinoin. Recent use of isotretinoin should be elicited prior to beginning any procedure, as there have been reports of increased risk of hypertrophic scarring when procedures are performed within 6 months of isotretinoin use.

Redness in the absence of papules, whether fixed or "flushing," is associated with ETR. The erythema and telangiectasia, especially of the nose, chin, and cheeks, can remain despite well-managed PPR.

Trophic changes to the nose, including increase in bulk or cobblestone texture, are hallmarks of phymatous rosacea.

Patients with ETR are likely to benefit from vascular light-based treatments. Smaller areas or discrete telangiectasia can be treated with lasers with a small spot size. Larger areas of erythema can be treated with larger spot sizes (10 mm or larger), long pulse durations (10 ms), and lower power (titrated to temporary color change in the treated spot). Pulsed dye laser is a common first-line choice. As summarized above, some articles cite the effectiveness of nonpurpuragenic settings (pulse durations 6 ms or higher, with fluence titrated to visible vasospasm). Other providers state that their experience guides them to offer purpuragenic treatment parameters (pulse duration 1.5 ms or shorter) with the possibility of requiring fewer treatments to reach clearance. The appearance of purpura, as prominent circles of purple on the face for a week to 10 days, should be clearly explained to the patient, preferably with photographs, to support decision-making.

Treatment with PDL is associated with a mild stinging sensation with each pulse. The use of cryogen to precool the skin aids in pain reduction. Topical lidocaine can be used in advance of treatment, though its application causes some vasoconstriction and could reduce the effectiveness of treatment. Therefore, treatment without lidocaine is preferred when the patient can tolerate the procedure.

Postoperative Care and Follow-Up

Post-procedure care involves gentle cleansing and application of emollient as needed, with aggressive sun avoidance measures. Treatment may be repeated after 4–6 weeks, when residual rosacea can be assessed. Parameters are adjusted as needed at each treatment. The endpoint for a treatment course is visual clearance that is deemed satisfactory to the patient and provider.

Education regarding rosacea triggers can be reinforced during and after the treatment course. Avoiding or mitigating triggers that are within a patient's control may slow the progression of new erythema in the future.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Treatments for ETR and PPR	
PDL is most commonly studied for treatment of ETR	N/A
Nd:YAG may have benefit in darker phototypes	C
Nonpurpuragenic PDL settings may be more acceptable to patients while offering efficacy	B
IPL has been shown effective in treating facial erythema	B
Small, non-controlled studies suggest that intradermal microdroplet botulinum toxin injections can provide temporary benefits	D
Studies have demonstrated noninferiority in pairwise comparisons of IPL, PDL, and Nd:YAG	B
Variability in parameters, procedures, and metrics precludes defining a single technology as superior	N/A
Treatments for rhinophyma	
CO_2 treatment applies laser to excise bulk and then to contour the nose	N/A
Outcomes are very good and can last for years	C
Patients' outcomes are similar with scalpel and CO_2; convenience and cost may impact the provider	D

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Self-Assessment Questions

1. The target of pulsed dye laser (595 m) in rosacea is thought to be
   (a) The epidermis
   (b) The dermis
   (c) The sebaceous gland
   (d) Demodex mites
   (e) Blood vessels

2. In treating rosacea, CO_2 laser has the most utility in improving
   (a) Nasal telangiectasia
   (b) Diffuse redness
   (c) Papules and pustules
   (d) Ice pick scars
   (e) Hypertrophic tissue

3. Recurrence after treatment is least common with
   (a) KTP
   (b) PDL
   (c) Nd:YAG
   (d) IPL
   (e) CO_2

4. The first line of treatment for papulopustular rosacea is
   (a) KTP
   (b) PDL
   (c) IPL
   (d) All of the above
   (e) None of the above

5. Studies presented in this chapter state the following based on their results: relative to PDL, IPL is
   (a) Better because it is more cost-effective
   (b) More dangerous because its use is regulated differently
   (c) More effective because of its wider light spectrum
   (d) Comparable in safety and effectiveness
   (e) All of the above

Correct Answers

1. e: PDL targets hemoglobin and therefore damages blood vessels by heat coagulation of the vessel walls. While there may be an effect on Demodex mites and heating of the dermis or sebaceous glands, these are not the main reason PDL reduces erythema.
2. e: CO_2 is used for debulking hypertrophic tissue in rhinophyma. While it may improve telangiectasia, redness, and new papules, it is not primarily intended for these endpoints. CO_2 can be used for treating acne scar, but ice pick scars are not generally caused by rosacea.
3. e: Rhinophyma treatments (with CO_2) results in much longer time to recurrence.
4. e: PPR is treated with topical or oral prescription medications.
5. d: Cost, user regulation, and the benefits of coherent light vs. IPL can be debated, but the controlled studies cited in his chapter demonstrated similar outcomes after PDL and IPL treatment.

Androgenetic Alopecia

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Maria Colavincenzo and Stefan G. Vanderweil

Abstract

Androgenetic alopecia (AGA) is a common, non-scarring form of hair loss characterized by progressive miniaturization of terminal hair follicles on the scalp. First-line therapy for AGA consists of medical therapy with topical minoxidil and oral anti-androgens. Two emerging procedural therapies, platelet-rich plasma (PRP) injections and low-level light therapy (LLLT), represent novel therapeutics for the management of AGA. The details of these procedural treatment modalities are discussed within this chapter.

Keywords

Androgenetic alopecia · Platelet-rich plasma
Low level light therapy

Introduction

Androgenetic alopecia (AGA) is a common, non-scarring form of hair loss characterized by progressive miniaturization of terminal hair follicles on the scalp. AGA encompasses what is commonly referred to as male pattern hair loss (MPHL) in men and female pattern hair loss (FPHL) in women. There is an abundance of data to suggest that AGA is an androgen-mediated process. Genetic predisposition is the main risk factor for the condition.

AGA is clearly the most common form of hair loss, though exact prevalence estimates are variable. Among men, age-dependent estimates range from 16% among young adults to as high as 96% in older adults [1]. Among women, estimates range from as low as 3% to as high as 38%, again with higher prevalence found in older age groups [2]. Racial disparities in prevalence are also recognized, with higher rates in Caucasians, lower rates in African Americans, and variable rates among different subsets of Asians [1].

Therapeutic Approach

First-line therapy for AGA consists of medical therapy with topical minoxidil and oral anti-androgens. There is strong evidence to suggest that topical minoxidil, in varying concentrations and vehicles, is effective in men and women with AGA. Oral anti-androgens, including finasteride and dutasteride, are heavily utilized in both genders, though robust data in support of efficacy are found for only male patients [3].

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Procedural interventions for AGA are generally considered either as adjuvant treatments for medical therapies or appropriate when the former approach is intolerable or inefficacious. Hair transplantation is both widely practiced and highly effective and addressed elsewhere in the text. Two emerging procedural therapies, platelet-rich plasma (PRP) injections and low-level light therapy (LLLT), are discussed in detail in this section. PRP entails the injection of patient-derived plasma, while LLLT refers to the use of a light-emitting device.

Platelet-Rich Plasma (PRP)

PRP is a novel technology for the treatment of androgenetic alopecia. PRP is an autologous blood product containing high concentrations of platelets and rich in growth factors such as platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor beta. These components are thought to stimulate angiogenesis and tissue repair and have found multiple applications across regenerative medicine [4]. It is prepared from a patient's blood sample and then injected into the affected areas of the scalp. While this basic algorithm is universal, there are many different collection systems differing in their use of additives and other modes of preparation. The volume of PRP utilized and the frequency of dosing also vary widely. Therefore, the procedure is far from standardized.

PRP has recently been applied to the treatment of androgenetic alopecia (AGA), with mounting evidence for its efficacy. However, its mechanism of action remains somewhat unclear. Experimental data has shown that PRP is capable of stimulating the hair follicle's mesenchymal component, the dermal papillae, to proliferate and induce hair follicle cycling [5]. PRP has also been shown to facilitate the telogen to anagen transition [6]. Other hypotheses regarding its mechanism include the stimulation of hair follicle stem cells and the promotion of neovascularization [7].

While PRP gains more popularity among clinicians in the treatment of AGA, precise estimates of its utilization are lacking.

Effectiveness of PRP

In recent years, multiple placebo-controlled trials have demonstrated PRP's efficacy in treating AGA. A recent meta-analysis analyzed data from multiple randomized controlled trials and identified a significant impact of PRP on hair follicle density (1a) [8]. Although not statistically significant, the authors also identified other favorable trends including increased hair shaft thickness. Data also exists that shows improvement in other hair parameters resulting from PRP injections, including an increased proportion of anagen hairs and decreased rates of shedding (1b) [9, 10]. PRP has also been studied as an effective adjuvant therapy to hair transplantation, resulting in increased yield (1b) [11].

Effectiveness of PRP may vary by gender, with one report showing earlier onset of hair growth in men but higher hair counts in women [12]. A placebo-controlled trial identified several factors that may influence response to PRP, with statistically significant favorable outcomes associated with male gender, onset of AGA after 25 years of age, disease duration over 10 years, and a positive family history of AGA (1b) [9].

While robust comparisons of different PRP preparation modalities are lacking, there are some reports demonstrating differences among them. One study in particular showed the superiority of a collection system that did not utilize calcium-activated PRP when compared with one that did [13]. Given the mixed outcomes of various trials, each utilizing different PRP preparations, it is reasonable to conclude that preparation modality influences patient response.

The duration of response to PRP injections is variable and generally falls within months to roughly a year [14].

The relative efficacy among the procedural interventions is largely unknown, given the lack of comparative trials. One study on PRP compared the injections in combination with either finasteride or minoxidil with the same medical therapies alone and found that the addition of PRP resulted in statistically significant improvement in multiple hair growth parameters (1b) [9]. Another study also found PRP in combination with minoxidil to be more efficacious than minoxidil alone (2b) [15].

Preoperative Evaluation, Safety, and Adverse Effects of PRP

Overall, PRP has an excellent safety profile. PRP injections are inappropriate for those with diminished or dysfunctional platelets. Current infections, both systemic and localized to the treatment area, hematologic malignancy, immunosuppression, anemia, and recent NSAID use, have also been proposed as contraindications in orthopedic procedures utilizing PRP [16].

Appropriate preoperative tests include a complete blood count and coagulation tests.

Side effects from PRP injections are generally mild and include injection site pain, erythema, and edema. Other less common complications include headache, infection, and cutaneous hypersensitivity reactions [12].

Low-Level Light Therapy (LLLT)

Early observations in animal studies and of paradoxical hypertrichosis in laser therapy were among the first indications that light devices might indeed be useful toward promoting hair growth [17–20]. In the subsequent years, several light-emitting devices were developed for commercial use. Low-level light therapy (LLLT), also called low-level laser therapy, refers to the use of a visible light-emitting device for photobiomodulation. LLLT is referred to as "low level" because its energy density is low compared with other forms of laser treatments [21].

Red or near-infrared laser light is known to possess tissue repair properties, and LLLT has been used for regenerative purposes in treatment of a wide range of medical conditions, from wound healing and nerve regeneration to joint pain relief [22]. LLLT devices that emit coherent monochromatic red light have been developed for various skin conditions, including hair growth. Chromophores are the receptors in biological tissue that can absorb photons. Wavelengths in the range of 650–1200 nm have maximal tissue penetration in biologic tissue (the so-called optical window of tissue). LLLT devices employ light within this therapeutic range, in the red or near-infrared spectrum (600–950 nm) [22–23].

LLLT is thought to result in the absorption of light by chromophores contained in the protein of components of the respiratory chain of the mitochondria, in particular cytochrome c oxidase (CCO), which results in photodissociation of nitric oxide (NO), leading to greater production of ATP [21]. While the exact mechanism by which this promotes hair growth is uncertain, it is thought that release of NO from CCO may increase anagen hairs. NO is known to be a potent vasodilator, and increased blood flow was reported in several studies [22, 24–25]. Possible downstream effects on the hair follicle are thought to include anagen reentry of telogen hair follicles, with prolonged anagen duration and increased anagen growth rate [22, 26–29].

Based on the available data in support of the benefit of LLLT as a treatment for AGA, the Food and Drug Administration granted the first clearance for a device indicated for treatment of AGA in men in 2007, and the category was expanded to include treatment of women with AGA in 2011 [22, 30–32]. Current LLLT devices for hair loss, for the most part, utilize a wavelength of 655 nm [26], including the HairMax LaserComb (Lexington Int. LLT, Boca Raton, FL) and Apira iGrow helmet (Apira Science Inc., Boca Raton, FL) [28], which represent the few FDA-cleared commercially available LLLT devices with published clinical findings in peer-reviewed journals [26, 31–34]. However, in recent years, many additional companies have received FDA clearance for similar LLLT devices. Commercially available home-use LLLT devices come in comb, helmet, or cap form, with variable pricing (costing from a few hundred dollars and upwards) and variable treatment regimens (number of minutes per treatment, number of times per week) [26].

Effectiveness of LLLT

Building upon a strong basis of in vitro and animal studies, there are a rapidly increasing number of clinical studies evaluating the potential effects of LLLT on AGA, the vast majority of

which suggest a benefit for LLLT in treatment of male and female pattern alopecia. There are a total of five RCTS evaluating LLLT for AGA in men/women [31–35]. All were double-blinded and used blinded evaluators to report changes in hair density at 16–26 weeks with LLLT compared to sham devices [26]. All RCTs found improvements in hair density/hair count in LLLT-treated subjects compared to the sham-treated subjects (1a) [26, 31–35]. Three trials noted a range of relative increases in hair density of 15.27–19.8 hairs/cm [2] in treatment groups compared to controls [31, 34–35]. Two separate studies in males and females conducted by the same group also noted an increased hair count, by 35% in males and by 37% in females, compared to controls [28, 32–33].

One systematic review examined 11 clinical studies of LLLT for AGA which evaluated a total of 444 males and 236 females [28]. The studies assessed hair count/hair density as an end point, and nine found statistically significant improvements in both males and females following LLLT treatment (1a). In another review of nine clinical studies, five assessing comb devices and four regarding helmet/cap devices, the same positive findings for LLLT in treating AGA were noted (1a) [26], although criticisms included the small sample sizes in some of the individual studies, lack of intention to treat analysis in many cases, and a lack of reported visual evidence (only one RCT provided global photographs). Other concerns include a relatively short follow-up period, generally 6 months.

The authors also noted that the positive effects of LLLT in the available clinical data also raise further questions to be clarified. For example, it is unclear whether the number of light sources or the type of light sources is important for efficacy of LLLT – whether it is a laser-emitting diode (LED), a laser diode, or a combination that is affecting the target area of interest. (As opposed to LED light, laser light is monochromatic, collimated, and coherent.) Similarly, while most devices advocate treatment for 15–20 min every other day or three times a week, the optimum treatment regimen or dosage for LLLT is not known [26]. Thus, the decision of which device and regimen to recommend to a given patient is not straightforward at this time [28].

Relative Effectiveness of LLLT

Indeed, LLLT, along with minoxidil and finasteride, was found to be in the highest level of evidence for benefit in a recent systematic review and meta-analysis of treatments for AGA (1a) [3]. However, as noted by previous reviews, a limitation remains the relatively smaller number of trials and patients evaluated with LLLT as compared to traditional, pharmacologic hair loss therapy [26], thus solid conclusions about the relative efficacy of LLLT compared to other treatments cannot be made at this time. While in clinical practice, the most common treatment plan may include a range of modalities including topical and systemic therapy, there has been relatively little reported on comparisons among different modalities of treatment, or combinations thereof.

One study compared the use of LLLT monotherapy to LLLT combined with minoxidil and/or finasteride in males and females (2b) [36]. All showed improvement, although no group demonstrated significant advantage over the others. In a recent RCT among women with AGA, LLLT was compared to minoxidil topical (5% bid) and to a combination of both LLLT and minoxidil [37]. The most improvement, judged by hair counts and dermoscopic assessments as well as patient satisfaction, was in the combination group.

Given the generally high level of evidence for minoxidil and finasteride, these treatments are typically, together, considered as first-line treatment for AGA. But LLLT should also be considered in parallel, especially given the increasing evidence for potential benefit which has been reported in the last several years.

Safety of LLLT

Safety is a major plus to LLLT in general, with such devices considered exceedingly safe.

Compared to medical therapy and surgical therapy, the risks are very low – so far there have been no serious adverse events reported. A minority of patients have reported minor side effects, such as headache, pruritus, or warm sensation in the treatment site [28]. Initiation of telogen effluvium has been observed in only one study and resolved after 2 months of treatment [21]. Some other possible considerations are presence of any atypical, precancerous, or malignant lesions on the scalp which could, in theory, be stimulated to grow by proliferative effects of LLLT [22, 38–39]. However, in the conducted clinical studies, only one case of a basal cell carcinoma on scalp was reported, which the authors felt was not likely related to the LLLT. In summary, the very low incidence of side effects gives LLLT an excellent safety profile [21].

Patient Characteristics and LLLT

It has been noted that the success of any LLLT device may well depend on individual differences, including in physical characteristics such as hair color, length, and skin color [26]. Notably, LLLT devices are cleared for use in individuals with Fitzpatrick skin type I to IV. In computer models, darker skin decreases transmission of light, presumably due to melanin [26], yet one clinical study reported that patients with Fitzpatrick skin type IV demonstrated a greater response to the LLLT therapy than patients with Fitzpatrick I, II, and III skin types (2b) [40]. Any clinically significant differences based on skin type remain to be validated.

As to other relevant considerations, one prospective study found that patients with intermediate severity AGA (Hamilton-Norwood III and IV and Ludwig I and II) showed the maximal response to LLLT (2b) [28, 36]. It is thought that perhaps, in patients with rather full hair density at baseline, this hair might pose a barrier to light penetration, while at the other extreme of severe alopecia the condition may be less responsive. Another study found that older subjects tended to respond better than younger subjects (2b) [40]. In terms of location of the treatment area, although both sexes showed significant benefit in all areas, in one study there was a greater improvement in the vertex area in men and temporal area in women (4) [38]. Further research will be needed to characterize the difference in response to LLLT in subpopulations [28].

Patient Preferences and Treatment Approach to AGA

Given the lack of controlled trials gauging the relative efficacy of different treatment modalities for AGA, patient preference often dictates the management strategy. For those patients wishing to utilize the most data-driven approaches, medical therapies are most often appropriate as first line. Procedural interventions then become useful adjuvants or replacements to these when the improvement is insufficient or the side effects intolerable. Safety considerations may also influence patient preference.

LLLT and PRP appear to be very safe, with generally less side effect considerations than systemic anti-androgen therapy, and likely even in comparison to topical minoxidil. Some patients prefer to avoid pharmacologic interventions altogether, for whom LLLT and PRP may have a unique appeal. In the particular case of women of childbearing potential with AGA, LLLT may be a primary consideration due to its excellent safety profile. PRP injections can be painful, and, therefore, highly pain-averse patients may wish to avoid this approach. Cost considerations factor prominently in patient choice as well, given that most approaches require out-of-pocket expense. Medical therapies are often the most affordable, while both LLLT and PRP are more costly, and hair transplantation typically requires a considerable investment.

Medical therapies require indefinite use and are limited by patient adherence. Similarly, the at-home time commitment of LLLT makes this therapy less desirable for patients not willing to commit additional time to use the device regularly.

Among the different currently commercially available LLLT devices, there is a range of inconvenience – e.g., hands-free devices, while more expensive, may be strongly preferable to some patients. Patients preferring to minimize their at-home treatment commitments may favor interventional therapy with PRP and have a lower threshold for seeking hair transplantation. In summary, personal preference is a central consideration in treatment of AGA.

After a patient is diagnosed with AGA, a discussion of both medical and procedural therapies should ensue. Baseline photographs are crucial for monitoring patient response to treatment. A typical initial approach for a treatment-naïve patient would be the use of either or both minoxidil and finasteride. Assessment of the efficacy and tolerability of these interventions is then gauged after 6–12 months. If the therapies are intolerable or their results are unsatisfactory, the addition of or substitution with PRP and LLLT should be discussed. Concomitantly, candidacy for hair transplantation should be considered, as is discussed thoroughly elsewhere in this text.

Conclusions

PRP and LLLT are procedural interventions for AGA that are supported by the available evidence. Data from multiple randomized controlled trials show that PRP and LLLT are effective and well-tolerated. There are no head-to-head comparative trials between these modalities and traditional medical therapies. In the absence of these, considering the much more substantial amount of data supporting medical therapies, PRP and LLLT largely play an adjuvant or second-line role at this time. However, many patients find these traditional interventions to be intolerable or ineffective, and therefore, these procedural interventions can offer patients an additional, effective, evidence-based treatment modality.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
PRP increases hair density in AGA	B
LLLT increases hair density in AGA	B
Topical minoxidil and oral anti-androgens are first-line therapies for AGA in men and women	A
PRP in combination with minoxidil or finasteride may be more effective than medical therapy alone	C
LLLT in combination with minoxidil or finasteride may be more effective than medical therapy alone	D
PRP may improve the efficacy of hair transplantation for patients with AGA	C
PRP is safe and lacks significant adverse effects	A
LLLT is safe and lacks significant adverse effects	A
Patient preference factors prominently in the therapeutic approach to alopecia when considering among medical, surgical, and procedural therapeutic options	A

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Self-Assessment Questions

1. Clinical studies have demonstrated that PRP significantly increases:
   (a) Hair follicle density
   (b) Hair shaft thickness
   (c) Hair shedding
   (d) Proportion of telogen hair follicles
   (e) Cutaneous vasoconstriction

2. Regarding treatment of AGA with LLLT:
   (a) Most devices utilize wavelengths of around 1000 nm
   (b) LLLT is known to be most effective in lightest skin types (Fitzpatrick skin type I and II)
   (c) LLLT is effective as monotherapy or combination therapy with topical minoxidil
   (d) LLLT is contraindicated in patients with a history of skin cancer, given the increased risk of scalp carcinogenesis
   (e) Comb-style devices lead to more effective light penetration compared to cap-style

3. Features of PRP and LLLT include:
   (a) Highly cost-effective
   (b) Decades of long-term outcome data
   (c) Highly powered trials compared to topical therapies
   (d) Excellent safety profile

4. A procedurally wary middle-aged male patient presents with moderate-to-severe AGA, having previously failed 1 year of treatment with topical minoxidil.
   (a) LLLT is the first-line treatment option.
   (b) PRP is the first-line treatment option.
   (c) Oral finasteride is the first-line treatment option.
   (d) Hair transplantation should be encouraged.

5. A female patient of childbearing potential not actively trying to conceive but not willing to practice contraception is distressed by progressive hair loss, diagnosed as AGA clinically after ruling out other possible contributing factors. She is using minoxidil topical but is not satisfied with the response after 6 months. You should:
   (a) Prescribe adjuvant oral anti-androgens such as spironolactone or finasteride.
   (b) Perform a hair transplant procedure so that additional or ongoing medical therapy will be unnecessary.
   (c) Recommend PRP given its excellent safety profile.
   (d) Recommend LLLT given its excellent safety profile.

Correct Answers

1. a: PRP has been shown to significantly increase hair follicle density and the proportion of anagen hair follicles. It has also been found to significantly decrease the rate of hair shedding. It may increase hair shaft thickness, though data from a clinical trial did not reach significance. Hypotheses regarding its mechanism include the stimulation of hair follicle stem cells and the promotion of neovascularization.
2. c: Clinical studies have demonstrated the effectiveness of LLLT both as monotherapy and in combination with medical therapy, though the relative effectiveness is still unknown. Most devices utilize wavelengths around 655 nm (within the red/near-infrared spectrum). The devices are FDA-cleared for use in individuals with Fitzpatrick skin type I to IV, and while some small studies have suggested a possible effect of skin type on response to LLLT, this remains to be clarified. LLLT is not considered a carcinogen or risk for patients with a history of skin cancer (though use would be deferred in the setting of any specific suspicious lesion within the treatment zone pending diagnosis and treatment). While it clearly affects patient preference and experience, the significance of device style (such as comb or cap or band) in terms of LLLT effectiveness, if any, is not known.
3. d: PRP and LLLT have excellent safety profiles, with a lack of significant reported adverse events. Considered together, they are effective therapeutic considerations for AGA but involve significant out-of-pocket expense for patients. While clinical trials support their use and potential benefit, there is a lack of long-term outcome data (with most trials averaging 6 months or less), along with generally lower sample sizes in comparison to trials which have evaluated medical therapies.
4. c: Medical therapy with minoxidil and oral anti-androgens are the most established treatments and should be offered/considered for all patients with AGA. After a detailed discussion of potential side effects, a decision can be made as to whether to pursue finasteride. Procedurally wary patients are not likely to seek hair transplantation or PRP injections, though these are treatment considerations for patients with inadequate response to minoxidil. LLLT would be a second-line consideration in the described patient, given its tolerability and effectiveness in clinical trials.
5. d: While safety studies in pregnancy are lacking for all therapies for AGA, in particular, medical therapies are not considered safe in pregnancy. Oral androgens are known teratogens and must not be prescribed to women who may become pregnant. Minoxidil topical should not be used in pregnancy. While hair transplantation surgery is a treatment consideration for women as well as men with AGA, it is best used in parallel with nonsurgical therapy, since it does not address the progressive nature of AGA and would be deferred in the setting of pregnancy. PRP and LLLT are both considerations for patients who cannot pursue and do not tolerate or respond to medical therapy; but in the setting of possible conception, the noninvasive nature of LLLT makes this the best choice for the described patient. In the setting of a known pregnancy, however, LLLT is usually deferred given the lack of explicit safety data in that setting, as is the case with many or most cosmetic treatments.

Cutaneous Carcinogenesis in Organ Transplant Recipients

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Joyce T. Yuan, Amanda R. Twigg, and Sarah T. Arron

Abstract

Organ transplant recipients (OTR) have a high risk of skin cancer, and skin cancer in OTR tends to be more aggressive. Skin cancer risk varies with immunosuppressive regimen. Azathioprine and cyclosporine are most associated with skin cancer, while sirolimus has a protective effect. OTR have a higher burden of actinic keratoses. Field treatments found to be safe and effective in OTR include diclofenac, imiquimod, 5-fluorouracil, and photodynamic therapy. Studies on ingenol mebutate in OTR are ongoing. Skin cancer chemoprevention with acitretin or nicotinamide should be considered in OTR with frequent skin cancers. Mohs micrographic surgery is often indicated in OTR. Dermatologic evaluation and management of OTR should include a thorough history taking and incorporation of patient preferences. There are currently no evidence-based consensus guidelines for skin cancer screening in OTR. Expert opinion recommends at least annual screening. A screening protocol for OTR based on a patient's specific risk factors has been proposed.

Keywords

Skin cancer · Cutaneous carcinogenesis
Organ transplant recipients

Introduction

The field of organ transplantation has greatly evolved since its inception six decades ago. In the United States, since 1988, there have been 398,792 solid organ transplants, with 17,878 transplants in 2015 alone [1]. The most commonly transplanted organs are kidney, liver, heart, and lung [1]. With advances in immunosuppressive regimens, control of infectious diseases, and improved access to HLA-matched organs, organ transplant recipients (OTR) are now living longer, with increased graft survival (2b, 2b) [2, 3]. While chronic graft failure is still the leading cause of death in OTR, death from other causes, including malignancy, is increasingly common [2]. Because OTR have a high risk for skin cancer, and skin cancer in OTR tends to be more aggressive, vigilant dermatologic care is warranted. Regular dermatology visits, treatment of actinic keratoses, consideration of chemoprophylaxis, and medical and surgical treatment of skin cancers are recommended in this patient population.

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Epidemiology

Organ transplant recipients (OTR) have a significantly increased risk of developing skin cancer, especially non-melanoma skin cancer (NMSC) (2b, 2b, 2b, 2b, 1b) [2, 4–7]. Chronic immunosuppressive medications in these patients impair immune surveillance mechanisms normally needed for eradication of precancerous skin lesions, and some may exert a direct carcinogenic effect [2]. Relative risk of NMSC in OTR has been reported as 108.6 in men and 92.8 for women [4], with sun-exposed areas more likely to be affected [4]. While basal cell carcinoma (BCC) is the most common skin cancer in the general population, squamous cell carcinoma (SCC) predominates in the OTR population [2, 5]. A single-center cohort study of heart and renal transplant recipients in Norway reported a 65-fold increased incidence of SCC compared to the general population, and the incidence of SCC of the lip was increased 20-fold [6]. Basal cell carcinoma incidence is increased tenfold in the OTR population [5]. Malignant melanoma incidence has been estimated as between twofold [7] and threefold in renal and heart transplant recipients (2b, 2b) [6, 8], although one large OTR cohort study did not find a significant increase in melanoma risk [4]. Other cutaneous malignancies, including Merkel cell carcinoma (MCC), seem to have an increased incidence in OTR as well (2b) [9]. While there are 65 melanomas for every one MCC in the general population, this ratio is decreased to 6:1 in OTR, suggesting that the chronically immunosuppressed posttransplant state decreases the threshold for developing MCC more than it does for melanoma [9].

Skin cancers in OTR are more aggressive, with a greater risk of local recurrence or metastasis (2b, 2b, 2b, 2b) [2, 8, 10, 11]. Risk of metastasis from SCC in OTR has been estimated at 7% [10]. Skin cancer mortality in OTR in the United States is at least 35.27 per 100,000 person-years (2b) [12], nine times higher than in the general population [12]. Organ transplant recipients at the highest risk of skin cancer, and also death from skin cancer, are white patients, men, thoracic transplant recipients, and patients at or above the age of 50 years at the time of transplant (2b, 2b, 2b, 1b) [8, 11–13]. Smoking history and increased ultraviolet (UV) radiation exposure also show a positive correlation with skin cancer in OTR (2b) [14]. Human papilloma virus (HPV) has been associated with SCC, although its biologic role in OTR cutaneous carcinogenesis is unclear (2b) [15]. Although SCC has a higher incidence than malignant melanoma in OTR, malignant melanoma in OTR is associated with higher mortality (11.48/100,000 person-years versus 4.94/100,000 person-years) [12]. Melanoma-specific mortality in OTR is about threefold higher compared to in non-OTR patients [8].

Medications and Skin Cancer Risk

Several medications have been studied and implicated with an increase in skin cancer risk in OTR. Short-term, intense immunosuppression, specifically with T-cell-depleting antibody agents, has been associated with late-stage melanoma (2b, 2b) [8, 16]. Maintenance immunosuppression with azathioprine in OTR seems to increase the risk of SCC (2b, 2b, 3b) [14, 17, 18], localized melanoma [8, 16], and MCC (2b) [19]. A proposed mechanism for this is synergism of azathioprine with ultraviolet radiation to promote carcinogenesis [8, 19]. Cyclosporine, a calcineurin inhibitor, has also been associated with NMSC in renal transplant recipients in multiple studies (2b, 2b, 1b, 2b) [6, 14, 20, 21]. These observations are supported by in vitro studies, in which cyclosporine was found to inhibit apoptosis and DNA repair in human keratinocytes exposed to UVB radiation (5, 5) [22, 23]. The observed effect of cyclosporine on skin cancer in renal transplant recipients appears to be dose-dependent, with fewer NMSC in patients on lower doses of cyclosporine [20]. Cyclosporine also increased the risk of MCC in OTR in one retrospective cohort [19]. The effects of cyclosporine

and the effects of azathioprine on MCC risk were found to be further increased in patients who had higher UV radiation exposure, as measured by lower latitude of residence [19]. A large 30-year cohort study of renal transplant recipients, however, did not find increased skin cancer risk secondary to azathioprine, cyclosporine, or tacrolimus (2b) [24]. Also, in heart transplant recipients, cyclosporine and tacrolimus were reported to have no effect on skin cancer incidence [17].

Mycophenolate mofetil was associated with a protective effect against SCC in heart transplant recipients [17] and in a cohort of solid OTR [18]. Prednisone has been associated with increased NMSC risk in non-OTR (3b, 2b, 3b) [25–27], but one prospective study found no such association (2b) [28]. In OTR, systemic corticosteroids have not been examined as an independent risk factor for skin cancer in OTR.

Voriconazole is frequently used in lung transplant recipients for antifungal prophylaxis. It carries a mortality benefit in lung transplant recipients who develop posttransplant *Aspergillus* colonization. Although one retrospective cohort study found no association between voriconazole exposure and NMSC risk in lung transplant recipients after statistically adjusting for demographic and clinical factors (2b) [29], voriconazole was independently associated with an increased risk of NMSC, and specifically SCC, in lung transplant recipients in several studies (2b, 2b, 2b, 2b) [30–33]. Risk of SCC was increased 2.6-fold with any voriconazole exposure in lung transplant recipients, and the risk was observed to be dose-dependent [31, 32]. In a majority of patients on voriconazole who develop SCC, acute phototoxicity in the first year of voriconazole exposure precedes development of actinic keratoses and progression to SCC (4) [34]. Especially in patients with signs of chronic phototoxicity [34] and in patients with risk factors for SCC, such as low Fitzpatrick skin type, high cumulative UV exposure, or older age, alternatives to voriconazole for antifungal prophylaxis should be considered [32].

Benefits of mTOR Inhibitor for Immunosuppression

Mammalian target of rapamycin (mTOR) inhibitors are newer immunosuppressants with reported antioncogenic effects; sirolimus and everolimus have been studied in OTR. Upregulated in SCC, mTOR is involved in the regulation of angiogenesis, cell proliferation, and survival (5) [35]. Mammalian target of rapamycin inhibitors increased MCC risk in OTR in one study [19]. However, overall, there has been strong evidence supporting the use of mTOR inhibitors in OTR for the secondary prevention of skin cancer. As concluded by two meta-analyses of randomized controlled trials and observational studies, in renal transplant recipients, conversion to a sirolimus-based immunosuppressive regimen, after the development of skin cancers, was associated with a reduced risk of NMSC (1a, 1a) [36, 37]. Switching from cyclosporine to sirolimus in particular had a protective effect [37]. While sirolimus was associated with decreased incidence of NMSC in clinical trials focused on kidney transplant recipients with a personal skin cancer history, findings may not be generalizable to the entire solid OTR population for primary prevention of NMSC (2b) [38]. In a large cohort study of solid OTR, risk of SCC was not associated with the use of sirolimus or with cumulative duration of sirolimus [38]. It has been suggested that in kidney transplant recipients, the observed beneficial effect of sirolimus may be due to the cessation of a calcineurin inhibitor, rather than a direct effect of sirolimus [38].

Although sirolimus was not associated with graft rejection, serious adverse events, such as pneumonitis, diarrhea, urinary tract infection, and unexplained fever, were more common with sirolimus than with calcineurin inhibitor in a phase III randomized clinical trial (1b) [39]. High rates of surgical site wound healing delay, 20–50%, have been reported in OTR on sirolimus; independent risk factors for sirolimus-related wound complications in renal transplant recipients were obesity, age greater than 40 years, acute graft rejection, thymo-

globulin for induction immunosuppression, and at least 35 mg of cumulative sirolimus by posttransplant day 4 (2b, 2b) [40, 41]. Waiting for transplant surgical sites to heal well prior to starting sirolimus is therefore advisable. While holding sirolimus prior to any major surgery is recommended based on current evidence, there is limited data to support stopping sirolimus for skin cancer surgery. In a retrospective review of dermatologic surgeries, OTR on sirolimus had a higher infection rate (19.2% vs. 5.4%) and more wound dehiscence (7.7% vs. 0%) compared with OTR not on sirolimus, but these values were not statistically significant (4) [42]. The morbidity of dehiscence and wound healing delay in dermatologic surgery is also low; therefore, the benefit-to-risk ratio favors continuing sirolimus in the setting of dermatologic surgery in most OTR.

Everolimus, an mTOR inhibitor with pharmacokinetics distinct from those of sirolimus (5) [43], has been associated with a reduced risk of NMSC mainly in kidney transplant recipients and also in heart and lung transplant recipients; these findings were based on case series and case reports (2b, 4, 5, 2b) [44–47]. Further clinical trials and prospective studies are warranted.

Management of Actinic Keratoses

Along with an increased risk of NMSC, OTR have an increased incidence of actinic keratoses (AK) (2b, 2b, 4) [15, 48, 49]. As in non-OTR, treatment of AK is indicated to avoid progression to SCC; the risk of malignant transformation in the general population has been reported as 0.60% at 1 year and 2.57% at 4 years (1b) [50]. Available management options are the same as those for the general population, although many agents are off-label in immunosuppressed patients (see Chap. 41 "*Treatment of Precancers with Topical Agents*"). In OTR, cryotherapy is frequently used for destructive treatment of individual AK. For increased numbers of AK, field treatment is warranted, especially since immunosuppressed OTR are more prone to wound healing delay and infection after undergoing destructive modalities [49]. For OTR with extensive areas of actinic dysplasia, field treatment is also helpful for increasing the signal-to-noise ratio, allowing for detection of persistent, cancerous lesions that would otherwise be difficult to distinguish in a field of uncontrolled AK. A proposed algorithm for AK management in OTR is presented in Fig. 60.1.

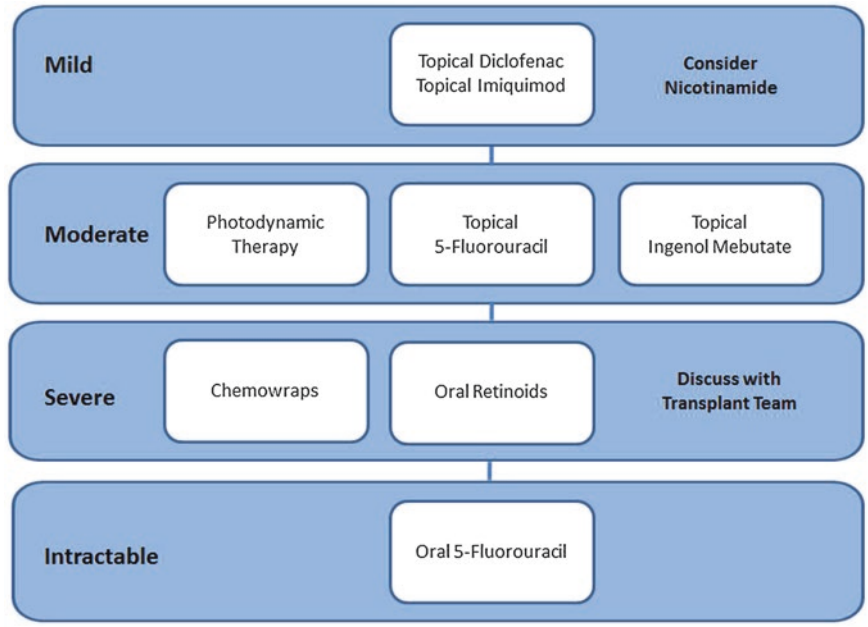

Fig. 60.1 Proposed algorithm for actinic keratosis management in organ transplant recipients

Safety and Efficacy

Topical field treatments studied specifically in OTR include diclofenac and imiquimod. Diclofenac 3% gel in 2.5% hyaluronic acid (Solaraze) is a nonsteroidal anti-inflammatory drug (NSAID), which is FDA-approved for the treatment of AK. In OTR, topical diclofenac was found to be safe, with no associated graft rejection, meaningful changes in laboratory values, or systemic side effects (4) [51]. In a placebo-controlled, randomized clinical trial of solid OTR, diclofenac 3% gel applied twice daily for 16 weeks resulted in complete clearance of AK in 41% of subjects, compared with 0% of subjects on the placebo regimen, 4 weeks after treatment (1b) [52]. Imiquimod modulates cellular immune responses through agonist activity at Toll-like receptor 7 (TLR7) (2b) [53]. It is FDA-approved for the treatment of AK, superficial BCC, and external genital warts, while use in immunosuppressed patients is currently off-label. Imiquimod is available as a 3.75% cream and as a 5% cream. Several studies in OTR have examined 16-week courses of imiquimod 5% cream, three times weekly; no graft rejections or laboratory evidence of graft dysfunction were noted (4, 2b, 2b, 2b) [49, 53–55]. Although clinical trials on imiquimod 5% cream in OTR have been small, varying efficacy in clearing AK has been confirmed in all studies [49, 53–55]. One multicenter, placebo-controlled, randomized clinical trial of 43 subjects found complete clearance of AK at 8 weeks posttreatment in 62.1% of subjects with imiquimod, versus 0% with placebo; and partial clearance of AK was achieved in nearly 80% of OTR subjects [54].

Topical 5-fluorouracil (5-FU) prevents DNA synthesis by competitively inhibiting thymidylate synthetase (2b) [56]. It is FDA-approved as a cream in 5% (Efudex), 0.5% (Carac), and 1% (Fluoroplex) formulations for the treatment of AK and is well studied in immunocompetent patients. In renal transplant recipients, 5-FU 5% cream applied to AK on the face twice daily for 3 weeks resulted in complete, 100% clearance of AK in 63% of subjects at 8 weeks, and in 0% of subjects at 12 months (4) [57]. Partial clearance rates (≥75%) were 100% at 8 weeks and 71% at 12 months [57]. Besides demonstrated efficacy, this medication was found to be safe and well tolerated in renal transplant recipients, with the only reported adverse event being mild hyperpigmentation, along with local skin reactions [57]. By anecdotal experience, for truly extensive field disease on the extremities in OTR, "chemowraps" with 20 g of 5-FU 5% cream applied topically under Unna boot occlusion and repeated weekly for 4–6 weeks are highly effective.

Ingenol mebutate gel (0.015% for the face and scalp and 0.05% for the trunk and extremities) is FDA-approved for the treatment of AK in immunocompetent patients. Ingenol mebutate is an off-label option for OTR, and a major advantage of this medication is its effectiveness (as studied in immunocompetent patients) with a short treatment course of 3 consecutive days on the face and scalp and 2 days on the trunk and extremities (1b) [58]. Two clinical trials to study the safety and efficacy of ingenol mebutate in OTR are currently in progress (ClinicalTrials.gov Identifier: NCT02866695, NCT02473848).

Photodynamic therapy (PDT), with either aminolevulinic acid (ALA) or methyl-aminolevulinic acid (MAL) as a topical photosensitizer, has been shown to be safe and effective in several trials in OTR (1b, 4, 1b, 4, 2b, 2b) [59–64]. In OTR, two treatments with MAL-PDT, spaced 1 week apart, resulted in a significant reduction in new AK lesions, with a complete response rate of 77% at 3 months in an open, intra-patient, randomized trial [59]. In a smaller trial of renal transplant recipients, two MAL-PDT treatments, with an interval of 2 weeks, resulted in a complete response rate of 72% at 3 months on the face and scalp and 40% on the dorsal hands [60]. In a randomized, blinded trial, one to two ALA-PDT treatments at a 6-month interval decreased the development of AK, but there was no observed reduction in the incidence of SCC at 2-year follow-up [61]. However, repeated ALA-PDT treatments at 4–8-week intervals for 2 years reduced the incidence of SCC in a case series of 12 OTR with high burden of disease at 1- and 2-year follow-up [62]. Methyl-aminolevulinic acid is not currently marketed in the United States.

Relative Efficacies

In a randomized, open-label, intra-patient study of eight OTR, two MAL-PDT treatments, with an interval of 1 week, was directly compared with 5-FU 5% cream, twice daily for 3 weeks, for the treatment of AK [63]. Subjects were evaluated at 1, 3, and 6 months posttreatment, and at all timepoints, MAL-PDT was found to be more efficacious than 5-FU in achieving complete resolution of AK (89% vs. 11%) and in reducing mean lesional area (100% vs. 79%); MAL-PDT was also superior in cosmetic outcome and patient preference [63]. In OTR, MAL-PDT has also been compared with routine spot treatment of AK, consisting mainly of cryotherapy, and excluding 5-FU and imiquimod [59]. Compared with routine spot treatment, MAL-PDT was more effective at preventing new AK lesions at 3 months after initial PDT treatment; at 27 months, the two treatments had similar efficacy, but MAL-PDT resulted in superior cosmetic outcome [59].

Skin Cancer Chemoprevention

Acitretin

Acitretin (Soriatane) is an oral retinoid, used off-label for the prevention of skin cancer in OTR (2b) [65]. Acitretin has been effective at decreasing SCC in OTR in several small clinical trials (2b, 2b, 2b, 2b) [65–68]; possible mechanisms of action include induction of apoptosis or growth arrest of tumor cells, immunomodulation, and promotion of normal cellular differentiation [65]. In a randomized, double-blind, placebo-controlled trial of renal transplant recipients, acitretin 30 mg oral daily for 6 months resulted in significantly fewer SCC during the treatment period; discontinuation of acitretin, however, resulted in relapse and loss of benefit within several months [66]. In an open, randomized 2-year crossover study of renal transplant recipients, significantly fewer SCC were observed during treatment with acitretin; reduction in BCC was also noted but did not reach statistical significance [67]. A retrospective study found that low-dose systemic retinoids (etretinate and acitretin) in OTR significantly reduced SCC during the first 3 years of treatment, and benefit for up to 9 years was observed [65]. However, in one trial of renal transplant recipients taking acitretin, no effect on skin cancer occurrence was noted; absence of a control group in this study may have accounted for the discrepancy [68].

Acitretin was found to be safe in OTR in all clinical trials; there was no association with graft dysfunction or major systemic side effects [65–68]. Common adverse effects reported in OTR were cheilitis, xerosis, palmoplantar desquamation, brittle nails, mild hair loss, epistaxis, hypertriglyceridemia, headache, and musculoskeletal symptoms [65–68]. Liver panel abnormalities were rare [67]; most studies did not report any effect on liver function tests [65–66, 68]. In two studies, side effects were significant in some subjects, requiring dose adjustments [68] or prompting subjects to withdraw from the trial [67]; in other studies, side effects were generally mild and well tolerated [65–66]. In a prospective cohort study of 29 OTR undergoing dermatologic surgery, 10–50 mg daily of oral acitretin was not associated with any increase in wound healing complications (1b) [69]. Doses of 0.2–0.4 mg/kg/day, with titration depending on results of lab monitoring and side effects, have been reported for chemoprevention in OTR [65]. Acitretin 30 mg oral daily was reported to be safe, well tolerated, and effective in renal transplant recipients [66]. George et al. (2002) observed the highest discontinuation rate (52.2%); of the subjects who continued with treatment, acitretin 25 mg daily or every other day was well tolerated and effective [67]. In the author's experience, starting at a low dose of 10 mg every other day and increasing to a goal of 25 mg daily or 0.4 mg/kg daily is advisable.

Nicotinamide

Oral nicotinamide, vitamin B3 in amide form, has been found to be effective for skin cancer chemoprevention in high-risk patients (1b) [70]. Nicotinamide is thought to boost levels of adenosine triphosphate (ATP) and indirectly aid in DNA repair and genomic stability (2b) [71]. Efficacy in immunocompetent, high-risk subjects, defined as having at least two NMSC

in the past 5 years, was demonstrated through a phase III, placebo-controlled, randomized trial; nicotinamide 500 mg twice daily resulted in a 23% reduction in NMSC at 12 months, which was statistically significant [70]. Actinic keratosis count was also observed to be significantly decreased at 3, 6, 9, and 12 months of treatment [70]. There was no benefit after discontinuation of the drug [70]. In OTR, only one small phase II clinical trial of nicotinamide 500 mg twice daily has been done; safety profile in OTR was excellent, and there was a 35% reduction in NMSC, although this value was not statistically significant (2b) [72]. Further phase III clinical trials are warranted in OTR. Meanwhile, considering the safety and observed efficacy, it is reasonable to prescribe nicotinamide in higher-risk OTR for modest skin cancer chemoprevention.

Skin Cancer Treatment

Skin cancer treatment options for OTR are the same as those for immunocompetent patients, following NCCN guidelines (for discussion of NCCN guidelines, please see Chaps. 4, 42–46 in this text). Surgical treatment options include electrodessication and curettage, wide local excision, and Mohs micrographic surgery. The Mohs Appropriate Use Criteria evaluates the evidence for benefit from Mohs surgery over other treatment modalities; Mohs is often recommended as appropriate for immunosuppressed patients [73], and the use of this guideline is recommended.

Managing Organ Transplant Recipients in Dermatology Clinic

When evaluating an OTR, a complete history should be taken, with questions that elucidate the level of skin cancer risk. These include the organ transplanted, date of transplantation, history of rejection episodes or complications, and, importantly, past and current immunosuppressive medications. A full medication list, including infection prophylaxis and any photosensitizing agents, should be reviewed. Personal and family history of skin cancer, previous dermatologic procedures and surgeries, and history of field treatments for AK, along with Fitzpatrick skin type, sun exposure history, and sun protection practices should be documented. A full-body skin exam should be performed, and patients should be counseled on their increased risk of skin cancer and on sun protection techniques. Depending on the severity of AK and frequency of NMSC, chemoprevention with nicotinamide or acitretin may be considered. Mohs preoperative evaluations in OTR are generally the same as those for immunocompetent patients. There is no evidence for routine wound infection prophylaxis with antibiotics in OTR undergoing Mohs.

Patient Preference

Dermatologic care of OTR should accommodate patient preference whenever possible. Organ transplant recipients often face treatment fatigue from numerous clinic visits, hospitalizations, and a long list of medications to manage. Discussing patient compliance, efficacy, and satisfaction with medications such as topical therapies can help guide treatment decisions. Photodynamic therapy and ingenol mebutate for field treatment of AK, for example, require much less patient compliance than 5-FU and imiquimod, which involve longer treatment courses. Insurance approval and cost may also play a role in treatment selection. Starting an agent such as acitretin for skin cancer chemoprevention requires patient agreement with lab monitoring and tolerance of side effects. As in immunocompetent patients, skin cancer treatment decisions should factor in patient preference after discussion of risks, benefits, and alternatives for each option; patient preference plays a greater role in skin cancer cases for which the appropriateness of Mohs is "uncertain" based on Mohs Appropriate Use Criteria.

Skin Cancer Screening

In the general population, the benefit of skin cancer screening has been debated. Skin cancer screening was implemented on a large scale in

Germany as part of the SCREEN (Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) project; the study found that the incidence of invasive melanoma increased, and melanoma mortality decreased, with screening (1b) [74]. As a result of these findings, Germany started a national mandatory skin cancer early detection initiative [74]. However, major biases and limitations of the SCREEN project have been discussed (5) [75], and the quality of evidence reporting benefit from skin cancer screening has been deemed low (3a) [76]. The United States Preventive Services Task Force (USPSTF), after conducting a systematic evidence review, concluded that the value of skin cancer screening for reducing mortality was unclear (3a) [77]. The benefits of screening, which are reduced morbidity and mortality from skin cancer, should outweigh the risks, which include unnecessary biopsies, cost, and patient anxiety. The USPSTF and other groups have therefore called for further research to better define screening protocols, particularly for high-risk populations who are most likely to benefit from skin cancer screening, such as OTR [75–77].

There are currently no formal, evidence-based consensus guidelines for skin cancer screening in OTR. Expert opinion from the International Transplant Skin Cancer Collaborative (ITSCC) has guided dermatologists thus far, with a general recommendation for annual skin cancer screening in OTR and screening with increased frequency for OTR with a history of AK or skin cancer (5) [78]. The Transplant Skin Cancer Network (TSCN) has recently created the "Skin Cancer Risk Evaluation aftEr traNsplant" (SCREEN) score, an evidence-based scoring algorithm for skin cancer incidence after transplantation. The prediction model is based on posttransplant incidence data for SCC, melanoma, and MCC. Skin cancer incidences were collected for a large retrospective cohort of 10,649 patients, from 26 transplant centers in the United States, with up to 10 years of follow-up. Statistically significant risk factors for skin cancer were assigned point values based on relative hazard; identified risk factors were white race (5 points), pretransplant skin cancer (3 points), age ≥ 50 years at the time of transplant (2 points), male sex (1 point), and transplanted heart or lung (1 point) (2b) [79]. A four-tier risk prediction scoring system was proposed, with categories of Low risk (0–3 points), Medium risk (4–6 points), High risk (7–9 points), and Urgent risk (10–12 points). Skin cancer incidence in the Urgent risk group was 65.6%, while that in the Low risk

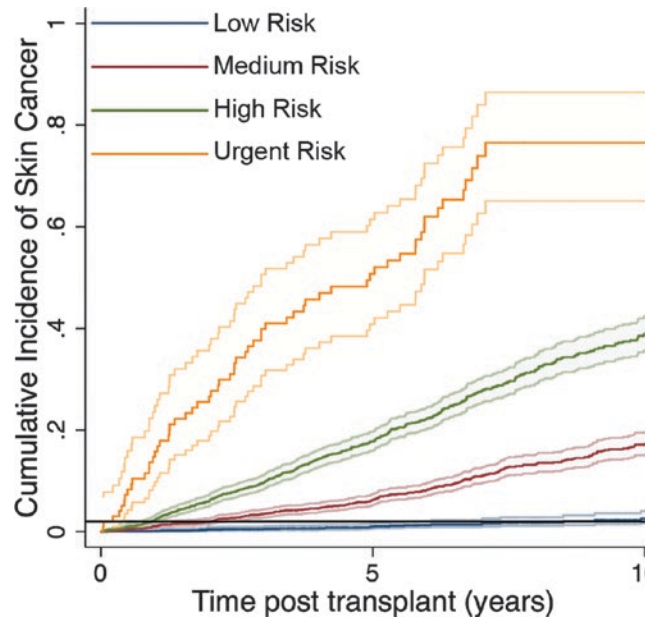

Fig. 60.2 Cumulative incidence function curves for the "Skin Cancer Risk Evaluation aftEr traNsplant" (SCREEN) Categories.

Table 60.1 Posttransplantation referral guidelines based on the "Skin Cancer Risk Evaluation aftEr traNsplant" (SCREEN) category

SCREEN risk category	Initial screening guidelines for referral to dermatology[a]
Low Risk	Problem/lesion focused (patient or provider initiated) at any time in the posttransplant period No routine posttransplant skin cancer screening recommended
Medium Risk	Problem/lesion focused (patient or provider initiated) at any time in the posttransplant period First posttransplant skin cancer screening by 5 years
High Risk	Problem/lesion focused (patient or provider initiated) at any time in the posttransplant period First posttransplant skin cancer screening by 2 years
Urgent Risk	Consider pretransplant skin cancer screening Problem/lesion focused (patient or provider initiated) at any time in the posttransplant period First posttransplant skin cancer screening by 6 months

[a]Referral to a specialized transplant dermatologist where available

group was 1.7% (Fig. 60.2). TSCN has proposed skin cancer screening guidelines based on expert opinion of these data. In Low risk patients, routine skin cancer screening is not recommended due to minimal skin cancer risk, but referral for evaluation of concerning lesions is recommended. Routine skin cancer screening, preferably by a transplant dermatologist, is recommended for Medium, High, and Urgent patients every 5 years, 2 years, and 6 months, respectively (Table 60.1) [79]. This decision support tool has been endorsed by ITSCC for use in the United States.

Hypothetical Case

A 65-year-old white male with a history of double lung transplant for idiopathic pulmonary fibrosis 3 years ago presents to dermatology clinic as a new patient; he was previously followed by an out-of-state dermatologist. A complete history reveals the following: He is Fitzpatrick skin type I. He grew up working on a farm and experienced multiple blistering sunburns as a child. Since his transplant, he has been vigilant about sun protection, wearing SPF 50 sunscreen and a broad-brimmed hat whenever outdoors; he also avoids the sun as much as possible. His skin cancer history consists of a BCC on the right nasal ala 5 years ago, and squamous cell carcinoma in situ (SCCIS) on his right forehead 2 years ago, status post Mohs and complex layered linear closure. One year ago, he had a left medial canthus SCC and left nasal sidewall SCC, both treated with Mohs and repaired by oculoplastics, and a right auricular helix SCC treated with Mohs and complex closure. He has no family history of skin cancer. He has been doing well with his lung transplant and has not had evidence of rejection. He has been maintained on an immunosuppressive regimen of tacrolimus 1 mg BID, prednisone 7.5 mg PO daily, and mycophenolate mofetil 500 mg PO BID. He has no history of field treatment for AK. He reports no recent skin changes or concerns. On exam, he has one 3 × 7 mm pink pearly papule on his chest concerning for malignancy; he also has 15 erythematous scaly papules on his face, consistent with AK. Otherwise, full-body skin exam is normal.

This patient is in a high-risk group for posttransplant skin cancer based on his age, sex, race, pigmentation, sun exposure, lung transplant, and history of skin cancer. He was extensively counseled on sun protection and on his risk of skin cancer. He was managed with the following: (1) cryotherapy of 15 AK lesions on his face, with PDT of the face and ears scheduled for within 2 months, (2) shave biopsy of the pink pearly papule on his chest, and (3) classification into SCREEN Urgent risk category based on his score of 12 points [79]. Accordingly, it was decided that he should be seen for routine skin cancer checks every 6 months or earlier as needed for new or concerning skin lesions.

Frequency of skin cancer was discussed with the patient's transplant team, who agreed to transition toward use of sirolimus for immunosuppression. The transplant team held mycophenolate mofetil, with plans to taper tacrolimus and

start sirolimus. From shave biopsy, pathology returned as a nodular BCC. Mohs Appropriate Use Criteria score was 5, defined as "Uncertain" evidence for benefit from Mohs micrographic surgery over other treatments. Electrodessication and curettage (ED&C) of the BCC was recommended and performed.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
OTR have an increased risk of skin cancer. They develop more aggressive skin cancers, with increased skin cancer mortality	A
Risk factors associated with skin cancer mortality in OTR include white race, male sex, transplanted heart or lung, and patients at or above 50 years of age	B
In OTR, azathioprine, cyclosporine, and voriconazole are associated with increased skin cancer risk	B
Sirolimus has been shown to reduce skin cancer risk in kidney transplant recipients with a personal history of skin cancer	A
Sirolimus has not been shown to be effective for primary prevention of skin cancer in OTR	C
Diclofenac is safe and effective for the treatment of AK in OTR	B
Imiquimod is safe and effective for the treatment of AK in OTR	A
5-Fluorouracil is safe and effective for the treatment of AK in OTR	B
Photodynamic therapy is safe and effective for the treatment of AK in OTR	A
Nicotinamide 500 mg BID is safe and appears to be modestly effective for skin cancer chemoprevention in OTR	C
Acitretin is safe and effective for non-melanoma skin cancer chemoprevention in OTR	A
For OTR, annual skin cancer screening, with increased screening frequency in patients with a history of AK or skin cancer, has been recommended based on expert opinion	D
A new evidence-based skin cancer screening protocol for OTR, with screening frequency directly based on a patient's risk factors for skin cancer, has been proposed	B

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Self-Assessment Questions

1. Which of the following is *not* a reported risk factor for skin cancer incidence in OTR? (Choose all that apply.)
   (a) White race
   (b) Transplanted heart or lung
   (c) Age 50 years or older at the time of transplant
   (d) Female sex
   (e) Immunosuppression with azathioprine

2. Evidence for reduction in skin cancer risk with conversion to sirolimus-based immunosuppression is strongest in which of the following patient populations?
   (a) Renal transplant recipient with personal history of skin cancer
   (b) Renal transplant recipient without personal history of skin cancer
   (c) Heart transplant recipient with personal history of skin cancer
   (d) Heart transplant recipient without personal history of skin cancer
   (e) Bone marrow transplant recipient without personal history of skin cancer

3. Which of the following have been shown to be safe and effective for the treatment of actinic keratoses in OTR? (Choose all that apply.)
   (a) Diclofenac
   (b) Ingenol mebutate
   (c) Imiquimod
   (d) 5-Fluorouracil
   (e) Photodynamic therapy

4. Which of the following is most commonly reported as a dose-limiting side effect of acitretin in OTR?
   (a) Acne fulminans
   (b) Periorbital edema
   (c) Mucocutaneous side effects (cheilitis, dry lips, palmoplantar desquamation, etc.)
   (d) Lymphopenia
   (e) Elevation in liver function tests

5. Which of the following is true regarding nicotinamide?
   (a) Grade A evidence supports the use of nicotinamide for skin cancer chemoprevention in OTR.
   (b) Nicotinamide is not safe in OTR.
   (c) Nicotinamide 500 mg PO BID is well tolerated in immunocompetent patients but not in immunocompromised patients.
   (d) Nicotinamide should be used for primary prevention of skin cancer in all OTR.
   (e) Nicotinamide has been shown to be effective for skin cancer chemoprevention in patients with frequent NMSC.

Correct Answers

1. d: White race, thoracic organ transplant, age 50 years or older at the time of transplant, and male sex are risk factors for skin cancer incidence in OTR. Azathioprine has been associated with increased risk of skin cancer in OTR in multiple clinical studies. See *Epidemiology, Medications, and Skin Cancer Risk* and *Skin Cancer Screening*.
2. a: Two meta-analyses concluded that, in renal transplant recipients, conversion to a sirolimus-based immunosuppressive regimen, after the development of skin cancers, was associated with a reduced risk of NMSC. Findings may not be generalizable to the entire solid OTR population for primary prevention of NMSC. In one large cohort study of solid OTR, which included nonrenal transplant patients, the risk of SCC was not associated with the use of sirolimus or with cumulative duration of sirolimus. See *Medications and Skin Cancer Risk – Benefits of mTOR Inhibitor for Immunosuppression*.
3. a, c, d, e: (At the time of publication, phase I study of ingenol mebutate in OTR is in progress). Diclofenac, imiquimod, 5-fluorouracil, and photodynamic therapy have all been shown to be safe and effective for the management of actinic keratoses in OTR. Ingenol mebutate is FDA-approved for the treatment of actinic keratoses in immunocompetent patients. At the time of publication, phase I study of ingenol mebutate in OTR is in progress. See *Management of Actinic Keratoses – Safety and Efficacy*.
4. c: Mucocutaneous side effects of acitretin, including palmoplantar desquamation, xerosis, and cheilitis, are very common and may be dose-limiting. Liver panel abnormalities occur rarely with acitretin, and monitoring of liver function tests is therefore recommended. Acne fulminans, periorbital edema, and lymphopenia are not commonly reported adverse effects of acitretin. See *Skin Cancer Chemoprevention – Acitretin*.
5. e: Based on Grade C evidence, nicotinamide 500 mg PO BID is safe, well tolerated, and modestly effective for skin cancer chemoprevention in OTR. Nicotinamide has been shown to be effective for secondary chemoprevention in patients with frequent NMSC, but there are no studies to support its use for primary prevention of skin cancers. See *Skin Cancer Chemoprevention – Nicotinamide*.

Leg Veins

61

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Abstract

There are multiple treatment modalities to address unwanted and/or symptomatic leg veins. When selecting treatment, variations in vessel size, depth, and type must be taken into consideration. Treatment options include sclerotherapy, endovenous ablation with laser or radiofrequency, ambulatory phlebectomy, transcutaneous lasers and intense pulsed light systems, as well as the more recently developed cyanoacrylate closure and mechanochemical ablation. This chapter reviews the effectiveness, safety, and appropriate selection of the above-listed procedures for treating leg veins.

Keywords

Sclerotherapy · Endovenous ablation
Phlebectomy · Venous insufficiency
Varicose veins · Reticular veins
Telangiectasias

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Epidemiology

Leg veins can largely be divided into deep and superficial systems defined by their relationship to the muscular fascia. Deep veins lie beneath the muscular fascia, whereas superficial veins are located above this deep fascia. Perforating veins penetrate the fascia and connect the superficial and deep venous systems.

To ensure blood return from the lower extremities to the heart and lungs, a system of muscular pumps and valves allows blood to flow from superficial to deep and from distal to proximal. Any dysfunction in this system, such as valvular incompetence, muscular pump failure, or chronic venous obstruction, may result in impaired venous outflow and reflux.

The most common form of venous disease is venous insufficiency from valve incompetence. Deep venous insufficiency typically occurs when valves are damaged by deep vein thrombosis. Superficial venous insufficiency occurs when a high-pressure leakage develops between the deep and superficial systems or within the superficial system, followed by sequential failure of the venous valves within the superficial veins. Over time, incompetent superficial veins can present as dilated and tortuous varicose veins, blue reticular veins, venulectasias, and telangiectasias. Varicose veins are a common problem, with incidence reported to range from 20% to 64% [1–4]. Telangiectasias are also extremely

common and have been reported to affect up to 80% of the population [5].

Although specific genetic risk factors for varicosities are not known, heredity does seem to play an important role. One study demonstrated that the risk of developing varicosities was 20% with two unaffected parents, 25% for males and 62% for females with one affected parent, and 90% with two affected parents [6]. There is also evidence that geographic region and race may play a role. In particular, the prevalence of venous disease has been found to be higher in westernized and industrialized countries [7].

Other risk factors for the development of venous disease include gender and age, with greater incidence in women and with advancing age. Highlighting this difference, the Tecumseh community health study from Tecumseh, Michigan, found that varicosities were present in 72% of women aged 60–69 years but only 1% of men aged 20–29 years [8]. An exception to this trend is the blue reticular varicosities involving the lateral lower extremities. While they are more common in females, these tend to occur earlier in life and do not increase in incidence with advancing age [9].

Regarding the greater incidence of venous disease in women, pregnancy has been shown to be an important risk factor. A significantly higher age-adjusted prevalence of varicose veins, reticular veins, and telangiectasias has been demonstrated in parous women compared with nulliparous women [5]. Further, a positive correlation has been shown between the prevalence of varicose veins and the number of pregnancies [10]. Development of varicose veins has additionally been attributed to environmental factors. Studies repeatedly showing that certain occupations, especially those that require prolonged standing, are associated with a greater incidence of varicosities [11, 12].

With progressive venous insufficiency, complications include stasis dermatitis, edema, and ulceration. Further, many patients report associated symptoms including pain, soreness, burning, aching, throbbing, cramping, muscle fatigue, and restless legs. In one study, up to 53% of patients with leg telangiectasias attributed associated symptoms [13]. Therefore, not only cosmetically bothersome, venous disease of the lower extremities can be extremely debilitating.

Treatment Overview

Variations in vessel type, size, flow, and depth preclude the possibility of a single effective treatment modality. Vessel types include varicosities, reticular veins, venulectasias, and telangiectasias [14]. This distinction is generally made based on size with varicose veins being greater than 4 mm in diameter, reticular veins ranging from 2 to 4 mm, venulectasias ranging from 1 to 2 mm, and telangiectasias being less than 1 mm.

Among the treatments for leg veins, the longest-standing technique is phlebectomy. Its use dates back to ancient times, when it was first described by Aulus Cornelius Celsus (25 BC–45 AD) [14, 15]. In 1956, Dr. Robert Muller, a dermatology-trained phlebologist from Switzerland reinvented and refined the technique that we now know as ambulatory phlebectomy [15]. Ambulatory phlebectomy involves the removal of varicose veins through small incisions using hooks and forceps. It can be performed under local anesthesia in an office-based setting. Ambulatory phlebectomy is considered a safe and immediately effective procedure for the treatment of varicose veins, although its need has been greatly reduced with the discovery of foam sclerotherapy [15].

Sclerotherapy remains the treatment of choice for most leg veins less than 4 mm in diameter [14, 15]. It involves the injection of dilated veins with liquid or foam agents to damage the endothelial cells and cause fibrosis of the target vessel. Sclerosing agents can be broadly divided into three categories: detergents such as polidocanol and sodium tetradecyl sulfate (STS), osmotic or hypertonic solutions such as hypertonic saline, and chemical irritants including glycerin [14]. Concentrations of these agents may be adjusted according to the size of the vein being treated.

Transcutaneous laser therapy and intense pulsed light (IPL) systems may be valuable alternatives in specific situations where sclerotherapy

is not preferred. These devices cause endothelial injury by heating hemoglobin and ultimately obliterating the vessel lumen [14, 15]. In general, however, treatment of leg veins with lasers and IPL devices are less predictable as compared to sclerotherapy. Several reasons may contribute to the variable response. These include the variability in depth and location of the leg veins, as well as differences in vessel wall thickness and diameter. Further, blood in leg veins tends to have a reduced oxygenation state that leads to a violaceous instead of red color. Therefore, each telangiectasia may have a slightly different optimal wavelength of absorption based on its color, in addition to its relative size and depth [15].

For treatment of reflux present at the saphenous veins, endovenous occlusion has become a widely utilized, less invasive alternative to surgical ligation and stripping [14, 15]. This procedure is performed percutaneously with ultrasound guidance. The two most frequently used endovenous ablation techniques utilize either laser or radiofrequency. Endovenous radiofrequency ablation was FDA approved in 1999 and was quickly followed by the clearance of endovenous laser ablation in 2000 [15]. In addition to the use of radiofrequency and lasers, other endovenous procedures have been developed in recent years. These include steam vein sclerosis, mechanochemical ablation, and injection of cyanoacrylate glue [16].

Sclerotherapy

Studies repeatedly show that sclerotherapy is more effective than placebo injections for the treatment of telangiectasias, reticular veins, and varicose veins [17–20]. In a clinical trial comparing polidocanol 0.5–1%, STS 1%, and placebo for treatment of telangiectasias and reticular veins, significantly more patients were satisfied with polidocanol (88%) than with STS (63%) or placebo (11%) [1b] [20]. Another study compared polidocanol 0.25%, STS 0.5%, heparsal, and placebo for treating telangiectasias [2b] [21]. The lower extremities of each patient were divided into four quadrants, and each area was treated with a different agent. Although all the agents except placebo were effective, polidocanol was found to have the fewest adverse reactions and provided the greatest patient comfort. When patients were given the choice of a sclerosant to treat the placebo-injected area, polidocanol was favored by all 20 patients.

In two separate studies, polidocanol was shown to be significantly more effective than placebo injections in obliterating non-saphenous varicosities, with success rates varying between 76.8% and 88.6% [2b] [17, 19]. It should be emphasized that only those with competent saphenous veins were included in these studies. On the other hand, long-term efficacy with sclerotherapy is unlikely if underlying reflux is present. In a separate study, varicose vein recurrence was found to be over 90% at 6 years post-sclerotherapy in those with underlying saphenous vein incompetence [2b] [22].

A Cochrane review was conducted on sclerotherapy for telangiectasias [2a] [23], and a separate Cochrane review was performed on sclerotherapy for varicose veins [2a] [24]. In both reviews, there was no evidence suggesting superior efficacy of any one sclerosant over another. Sclerosing agents for treating telangiectasias included polidocanol, STS, chromated glycerin, hypertonic saline, and hypertonic dextrose. For treating varicose veins, polidocanol, STS, ethanolamine, and hypertonic saline were included. However, there was a discrepancy among these sclerosants regarding the risk of adverse events. For example, when treating telangiectasias, STS 1% was more likely to cause adverse reactions than polidocanol 0.5%. In another trial comparing polidocanol and hypertonic saline for treating telangiectasias and reticular veins, there were no significant differences in overall improvement between the two agents [2b] [25]. However, hypertonic saline caused 2.35 times as much pain during the injections, and there was a higher risk of tissue necrosis.

Also important in determining the risk of adverse events is the concentrations of the sclerosing agents. Polidocanol 0.25%, 0.50%, 0.75%, and 1% were compared with regard to clinical effectiveness and safety in treating telangiectasias

[2b] [26]. While there was no evidence of increased efficacy at any particular dose of polidocanol, hyperpigmentation was found to be more likely at a concentration of 1% when compared with lower concentrations. In the continued search for the "ideal" sclerosant concentrations, a recent study reviewed the effects of varying concentrations of STS and polidocanol. Based on both histologic evaluation and clinical correlation, STS 0.15% and polidocanol 0.31% were found to be the best concentrations for the treatment of leg telangiectasias from 0.8 mm to 1.0 mm [2b] [27]. However, no exact standard exists at this point. As for larger varicosities, polidocanol 1% and 3% foam were compared for treating great saphenous vein incompetence [1b] [28]. It was demonstrated that both concentrations had equivalent efficacy in treating veins less than 8 mm in diameter. At 2-year follow-up, reflux was absent in 69% of the 3% group and 68% of the 1% group. With the idea that the optimal sclerosant concentration depends on vessel size, most studies examining the effectiveness of sclerotherapy on variably sized varicosities tend to adjust the concentration of the sclerosant according to vessel diameter [19, 29].

Multiple studies have demonstrated that foam sclerotherapy, with ultrasound guidance if the varicosity is not readily visible from the skin surface, can be more effective than liquid sclerotherapy when treating larger vessels [18, 30–33]. In a crossover, randomized, controlled trial comparing foam and liquid sclerotherapy for treating varicose veins, total occlusion rates were significantly higher with foam sclerotherapy (92%) compared to liquid sclerotherapy (76%) [2b] [32]. These results are consistent with a subsequent study comparing foam and liquid sclerotherapy in combination with endovenous laser ablation [2b] [34]. There was no difference in terms of closure of the saphenous veins with endovenous laser ablation, but successful sclerosis of the varicose tributaries was significantly higher with foam sclerotherapy (92.7%) than liquid sclerotherapy (71.8%).

The greater effectiveness of foam is attributed to the fact that foam completely fills and displaces the blood in the vein, so that very little of the solution is diluted by blood. Therefore, the full strength of the sclerosant is in contact with the vein wall, maximizing endothelial injury. At the same concentration, foam is nearly four times as strong as its liquid counterpart [33, 35]. Ultimately, foaming allows one to use a lower concentration and less volume of sclerosant, which also translates to decreased side effects. For smaller vessels, however, foam runs the risk of rupturing the thin walls with risk of increased pigmentation and matting. Therefore, liquid sclerotherapy is preferred for these vessels. As a general rule, foam should be reserved for vessels that are larger than 1 mm, although there is no strict consensus on amount or concentration of sclerosant [5] [36].

Lasers and IPL Systems

While sclerotherapy remains the gold standard for treating most leg veins, transcutaneous lasers and intense pulsed light (IPL) devices may be indicated in select situations. Lasers for treating leg veins include the 532 nm potassium titanyl phosphate (KTP) laser, 585–595 nm pulsed dye laser, 755 nm alexandrite laser, various 800–980 nm diode lasers, and 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser. The evidence for using each device will be briefly discussed below.

The 532 nm KTP laser has high absorption by both hemoglobin and melanin and has a penetration depth of about 0.75 mm. Studies show that the KTP laser is mainly effective in treating leg veins smaller than 1 mm in diameter [37–41]. Clearing of over 50% of leg veins was noted after a single treatment session [38, 39] and over 75% of veins after two treatments [37]. Only a few studies investigated the efficacy of the KTP laser for the treatment of larger veins. One study reported good results for treating leg veins that are 1–2 mm in diameter [2b] [42]. After two treatment sessions, 67% of patients had a greater than 50% clearance. Other studies found no improvement after three sessions [43, 44].

Absorption by hemoglobin is also strong with the 585–595 nm pulsed dye laser although lower

than at 532 nm. However, there is deeper penetration at this longer wavelength with depth of vascular damage for a short-pulse duration estimated to be 1.5 mm. Like the KTP laser, studies show that the pulsed dye laser is more effective in treating veins smaller than 1 mm in diameter [45–49]. In a study demonstrating that efficacy decreases with increasing vessel size, vessels <0.2 mm showed the greatest response with 100% having complete clearance after two treatments [2b] [50]. For vessels 0.2–1 mm, 13% had complete clearance, while 78.3% had greater than 75% improvement. Vessels 1.1–2 mm were the least likely to respond with none showing complete clearance and only 22.2% showing greater than 75% improvement. In a few comparative studies, the pulsed dye laser has been demonstrated to be slightly superior to the KTP laser in the removal of leg veins [40, 41].

The 755 nm alexandrite laser has a high relative absorption by hemoglobin, although absolute absorption by hemoglobin is significantly lower than with the KTP and pulsed dye lasers. Its main advantage over the KTP and pulsed dye lasers is its penetration depth, which can theoretically reach up to 2–3 mm. Therefore, this laser may be useful for deeper and more resistant vessels. The alexandrite laser is considered to be the most effective for leg veins 0.4–3 mm in diameter [2b] [51].

Multiple diode lasers are available and include wavelengths of 800, 810, 900, 940, and 980 nm. Similar to the alexandrite laser, the various diode lasers are generally used for the treatment of larger vessels that are located deeper in the dermis. In one study, veins with a diameter of 3–4 mm showed the most response [2b] [52]. Another study examined the use of the diode laser for treating telangiectasias and venulectasias and found that only 13.3% of telangiectasias less than 0.4 mm had greater than 75% clearance [2b] [53]. On the other hand, 88.2% of vessels between 0.8 and 1.44 mm obtained more than 75% clearance. In a comparative study between 1064 nm Nd:YAG, alexandrite, and 810 nm diode lasers, the diode laser produced less predictable results and less clearance of leg veins up to 3 mm in diameter [2b] [54].

Among all vascular lasers, the 1064 nm Nd:YAG laser has been the most extensively studied for the treatment of leg veins. There is weak hemoglobin, melanin, and water absorption at this wavelength. However, it has the deepest penetration with a depth of more than 4 mm at its peak, making this laser a suitable treatment modality for more deeply located veins. The first report using the Nd:YAG laser to treat leg veins included veins ranging in size from 0.5 to 3 mm [2b] [55]. At 3 months follow-up, 75% improvement was noted at the treatment sites. In a subsequent study, 64% of patients achieved 75% or greater clearing of 0.2–4 mm diameter vessels after a maximum of three treatment sessions [2b] [56]. Overall, the Nd:YAG laser is considered to be better for veins larger than 1 mm in diameter, although good results have also been reported for smaller veins [43, 57, 58]. In a study including 21 lower extremity sites, 58% of 0.25–1 mm vessels, 83% of 1.1–2 mm vessels, and 100% of 2.1–4 mm vessels showed significant clearing after two treatments [2b] [58]. Recurrence after treatment with the Nd:YAG laser has been reported to be infrequent with less than 10% of leg veins recurring after 1 year [56, 59].

IPL systems emit a broad-spectrum light, from 500 to 1200 nm, although cutoff filters can be used to exclude certain wavelengths. Clinical evidence for IPL in the treatment of leg veins is scarce, but particularly, small vessels are believed to respond well to IPL treatment. In a multicenter trial of 159 patients, clearance rates of greater than 75% were found in 80% of vessels smaller than 0.4 mm, 87% of vessels 0.4–1 mm, and 61% of vessels 1–3 mm in diameter [2b] [60].

Endovenous Ablation

The two most commonly used endovenous ablation techniques are endovenous laser ablation and radiofrequency ablation. These will be the focus of this section.

Successful occlusion of the great saphenous vein following endovenous laser ablation has been reported to vary between 77% [61] and 99% [62] at 1 year. A recent meta-analysis of studies

with a 4- to 5-year follow-up for endovenous thermal ablation of the great saphenous vein found success rates of 84.8% with endovenous laser ablation and 88.7% with radiofrequency ablation [2a] [63]. Endovenous thermal ablation of the small saphenous vein has also demonstrated excellent results with success rates of 96.2–98.5% [64–66]. In a study that followed patients to 2 years after endovenous laser ablation of the small saphenous vein, 81.2% of patients had continued occlusion [2b] [65].

To reduce potential side effects, endovenous lasers with higher wavelengths have been introduced. Higher wavelength lasers (1320, 1470, 1500 nm) predominantly absorb water, as opposed to the lower wavelength lasers (810, 940, 980, 1064 nm) that more specifically absorb hemoglobin. These higher wavelength lasers have the theoretical advantage of contracting the vein with less heat generation and fewer risks than with the hemoglobin-absorbing wavelengths. A retrospective review was conducted on endovenous thermal ablation with an 810 nm diode, a 1320 nm laser, and a radiofrequency device to treat great and small saphenous vein incompetence [2b] [67]. Successful ablation rates were reported to be 80.8% with 810 nm, 93.7% with 1320 nm, and 78.2% with radiofrequency at 1-year follow-up. At 5-year follow-up, successful ablation rates were 65.7% with 810 nm, 84.7% with 1320 nm, and 61.7% with radiofrequency. Other studies show equal occlusion rates with the higher wavelength lasers when compared to lower wavelength lasers, although less postoperative pain has been reported with the higher wavelength lasers [68–71].

New endovenous laser fiber tips have also been developed to increase efficacy and reduce potential adverse events. The standard bare fiber creates unequal energy delivery at the vein wall resulting in local vein wall perforations and surrounding tissue destruction. New fibers have been designed to increase the heated surface area, resulting in the need for lower energy density [72, 73]. A randomized controlled trial reported fewer side effects and an equal occlusion rate using a newer tulip fiber compared with a bare fiber [1b] [73].

Overall, it appears that endovenous laser ablation and radiofrequency ablation have similar occlusion rates. However, a definitive conclusion cannot be drawn given the great variability in the devices and limited studies that compare across each of these variations. In addition to differences in laser fiber tips (bare fiber versus the newer fibers) and wavelengths, there are also variations in radiofrequency catheters (older ClosurePlus versus newer ClosureFast). In a short-term outcome analysis comparing the two generations of radiofrequency catheters, ClosureFast was found to be superior to ClosurePlus in terms of great saphenous vein obliteration (98% with ClosureFast versus 88% with ClosurePlus) [2b] [74]. To date, there are no trials comparing the use of the ClosureFast catheter with higher wavelength lasers and with the newer fiber tip design.

Ambulatory Phlebectomy

Phlebectomy may be performed as an adjunctive treatment to surgical stripping or endovenous ablation of the main refluxing truncal vein [75–77]. It may also be performed as an exclusive procedure for the treatment of branch varicosities [78, 79]. Most types of primary and secondary varicose veins may be removed by ambulatory phlebectomy, except when junctional saphenous incompetence is present. When any important sources of reflux are present, such as at the saphenofemoral junction or saphenopopliteal junction, these need to be corrected before any effort is made to address the end-branch disease with phlebectomy. Vessels most readily treated with phlebectomy include accessory saphenous veins of the thigh, reticular veins in the popliteal fold or on the lateral thigh or leg, veins of the ankle, and the dorsal venous network of the foot. Studies have shown that ambulatory phlebectomy is a safe and immediately effective procedure [78]. Development of new varicosities or recurrence following ambulatory phlebectomy has been found to range from 2% to 11% at a minimum of 6 months follow-up [78, 80, 81].

Compression After Venous Intervention

Some providers use compression stockings alone as initial treatment in the early stages of varicose veins without ulceration. Of note, while most studies report a subjective improvement of symptoms with compression, a 2013 Cochrane review reveals insufficient evidence to determine whether compression, as the sole intervention, is effective in the treatment of early varicosities [1a-] [82]. However, the recommendation of compression after other interventions for leg veins remains common.

Compression therapy is commonly used after endovenous thermal ablation. A randomized controlled trial demonstrated that the use of 35 mm Hg compression stockings for 7 days after endovenous laser ablation of the great saphenous vein significantly reduced pain and improved physical function when compared with use for 2 days [1b] [83]. Another randomized trial compared the use of thigh-high 23–32 mm Hg compression therapy for at least 2 weeks with no compression therapy following endovenous laser ablation of the great saphenous vein [1b] [84]. It was concluded that compression therapy reduced the severity of pain and edema during the first week post-procedure. However, there were no significant differences in the quality of life or in the mean time to return to work between the two groups.

Compression therapy is also routinely used after sclerotherapy. Studies show that post-sclerotherapy compression improves the clinical appearance of vessels and reduces post-sclerotherapy pigmentation and bruising [85, 86]. In one study, 3 weeks of continuous compression led to best results, although even 3 days of compression resulted in greater improvement than no compression [2b] [87]. The use of graduated compression stockings was shown to reduce the risk of post-sclerotherapy pigmentation, telangiectatic matting, and cutaneous necrosis, even when treating vessels less than 1 mm in diameter. However, when low compression profile (15–20 mm Hg) stockings were used after foam sclerotherapy of larger veins, there was no effect on efficacy, side effects, or satisfaction scores when compared with a control group without compression [1b] [88]. Most clinicians believe Class I (20–30 mm Hg) compression is necessary for treating telangiectasias, whereas Class II (30–40 mm Hg) or Class III (40–50 mm Hg) compression is indicated for larger varicosities [5] [36].

Most recently, an evidence-based review of the use of medical compression stockings in venous and lymphatic disorders was performed. A recommendation of early compression after GSV intervention, such as using thigh-length 20–40 mm Hg stockings for 1 week, was made to reduce post-procedure side effects (Grade 1B) [89]. No clear benefits were appreciated with compression periods of longer than 1 week. Additional eccentric compression along the treated vein may be beneficial in reducing side effects as well (Grade 1B). In terms of increasing efficacy of the treatment and improving outcomes, medical compression stockings were recommended after treatment of C1 veins with liquid sclerotherapy (Grade 2B), but not after treatment of the GSV [89]. However, there continues to be significant variations in clinical practice in terms of compression following leg vein interventions.

Incompetent Saphenous Veins: Surgery Versus Endovenous Ablation Versus Foam Sclerotherapy

In multiple recent studies comparing conventional surgery with endovenous thermal ablation and ultrasound-guided foam sclerotherapy for treating incompetent great saphenous vein, residual reflux has been found to be significantly more common after foam sclerotherapy compared with the other two treatments [62, 90–92]. In the trial with the longest follow-up of 5 years, success rates were 85% with surgery, 82% with endovenous laser ablation, and 41% with foam sclerotherapy [2b] [93]. The difference in success rates of surgery and endovenous ablation was not statistically significant.

A large trial including 798 patients compared surgery, endovenous laser ablation, and foam sclerotherapy (STS 3%) for the treatment of both

great and small saphenous vein reflux [1b] [94]. Complete success rate after 6 months was 78% for surgery, 82% for endovenous laser ablation, and 43% for foam sclerotherapy. Disease-specific quality of life was also significantly improved in all three groups after the intervention, although comparatively worse for foam sclerotherapy.

While few randomized controlled trials exist specifically comparing treatment modalities for small saphenous vein incompetence, a meta-analysis found success rates to be higher with endovenous thermal ablation as compared to surgery [2a] [64]. Anatomical success rates were 58% with surgery, 98.5% with endovenous laser ablation, 97.1% with radiofrequency ablation, and 63.6% with foam sclerotherapy. A recent Cochrane review further analyzed the available data to date. Three randomized controlled trials, comparing endovenous laser ablation and surgery, included 289 participants and revealed less frequent recanalization or persistence of reflux at 6 weeks in the endovenous laser ablation group with an odds ratio of 0.07 [1a] [95]. At 1 year, recurrence of reflux was less commonly seen in the endovenous laser ablation group, although no difference in clinical recurrence of reflux was appreciated. Insufficient data was available to distinguish a difference in recurrence or persistence of reflux between foam sclerotherapy and surgery.

Varicose Veins: Ambulatory Phlebectomy Versus Sclerotherapy

Although both sclerotherapy and ambulatory phlebectomy are useful tools in treating varicose veins, there are very limited studies comparing the two. In the most recent study comparing the recurrence rates of varicose veins after sclerotherapy and ambulatory phlebectomy, it was found that there were significantly fewer recurrences with ambulatory phlebectomy (1/48) when compared to liquid sclerotherapy (12/48) *at 1-year follow-up [2b]* [78]. At 2-year follow-up, six additional recurrences were found with sclerotherapy but none with phlebectomy. In a separate study, rate of recurrence or development of new varicosities was found to be similar between the two treatment modalities (11% with ambulatory phlebectomy versus 12% with sclerotherapy) [2b] [80]. In addition, there was no significant difference in patient satisfaction between the two groups.

Reticular Veins and Telangiectasias: Lasers and IPL Systems Versus Sclerotherapy

Studies comparing lasers and IPL systems with sclerotherapy are also scarce. Among the various devices, the Nd:YAG laser has been the most extensively studied. This is understandable as the Nd:YAG laser is considered the most effective, especially for treatment of larger leg veins. In a trial comparing Nd:YAG, diode, and alexandrite lasers for treating 0.3–3 mm leg veins, greater than 75% improvement was observed in 88% with the Nd:YAG laser, 29% with the diode laser, and 33% with the alexandrite laser [54]. Similarly, when compared to KTP, Nd:YAG has been found to provide superior clearance of vessels greater than 1 mm and comparable if not better clinical improvement of vessels less than 1 mm in diameter [40, 43]. However, the KTP laser may be preferred for treating smaller vessels given its more favorable side effect profile. Another study compared the clinical efficacy of Nd:YAG and IPL. Again, the results were in favor of the Nd:YAG laser [2b] [96].

In a prospective randomized trial comparing the Nd:YAG laser to sclerotherapy, 56 patients with telangiectasias and reticular veins were included and were followed up to 6 months [2b] [97]. It was demonstrated that both sclerotherapy and Nd:YAG laser have similar effectiveness with a significant clinical improvement of >70% after two treatment sessions of each. However, improvement was achieved more quickly with sclerotherapy, and the Nd:YAG laser was considered to be more painful. Prior smaller studies found similar results [98–101]. Overall, however, these studies lack long-term follow-up with the longest follow-up of 6 months. Therefore, a comparison of recurrence rates cannot be made.

Preoperative Evaluation and Patient Selection

A preliminary assessment is performed to understand whether there is an underlying source for the varicose veins and their regions of involvement.

After a thorough history is obtained, a complete examination of both legs needs to be performed. The physical exam serves to identify cutaneous complications of venous insufficiency and directs the need for noninvasive diagnostic imaging prior to treatment. In particular, cutaneous findings may provide clues as to whether there is an underlying source of reflux, such as from regions of the great saphenous vein, small saphenous vein, or lateral venous system. For example, evidence of chronic venous stasis, particularly of the medial ankles or lower legs, is a sign of great saphenous vein incompetence. On the other hand, skin changes or ulcerations on the lateral ankles are likely to be related to small saphenous vein insufficiency. Clues for reflux in the reticular veins of the lateral venous system include telangiectatic webs on the lateral and posterior thighs [102].

As a general rule, when a patient presents with bulging varicosities, complains of leg pain or swelling, has history of prior vein surgery, or has strong family history of varicose veins and presents with an abundance of veins in the area served by the saphenous veins, diagnostic imaging with Duplex ultrasound is indicated. The Duplex ultrasound can easily detect unusual venous anatomy, valvular incompetence, and venous obstruction [103–105]. The cutoff values defining valvular reflux during ultrasound examination are retrograde flow longer than 500 ms for the saphenous, tibial, and deep femoral vein, longer than 1 s for the femoral and popliteal vein, and longer than 350 ms for the perforating veins [106].

It should be noted that traditional clinical tests such as Trendelenburg and Perthes have proven unreliable in the mapping of venous incompetence [107, 108]. Therefore, have been largely replaced by diagnostic imaging.

If an underlying source of reflux is located, this should be treated prior to proceeding with treatment of branch varicosities and telangiectasias. If the area of reflux is left untreated, there is high risk of treatment failure and recurrence [22].

Procedure Selection

Incompetent Saphenous Veins: Surgery Versus Endovenous Ablation Versus Foam Sclerotherapy

For saphenous varicosities, endovenous occlusion using radiofrequency or laser is strongly preferred over surgical ligation and stripping and has now become the standard of care in the United States. There is comparable efficacy but significantly fewer side effects with endovenous ablation as compared to surgery [14, 15].

When comparing sclerotherapy and endovenous procedures, there is a higher recanalization rate with sclerotherapy [94]. However, foam sclerotherapy may be an attractive option to treat superficial incompetence in elderly and frail patients or those with venous leg ulcers. With sclerotherapy, patients would need to be informed that repeat treatment may be needed.

Varicose Veins: Ambulatory Phlebectomy Versus Sclerotherapy

Foam sclerotherapy or ambulatory phlebectomy can both be used to treat varicose tributaries. Phlebectomy may be preferred for patients who want to pursue a more definitive treatment for their varicose vein, as vessel removal by this method are gone permanently. In addition, results are immediate, so it may be preferable for patients who do not want to wait for sclerotherapy results. In the case of recurrent varicose veins after phlebitis or sclerotherapy, these may be particularly difficult to extract with phlebectomy because of adhesions and local scar tissue from prior inflammation. Therefore, sclerotherapy would be preferred in this case. Additionally, selection may be made based on vein wall thickness. Visible blue veins are an indication that the vein wall is so thin that blood is easily visualized within it. Removal with phlebectomy would easily shred these veins so sclerotherapy would be preferred.

Reticular Veins and Telangiectasias: Lasers and IPL Systems Versus Sclerotherapy

When considering smaller veins, a consideration is between sclerotherapy and lasers or IPL devices. Sclerotherapy is the gold standard for most of these leg veins as it is relatively safer, less expensive, and easier than laser therapy [15]. For example, when treating arborizing telangiectasias, injection of a sclerosing agent into the supplying vein is often sufficient, whereas the affected area needs to be treated vein by vein with laser therapy. In addition, the variability of leg veins among patients, and even within the same patient, means that laser settings need to be constantly adjusted, or a different laser modality may need to be used altogether [15]. Still, lasers may be preferred in patients who are needle phobic, have concerns of allergy to sclerosants, have severe hypercoagulability, have previously developed unwanted side effects from sclerotherapy, have failed sclerotherapy, or have telangiectasias that are so small in caliber that they cannot be cannulated even with the smallest of needles. In addition, laser therapy may be preferred in areas prone to ulceration, such as the ankle [14, 15].

Typical Treatment Plan

Case 1

A 40-year-old woman presents with leg veins that bulge and ache constantly. She also complains of leg pain and swelling after a long day at work as a waitress. Family history is notable for mother and sister with varicose veins.

On exam, prominent varicosities are present from her right medial knee extending over the posterior calf and down to the ankle, and a small varicosity is present on the left medial calf.

Duplex ultrasound is performed, revealing an incompetent right small saphenous vein and incompetent left great saphenous vein.

The right small saphenous and left great saphenous veins are treated with 1320 nm endovenous laser ablation. At 6-week follow-up, remaining superficial varicosities are treated with duplex-guided sclerotherapy with polidocanol 0.5% foam. The patient is advised to wear 30–40 mm Hg compression stockings for 2 weeks posttreatment.

Especially given the patient's young age and genetic susceptibility, she is advised to follow up annually to examine for recurrence and for the development of new varicosities.

Case 2

A 45-year-old woman complains of the appearance of veins on her lateral thigh. They appeared during pregnancy and have worsened over the past 10 years. No significant symptoms are noted.

On exam, a prominent blue reticular network with associated telangiectasias is noted on her left lateral thigh.

Duplex ultrasound is not performed as this patient presents with the commonly seen pattern of an abnormal lateral venous system without other venous abnormalities.

Two sessions are performed 6 weeks apart using polidocanol 0.5% foam for the prominent reticular veins and chromated glycerin 72% for the telangiectasias. The patient is advised to wear 20–30 mm Hg compression stockings for 2 weeks after each treatment.

Case 3

A 70-year-old woman presents with a red to violaceous spider telangiectasia on the ankle without associated symptoms.

On exam, an isolated spider telangiectasia is noted on the right medial ankle.

Duplex ultrasound is not performed as this patient presents with an isolated telangiectasia without signs or symptoms of underlying venous insufficiency.

The option of laser or low-concentration liquid sclerotherapy is discussed with the patient. Given her fear of needles and location on the

ankle, she opts for laser treatment. Resolution is achieved with a single session of the 1064 nm Nd:YAG laser.

Emerging Therapies

Few novel therapies for leg veins have recently gained acceptance. Endovenous cyanoacrylate closure (CAC) of the saphenous veins is now FDA approved and is a method that does not require tumescent anesthesia or post-procedure compression. The cyanoacrylate acts as an adhesive that seals off incompetent veins. Early studies showed high closure rates with mild procedural pain, limited side effects, and 98% patient satisfaction [2b] [109]. An initial study comparing cyanoacrylate closure to radiofrequency ablation in 222 patients showed noninferiority with a 1-month closure rate of 100% and 87% in CAC and radiofrequency ablation, respectively. At 12 months, the complete occlusion rate was 97.2% and 97.0% in CAC and radiofrequency ablation, respectively [1b] [110, 111]. Similarly, a retrospective comparison between CAC and endovenous laser ablation showed a 12-month closure rate of 98.6% and 97.3%, respectively, with less side effects in the CAC group [2b] [112].

Another novel therapy is known as mechanochemical endovenous ablation. This involves applying endovenous mechanical damage to the vessel wall using a rotating catheter tip, combined with the infusion of a liquid sclerosant from the catheter tip upon withdrawal, causing chemical damage. Again, tumescent anesthesia is not required and the process does not involve heat. An initial prospective, multicenter study of 126 patients with great saphenous vein reflux involving the saphenofemoral junction revealed closure rates of 100% at 1 week, 98% at 3 months, 95% at 12 months, and even 92% maintained at 24 months [2b] [113, 114]. Recent, larger studies have confirmed the procedure's efficacy in treating both the great and short saphenous veins [115]. Further comparative studies, with longer follow-up, are necessary to fully understand the role of these novel therapies in the treatment of leg veins.

Safety

Sclerotherapy

The most commonly encountered complications of sclerotherapy are telangiectatic matting, hyperpigmentation, and cutaneous necrosis. Other complications that are not minor but rare in incidence are inadvertent arterial injection and nerve injury.

Telangiectatic matting refers to tiny new red telangiectasias that appear after sclerotherapy or surgical removal of varicose veins. The incidence is between 15% and 24% [26, 116] and usually resolves spontaneously in 3–12 months [116, 117]. The precise cause of matting remains unknown although using the minimum concentration of sclerosant, small volumes, and low infusion pressure can reduce this complication [117–119]. The use of chromated or nonchromated glycerin also decreases the risk of matting [2b] [120].

Post-sclerotherapy pigmentation is a persistent pigmentation along the course of the vessel that has been treated with sclerotherapy. The etiology is thought to be from a combination of post-inflammatory hyperpigmentation as well as direct hemosiderin deposition. Its incidence ranges from 10% to 30% and may appear up to 12 weeks after treatment [117, 118, 121]. Spontaneous resolution occurs in 70% of patients by 6 months but may persist longer than 1 year in up to 10% of patients [121]. Pigmentation has been found to be more likely at higher sclerosant concentrations. For example, polidocanol 1% is more likely to cause pigmentation than 0.5% [2b] [117]. Likewise, the incidence of pigmentation at higher concentrations of STS is reported to be 30–80%, while the incidence decreases to 11% with STS at 0.1% [2b] [118]. Further, evidence suggests that glycerin is less likely to cause pigmentation compared to certain concentrations of STS, hypertonic saline, and polidocanol [120, 122].

Cutaneous necrosis occurs most commonly due to extravasation of sclerosant into perivascular tissues. It occurs commonly with hypertonic saline and rarely with polidocanol, STS, and glycerin.

Fortunately, it is infrequent and has been reported to affect 0.23% of patients treated with sclerotherapy [123]. It has usually been reported to occur after perivascular injection of sclerosants in higher concentrations and rarely after properly performed intravascular injections in various concentrations [118]. Cutaneous necrosis may also occur with direct intra-arterial injection, reactive vasospasm, and excessive compression of skin overlying the treated vein. Accidental intra-arterial injection, with and without ultrasound guidance, causing acute ischemia has been reported in at least 18 patients [123–132].

Neural injury may occur following direct injection into the nerve but also from perineural leakage of a sclerosant. The nerves most commonly affected are the saphenous and sural nerves, which lie close to the great and small saphenous veins, respectively [133].

Superficial thrombophlebitis may also occur after sclerotherapy and have been reported to occur in 4–7.5% of patients [134]. It occurs primarily after treatment of larger varicose veins and presents as an area of erythema, warmth, and tenderness over an indurated venous segment.

Overall, foam and liquid sclerotherapy have been associated with similar adverse events, except transient visual disturbances and headaches, which are more common with foam sclerotherapy. Particularly for patients with a patent foramen ovale, foam solution can communicate into the arterial system and cause neurological side effects. Two cases of stroke and one case of transient ischemic attack have been described during foam sclerotherapy, and all were found to have a patent foramen ovale [135, 136].

Lasers and IPL Systems

The most common sclerotherapy side effects of telangiectatic matting and hyperpigmentation have also been found to occur following laser therapy of leg veins [98, 99, 101]. A study was conducted comparing Nd:YAG laser and sclerotherapy with STS for treating small diameter leg veins [2b] [98]. The incidence of matting was 28% with laser and 17% with sclerotherapy, whereas the incidence of hyperpigmentation was 57% with laser and 67% with sclerotherapy. In another study comparing Nd:YAG laser and sclerotherapy with polidocanol 0.5% foam, incidence of matting was seen in 20% of patients with either therapy, while hyperpigmentation was more common with sclerotherapy (67.9% with sclerotherapy versus 39.3% with laser) [2b] [97].

Further, laser therapy has proven to be more painful than sclerotherapy and is associated with less favorable patient satisfaction scores [98, 99, 101]. Other risks inherent to lasers include hypopigmentation [137, 138], especially when treating patients with darker skin types, epidermal necrosis, scarring, and purpura. Understandably, the risks vary depending on the laser and settings used. When using infrared lasers, and particularly the Nd:YAG laser, there is a greater risk of bulk tissue heating and necrosis. Therefore, pulse stacking or overlap between pulses should be avoided. On the other hand, there is a greater risk of hypopigmentation with the shorter wavelength KTP and pulsed dye lasers, as these wavelengths have higher absorption by melanin. For IPL devices, the use of multiple wavelengths implies a significant risk of damaging nonvascular structures.

Endovenous Ablation

The most important factor in minimizing complications from endovenous thermal ablation is the use of tumescent anesthesia. It is injected around the target vessel to protect the surrounding tissue from heat generated during treatment. With this technique, postoperative complications from endovenous ablation are limited. Reported complications include thrombophlebitis (7%) [139], hyperpigmentation (5%) [139], paresthesia (1–2%) [140, 141], thermal skin injury (<1%) [139], bruising, and hematomas (0–7%) [140–143]. Given the proximity of the sural nerve to the small saphenous vein at the distal calf, access at the lateral malleolus results in a higher paresthesia rate compared with the mid-calf [2b] [144]. In line

with this, endovenous laser ablation of the small saphenous vein has been associated with a significantly higher incidence of sensory disturbance compared with ablation of the great saphenous vein [2b] [145].

When compared to surgery, patients treated with endovenous thermal ablation have less pain [61, 141–143, 146], swelling, bruising, paresthesia, and a faster return to normal activities [66, 147]. Additionally, surgically treated patients are more likely to develop complications such as wound infection (2–6% with surgery versus 0% with endovenous thermal ablation) [146] and hematomas (5% with surgery versus 2% with endovenous thermal ablation) [139]. However, the risk of superficial thrombophlebitis was found to be significantly higher with radiofrequency ablation than with surgery [2a] [146].

In a comparative study on the use of lower and higher wavelength endovenous lasers, the higher wavelength 1320 nm laser caused fewer side effects compared with the 940 nm diode laser [2b] [70]. There was significantly reduced ecchymosis and pain in those treated with the 1320 nm laser. In a subsequent randomized clinical trial, the higher wavelength 1500 nm endovenous laser was again found to cause fewer side effects than the 980 nm diode laser [2b] [71]. Patients treated with a 1500 nm laser had less induration around the treated vein, less need to take analgesics (1.8 days versus 2.9 days), and had a better postoperative quality of life.

In a meta-analysis, the incidence of deep vein thromboses was found to vary between 0.2% and 1.3% with endovenous thermal ablation and seemed to be higher in patients treated with radiofrequency than laser ablation [2a] [148]. However, it mainly included studies using the old radiofrequency ablation techniques and endovenous laser ablation with bare tip fibers and lower wavelengths. Development of thrombus extension at the saphenofemoral junction could be found in a limited number of cases, with case series reporting a frequency varying between 0.3% and 7.8% [149–151]. Pulmonary embolism has also been reported in up to 3% of patients after endovenous laser ablation [149, 151].

While foam sclerotherapy is associated with somewhat less postoperative pain than endovenous laser ablation, there was no significant difference in the rating of postoperative pain when radiofrequency ablation was compared with foam sclerotherapy [1b] [91].

Ambulatory Phlebectomy

In comparison to sclerotherapy, phlebectomy avoids the risks of intra-arterial injection, extravasation skin necrosis, and residual pigmentation. However, complications observed with phlebectomy include edema (5–17.5%), especially at the dorsum of the foot, hematoma formation (4.9–95%), superficial phlebitis (2.4–13%), temporary hyperpigmentation (1.2–3.3%), nerve injury (9.5–39%), and telangiectatic matting [152, 153]. Further, scar formation was found to be significantly more likely with phlebectomy (17%) than sclerotherapy (0%) [78].

Postoperative Care and Follow-Up

Studies suggest that clinical symptoms and findings on diagnostic imaging are not necessarily correlated. When a cohort of patients treated with endovenous laser ablation for great saphenous vein incompetence were followed up to 6 years, symptomatic clinical failures occurred in 11.6%, while echo-color-Doppler confirmed failures were present in 30% [2b] [154]. Among them, only 1.1% had both symptomatic clinical and echo-color-Doppler confirmed failures. Similarly, following ultrasound-guided foam sclerotherapy, 5-year recurrence rate on Duplex ultrasound was found to be 64%, whereas clinical recurrence was present in 4% [2b] [155]. Given the fact that reflux may be present at truncal veins without associated symptoms, it would be reasonable to follow patients at regular intervals to examine for recurrence. In particular, certain patients may be at greater risk for developing new varicosities and recurrence, such as those with a strong family history of varicosities or those who present

with venous disease at a younger age. For these patients, a closer follow-up may be warranted.

In general, however, there is little evidence regarding the appropriate schedule for monitoring patients for recurrence or for the development of new leg veins.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Duplex ultrasound is the diagnostic test of choice to evaluate venous anatomy and to identify sources and patterns of reflux	A
Endovenous thermal ablation (with laser or radiofrequency) is safe and effective and is recommended over surgery and foam sclerotherapy for the treatment of incompetent saphenous veins	B
Phlebectomy or foam sclerotherapy is recommended for the treatment of varicose tributaries	B
Liquid or foam sclerotherapy is recommended for treating reticular veins and telangiectasias	A
Foam sclerotherapy should be reserved for treating vessels greater than 1 mm in diameter	D
The optimal treatment approach for sclerotherapy is to match a given vessel diameter with the lowest concentration of sclerosant to achieve the desired effect	B
Transcutaneous lasers may be indicated for treatment of reticular veins and telangiectasias, only when sclerotherapy is not an option	C
The 1064 nm Nd:YAG laser is the laser therapy of choice for leg veins, especially for those greater than 1 mm in diameter	B
Post-procedure compression is recommended following endovenous thermal ablation and sclerotherapy	A

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Self-Assessment Questions

1. A 60-year-old woman presents with bulging varicosities along the right medial calf. What is the next diagnostic or therapeutic intervention?
   (a) Perform Trendelenburg test to determine whether the congestion is caused by superficial venous reflux or incompetence of the deep venous system
   (b) Perform Duplex ultrasound to examine for underlying sources of reflux
   (c) Immediately proceed with foam sclerotherapy to treat the patient's primary complaint
   (d) Immediately proceed with ambulatory phlebectomy to treat the patient's primary complaint
   (e) Explain that treatment would not be possible due to the size and extent of the varicosities

2. The patient from question 1 is found to have reflux of the great saphenous vein on Duplex ultrasound. What is the treatment of choice?
   (a) Endovenous thermal ablation with laser or radiofrequency
   (b) Surgical stripping and ligation
   (c) Ultrasound-guided foam sclerotherapy
   (d) Ultrasound-guided liquid sclerotherapy
   (e) No treatment is recommended for this patient

3. A patient presents with an isolated arborizing telangiectasia on the left lateral thigh. What is the treatment of choice?
   (a) Sclerotherapy with polidocanol 0.25% liquid
   (b) Sclerotherapy with hypertonic saline 23.4%
   (c) Sclerotherapy with STS 1% foam
   (d) Laser therapy with 1064 nm Nd:YAG
   (e) Laser therapy with 532 nm KTP

4. For the patient from question 3, which post-sclerotherapy compression therapy would be recommended, if any?
   (a) 15–20 mm Hg compression stockings
   (b) 20–30 mm Hg compression stockings
   (c) 30–40 mm Hg compression stockings
   (d) 40–50 mm Hg compression stockings
   (e) No compression therapy is recommended

5. A patient presents for treatment of blue reticular veins on the legs that are 2–3 mm in diameter and refuses any treatments that involve needles. Which laser is the treatment of choice?
   (a) 532 nm KTP
   (b) 585 nm Pulsed dye laser
   (c) 810 nm diode
   (d) 755 nm Alexandrite
   (e) 1064 nm Nd:YAG

Correct Answers

1. b: Duplex ultrasound allows for the examination for underlying sources of reflux, as well as evaluation of venous anatomy and evidence of obstruction. It has largely replaced traditional clinical tests such as Trendelenburg and Perthes. If there is underlying reflux, it should be treated prior to treating the varicose tributaries.
2. a: Endovenous thermal ablation has been demonstrated to be as effective but safer than surgery in the treatment of great saphenous vein incompetence.
3. a: For a given vessel diameter, the lowest possible concentration of sclerosant should be used to reduce potential side effects. In addition, foam sclerotherapy should be reserved for vessels greater than 1 mm in diameter, while hypertonic saline is associated with significant pain without increased effectiveness when compared to polidocanol. Laser therapy should be reserved for treating leg veins only when sclerotherapy is not an option.
4. b: 20–30 mm Hg post-sclerotherapy compression is recommended following treatment of telangiectasias, whereas 30–40 mm Hg or 40–50 mm Hg compression is indicated for larger varicosities.
5. e: For leg veins greater than 1 mm in diameter, the 1064 nm Nd:YAG laser is the preferred laser therapy. For leg veins less than 1 mm in diameter, the pulsed dye laser or KTP laser may also be effective.

Invasive Melanoma

62

David Panther and David G. Brodland

Abstract

Melanoma remains one of few malignancies with increasing incidence. Surgical removal of invasive melanoma is the first and most important therapeutic intervention. Historically, margins of up to 5 cm have been recommended for a wide local excision (WLE). However, randomized controlled trials comparing margin width have significantly narrowed the size of an appropriate WLE to 1–2 cm, depending on Breslow depth. Narrow margins have not been shown to worsen survival in these trials. More recently, refinements in Mohs surgery have allowed for the highest rate of local control when immunohistochemistry is employed, particularly for head and neck melanomas, which have a poor rate of local control with WLE. Perioperative issues include appropriate examination and counseling, consideration of sentinel lymph node biopsy, and taking patient preference into account. Safety of the various surgical modalities is related to the size of the excision and the delay between excision and repair, with advantages noted for smaller excisions and same-day repair.

Keywords

Melanoma · Excision · Mohs · Surgery Complication

Epidemiology

The incidence of invasive malignant melanoma (IMM) has been steadily increasing in the USA by 1.4% each year (2c) [1], though recently declining incidence in those under age 50 may herald a coming stabilization or reversal in the overall trend (2c) [2]. Approximately 2.1% of men and women born today will be diagnosed with in situ or invasive melanoma of the skin at some point during their lifetime, based on 2011–2013 data, and the annual incidence now stands at 21.8 per 100,000 men and women per year. Upon initial diagnosis of IMM, 84% of patients have local disease, 9% have regional involvement, and 4% have distant metastases, with the other 3% being unstaged [2]. Mortality from IMM is 2.7 per 100,000 per year [1]. The 5-year melanoma-specific survival rate for patients whose IMM is diagnosed before detectable metastasis is 98%. This falls to 63% when regional metastasis has already occurred and

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17% for those with distant metastasis at initial diagnosis [2]. The depth of invasion predicts prognosis, with increasing depth portending a poorer survival probability (Fig. 62.1) (2c) [3].

Based on 2009–2013 data, the median age at diagnosis is 63 [1], and age is one of many known risk factors for developing melanoma (2c) [4]. A white male over the age of 85 has a nearly ninefold higher risk for melanoma than one in the 45–49 age group, and more than 90 times the risk of one in the 20–24 group (Fig. 62.2) (2c) [5]. Although incidence is lower in the young, invasive melanoma represents a greater proportion of all cancers; melanoma is the second most common cancer in females in their third decade of life (2c) [6]. Other non-modifiable factors include male sex (except before age 50, when incidence is slightly higher in women (Fig. 62.2)), a personal or family history of melanoma, numerous clinically atypical melanocytic nevi, and lighter skin type (especially those who are unable to tan, have blonde or red hair, or have blue eyes), as well as more recently discovered heritable genetic mutations such as the CDKN2A gene (2a-3a) [7–11]. Each of the four main body sites (head and neck, trunk, upper extremity, and lower extremity) have their own unique incidence profile, which varies based on age and sex (Fig. 62.2b, c). Avoidable risk factors are the key to prevention efforts, and the most significant is ultraviolet radiation (UVR) exposure. One study estimated 86% of melanomas diagnosed in the UK were related to UVR from the sun

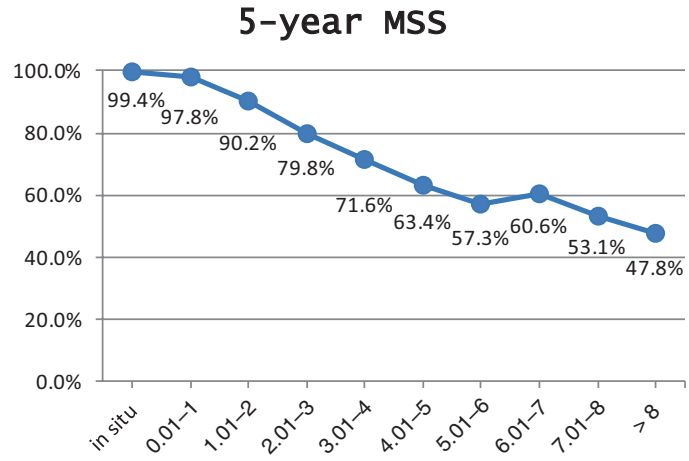

Fig. 62.1 Melanoma-specific survival (MSS) decreases with increasing Breslow depth of a primary melanoma, based on cases diagnosed between 2004 and 2008 and reported to SEER

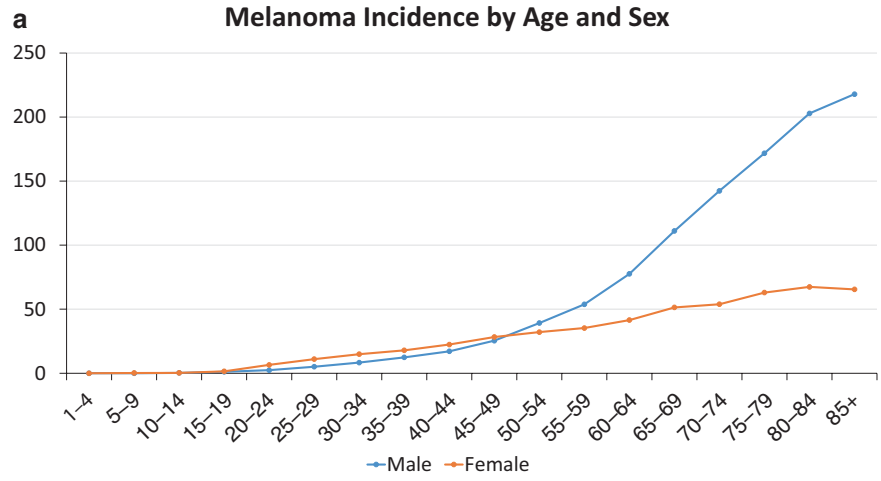

Fig. 62.2 Incidence increases with age and male sex. Incidence is reported in cases per year per 100,000 people

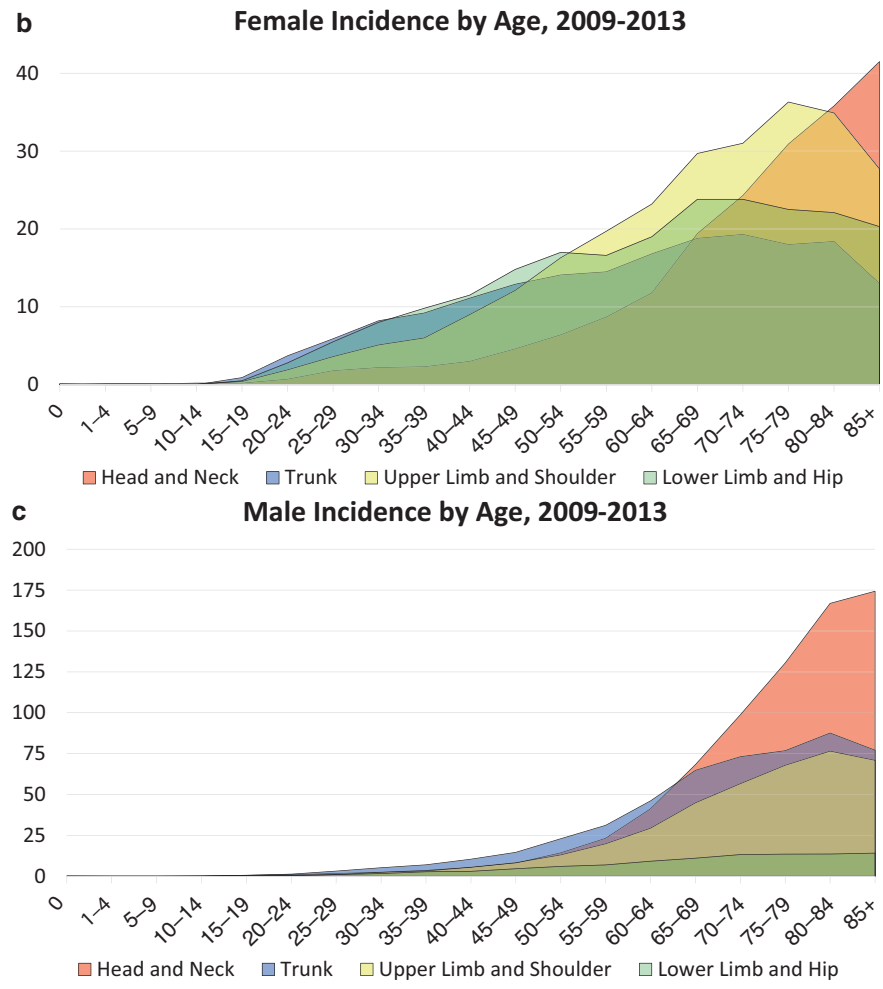

Fig. 62.2 (continued)

(2c) [12], and risk doubles with a history of more than five sunburns (2c) [13]. Indoor tanning has also been shown to have a strong association with melanoma incidence (2b) [14]. Reduction of UVR exposure by daily application of sunscreen was shown to be associated with halving the incidence of new melanomas in Australia (1b) [15].

Treatment Overview

Introduction

The backbone of treatment for primary cutaneous melanoma is complete surgical removal of the tumor [16]. This may be accomplished in a number of ways (Fig. 62.3), the most common of which is wide local excision (WLE). The visually delineated tumor, plus a predetermined (based on Breslow depth) safety margin of clinically normal skin (1b) [16–18], is removed and sent to a pathologist, and the wound is closed. The specimen is then sampled by sectioning perpendicular to the margin to give several cross-sectional views of the specimen. The histologic margin visualized by standard perpendicular sectioning is approximately 0.01% of the true margin [19], leading to the specter of a false negative if melanoma extends through the margin between the cross-sectional planes. There is no national standard for how melanoma is processed after WLE. Lab manuals often specify between 2- and

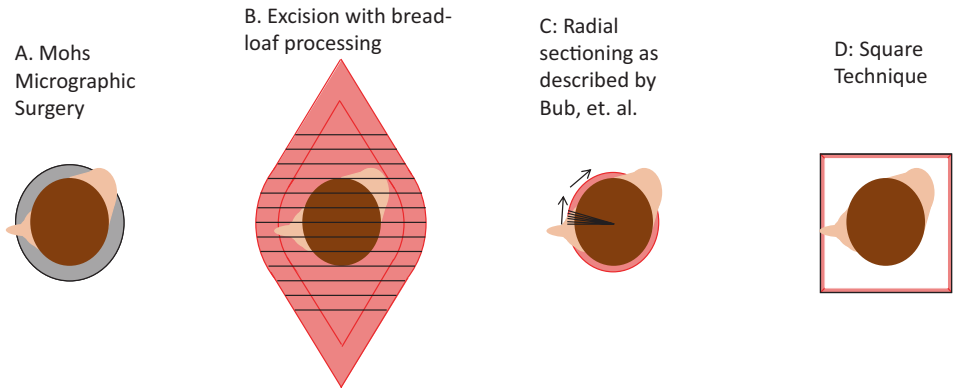

Fig. 62.3 Excisional techniques (first stage) compared for a 1.5-mm deep melanoma. Melanocytic lesion is brown and subclinical extensions are flesh-colored. Peripheral surgical margins are black when pathologically examined and red when not examined; deep surgical margins are gray where examined and pink where not examined. (**a**) MMS excision, with initial 6-mm margin and two areas of confirmed positive margins, which will be removed in subsequent 3 mm layers. 100% of peripheral and deep margins are examined, and immunostains are frequently used due to the small number of slides generated. (**b**) WLE, shown with both 1-cm and 2-cm margin options (reflecting range in guidelines for 1.01 – 2-mm deep melanomas). If 1-cm margins are chosen, the 1 o'clock peripheral margin is close but clear, while the area between 8 and 9 o'clock is biologically positive. Whether this will be seen as a positive margin on pathology depends on how the specimen is cut, which is not standardized. Some lab protocols dictate bread-loaf sections throughout the specimen at varying intervals, while others allow for "representative" margin sampling at larger intervals when specimens are very large. While a 2- cm margin will clear most melanomas regardless of thickness, the resulting defects are often substantially larger than those created by any other method. Immunostains are not typically done, due to the large number of slides generated. (**c**) Radial sectioning every 1 mm is likely to identify the vast majority of biologically positive margins, including those shown in this example. Subsequent surgeries remove 2–3 mm of tissue, until clear margins are obtained. Coupled with the described practice of reoperating when margins are only clear by 1–2 mm, this is a rigorous margin assessment, though a large number of slides are generated and immunostains are not used. (**d**) The square technique requires angular margins to allow for high-quality en face sectioning and examines 100% of the peripheral margin. The 1-cm initial margin is positive, which prompts another removal 0.5 cm beyond the original margin. Deep margins are sampled at the discretion of the surgeon and dermatopathologist, and the timing of this sampling depends on the clinical situation. Typically, only H&E stain is performed

5-mm intervals for specimens small enough to be completely embedded; very large excisions are difficult to embed entirely, and margin sampling is at the discretion of the physician or technician performing the work [20].

Mohs micrographic surgery (MMS) was developed and refined to assess 100% of the surgical margin for contiguous cutaneous tumors and has been successfully applied to invasive melanoma (2b-4) [21–24], allowing for complete, histologically confirmed tumor extirpation and reconstruction in a single day. A narrow margin of clinically normal skin is removed (3-mm–1-cm margins have been reported, depending on surgeon and tumor characteristics) [21, 24], and the entire peripheral and deep margin is laid flat and processed via frozen section immediately. This allows for 100% of the surgical margin to be visualized and mapped to define areas of remaining melanoma, which are selectively removed in a series of excisions until all margins are clear (Fig. 62.4). The central portion of the specimen containing any residual tumor is typically sent out for permanent sections to confirm staging, though some may opt to view them as frozen sections first, then thaw and send out for permanents [24]. Each round of specimen processing takes approximately 1 h when immunostains are used [25].

Variations of staged excision (SE) have been described to improve on WLE and ensure the entire surgical margin is visualized prior to delayed closure [26–30]. The term "margin-controlled excision" (MCE) will be used to lump all techniques that evaluate 100% of the surgical margin (such as MMS and some staged excision protocols). The basic premise of SE is to begin

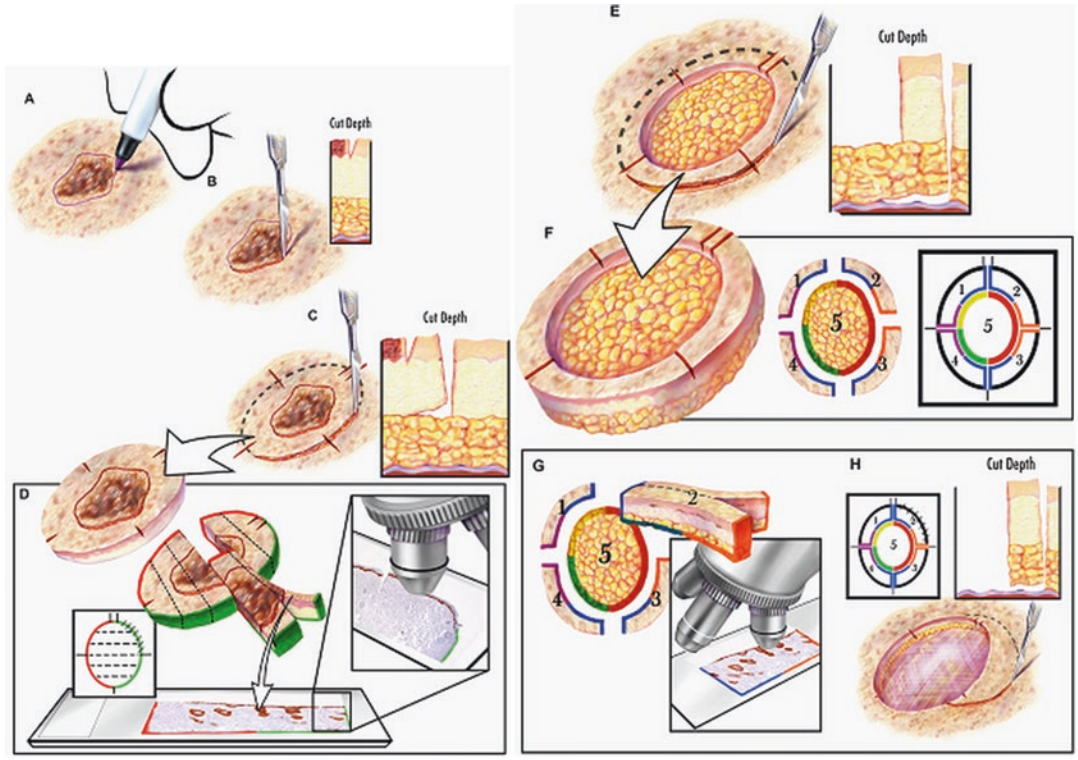

Fig. 62.4 Steps for Mohs micrographic surgery technique for melanoma at the Hospital of the University of Pennsylvania. (**a**) The scar and clinically visible residual melanoma at the site of the original biopsy are outlined. Additional pigmented lesions near the primary melanoma are also outlined and documented with photography in case they would collide with either the surgical margin or reconstruction. (**b**) An incision is made to the level of the papillary dermis at the exact clinical margin of the melanoma. (**c**) The visible tumor is excised to the superficial fat with a peripheral margin of at least 2–3 mm of clinically normal-appearing skin (larger margins may be excised for higher risk tumors). (**d**) The peripheral margins of the debulking specimen are inked with tissue dye and a map is drawn to record the grossing strategy. The debulking excision is grossly sectioned in breadloaf fashion at 2–3-mm intervals and vertical sections are cut for microscopic examination. The inset demonstrates tumor extending beyond the hash mark at the clinical margin of the tumor (made in step B) to the green-dyed edge. (**e**) The Mohs layer is excised around the entire defect from the debulking excision to the fascia with an additional peripheral margin of at least 2–3 mm of clinically normal-appearing skin (larger margins may be excised for higher risk tumors). Hash marks are made on the skin surface to maintain orientation relative to the patient. (**f**) The Mohs layer specimen is grossly sectioned to separate the epidermis, dermis, and a thin layer of subcutaneous fat from the deep fatty margin. Free cut edges of all grossly sectioned specimens are inked, and surgical maps are drawn to represent the method of gross sectioning. (**g**) Microscopic frozen sections are cut from the complete peripheral and deep margins for evaluation by the Mohs surgeon. In this example, piece 2, which corresponds to the site of the positive margin on the debulking excision (see step D), has tumor at the margin. (**h**) The presence of tumor at the margins is indicated on the Mohs map, and additional layers around the positive margin are excised until there is no evidence of microscopic disease. A minimum of a 2–3-mm peripheral margin was excised on subsequent stages, but larger margins were sometimes excised if the previous stage was strongly positive (Reprinted with permission from Etzkorn et al. [24])

with a relatively narrow margin (between 2 and 10 mm), with subsequent selective removal of melanoma found remaining at the margin. Excised tissue is usually oriented for en face (parallel along the true margin) overnight permanent sectioning, and subsequent removals and closure are done on separate days. One described variation of this technique involves radial (perpendicular) sections at 1-mm intervals with further removal warranted when melanoma approaches within 2 mm of the true margin, in an attempt to account for tumor extensions between the radial cuts (Fig. 62.5) [26]. "Peripheral incontinuity tissue examination" has been used to

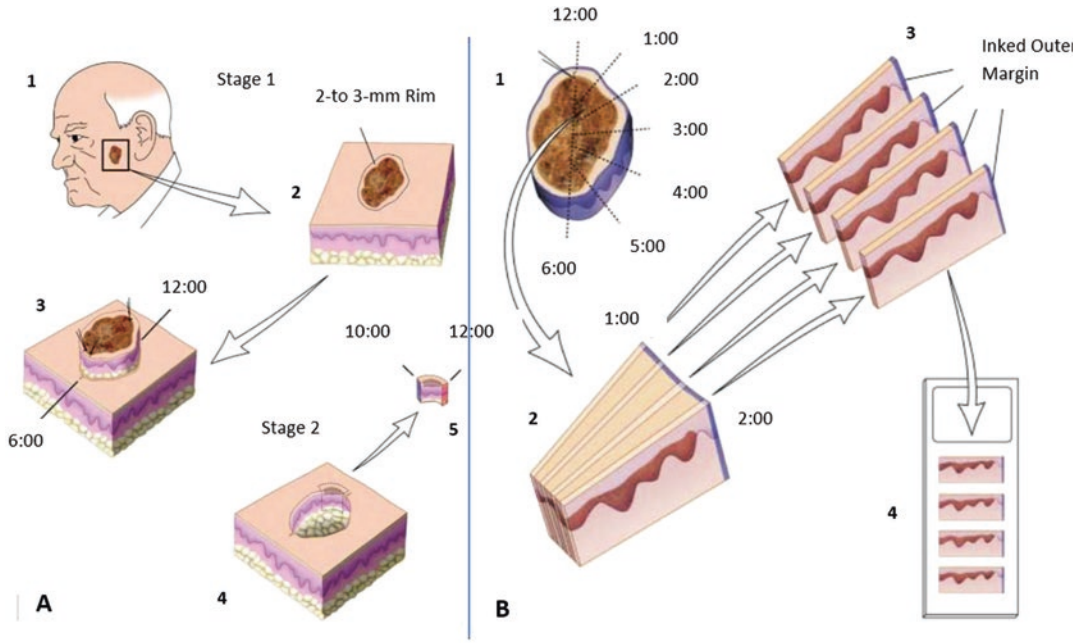

Fig. 62.5 (**a**) Staged excision. Stage 1: A 2–3-mm margin is demarcated around the tumor (2). A perpendicular incision is made into subcutaneous tissue and the specimen is oriented in respect to the face of a clock (3). Sutures in the specimen and incision nicks in perilesional skin demarcate 12 and 6 o'clock positions. The specimen is sent to pathology for radial sectioning (B). Stage 2: The patient returns the following day. In this example, tumor is present at the 11 o'clock position (4). A 2–3-mm rim is again demarcated, and tissue is excised with a perpendicular incision from approximately the 10–12 o'clock positions. To maintain orientation, the 10 and 12 o'clock margins are inked blue and orange, respectively (5). Further stages are performed until negative margins are achieved. (**b**) Pathology processing. 1, Margins are inked to maintain orientation; the specimen is bisected and then divided radially (like pieces of a pie) according to the numbers on a clock face. 2 and 3, Each pie wedge is placed in a cassette, embedded in paraffin, and sectioned radially. 4, The sections are placed on a glass slide for examination by the pathologist. Radial sectioning allows for examination of the centrifugal progression of the entire lesion, facilitating identification of the transition between lentigo maligna, atypical junctional hyperplasia, and normal histologic features (Reprinted with permission from Bub et al. [26])

describe the use of en face frozen section histology with a separate surgeon and pathologist [31], though its specific application to melanoma has not been reported and may be limited by the pathologist's ability to process multiple rounds of frozen section pathology for the surgeon in a day, especially in the setting of an inpatient OR.

Non-excisional modalities lack the ability to confirm histologic clearance but may be appropriate in limited circumstances. Although utilization of these alternatives remains infrequent, brief mention is merited. Radiation has been used with a degree of success for invasive lentigo maligna melanoma (4) [32–34] but is more commonly used as adjuvant therapy for desmoplastic melanoma (4) [35]. Cryotherapy is primarily thought of as an alternative for in situ disease, but one report does mention its use for invasive melanoma as well (4) [36].

Effectiveness of Treatments

The goal of excision is the complete removal of all cancerous tissue by achieving histologic tumor-free margins [16], to eliminate the chance of marginal persistence and subsequent clinical recurrence. Ultimately, the purpose is to eliminate ongoing risk of regional and distant metastases originating from unresected tumor. Permanent cure will never be guaranteed by any form of local treatment, since melanoma may have already

metastasized by the time of presentation, but ensuring the complete removal of the original tumor is the first and most important step to minimize poor outcomes. Some reports indicate patients who experience local recurrence (LR) go on to die from metastasis roughly 80–90% of the time (2b) [37, 38], although LR definitions often include in-transit and satellite metastases which are indicative of stage IIIB/C disease rather than true marginal recurrence. When a strict definition of local recurrence is employed which excludes satellite or in-transit metastases, the consequences of inadequate excision are less pronounced but still undesirable, with 33% recurring as a thicker melanoma and 25% of those with thicker recurrence dying after just under 3 years of follow-up in one study (2b) [39].

Wide excision using visual inspection to define the melanoma's margins with subsequent cross-sectional pathological margin assessment is the historical standard. For much of the twentieth century, 3–5-cm margin and even amputation was the standard of care, yet this more radical surgical concept has its roots in an autopsy finding of a single patient with lymphatic metastasis (5) [40]. The width of clinical margin recommended to bring about acceptable recurrence rates has decreased through the years, thanks to a number of randomized controlled trials (1b) [38, 41–52]. What is now termed "wide" local excision (1–2 cm) has been historically viewed as "narrow" margins. The NCCN and AAD guidelines are currently identical for invasive melanoma, recommending a 1-cm clinical margin for lesions with Breslow thickness </= 1.00 mm, 1–2-cm margin for lesions 1.01–2.00 mm thick, and 2-cm margin for lesions >2 mm thick. The key findings of the

Table 62.1 Rates of recurrence and overall survival in RCTs of primary cutaneous melanoma

Wide excision study	Inclusion/exclusion criteria	Breslow thickness (mm)	Surgical margin (cm)	No. of patients	Rate of local recurrence[a] (%)	Overall survival (%)
WHO	Exc: face, fingers, toes	≤2.0	1	305	LR at 12 years, 2.6	At 12 years, 87.2
			3	307	LR at 12 years, 1	At 12 years, 85.1
French	Exc: finger, toe, nail, acral, or from lentigo/melanosis	≤2.0	2	161	LR at 10 years, 0.6	At 10 years, 87
			5	165	LR at 10 years, 2.4	At 10 years, 86
Swedish I	Inc: trunk, extremity	0.8–2.0	2	476	LR at 10 years, 0.6	At 10 years, 79
	Exc: hands, feet		5	513	LR at 10 years, 1	At 10 years, 76
Intergroup	Inc: trunk, extremity proximal to knee/elbow	1.0–4.0	2	244	LR at 10 years, 2.1	At 5 years, 79.5[b]
	Exc: desmoplastic or lentigo maligna subtypes		4	242	LR at 10 years, 2.6	At 5 years, 83.7[b]
UK	Inc: trunk or extremity where > 3 cm margin was possible	2.0	1	453	LR at 5 years, 3.3[c]	At 5 years, 68.2
	Exc: palms, soles		3	447	LR at 5 years, 2.8[c]	At 5 years, 70
Swedish II	Inc: trunk, extremities	>2.0	2	465	LR at 5 years, 4.3	At 10 years, 50
	Exc: hands, feet		4	471	LR at 5 years, 1.9	At 10 years, 50

All *p* values are > 0.05 unless otherwise specified

[a]Definitions of local recurrence, by study:

WHO: cutaneous or subcutaneous nodules that appeared along the scar or in an area of 1 cm or less in radius from the surgical scar

French: recurrence within 2 cm of the scar

Swedish I: recurrence in the scar or transplant

Intergroup: within 2 cm of the surgical scar, unless multiple in-transit lesions or metastases were present (then the recurrence was presumed to be in-transit or metastatic, respectively)

UK: within 2 cm of the scar or graft

Swedish II: recurrence in the scar or transplant

[b]MSS at 10 years was 70% for 2 cm arm and 77% for 4 cm arm

[c]Locoregional recurrence at 5 years was 37.1% in 1 cm arm and 31.0% in 3 cm arm, p = 0.05

trials supporting these recommendations are summarized and compared in Table 62.1. The range of 1–2 cm for 1.01–2.00-mm-thick melanoma has been interpreted by some to mean 2 cm is preferable given the lower local recurrence (LR) rate in the Intergroup trial versus the WHO trial (0.6% vs 4.5%) (5) [53], although conclusive evidence for 2 cm superiority cannot be assured by comparing separate RCTs with different LR definitions (Table 62.2). More recently, a 2-cm margin was retrospectively shown to have a significantly lower LR rate than 1 cm in this population (0.9% vs 3.6%, respectively) (2b) [54]. The 1 cm group was significantly skewed toward head and neck location, suggesting that the choice to reduce margin width is often based on anatomic constraints, and this choice may result in increased LR. Without examining 100% of the margin, a 1-cm margin may increase the risk of LR for this 1.01–2.00 mm category. A new RCT is ongoing and may help to differentiate the risk/benefit profile of 1-cm versus 2-cm margins in melanomas >1 mm deep, but the expected completion date is 2029 [55]. Although a recent meta-analysis attempted to define narrow margins as 1–2 cm and deemed the entire category unsafe when compared with wide margins (3–5 cm) (1b) [56], the study design and conclusions are flawed. Lumping 1-cm and 2-cm margin excisions together obscures whether the detrimental effect could be attributable to the 1 cm category alone. While 1 cm is often inadequate in thick melanomas without 100% margin control (2b) [22, 51, 57], a 2-cm margin is enough to excise nearly all melanomas regardless of thickness or location (2b) [58].

Deep margin boundary has not been subjected to RCT scrutiny and remains a topic of discussion among surgeons. Some advocate for inclusion of fascia, but preserving fascia has been compared and found to be safe even for thick melanomas (2b) [59]. Biologically, the possibility of in situ tumor extension down adnexal structures necessi-

Table 62.2 Advantages and disadvantages of excision techniques

	Advantages and disadvantages to the three key categories of surgery	
	Advantages	Disadvantages
MMS	Lowest marginal recurrence rate for all locations	Paucity of surgeons employing this method causes access difficulty
	Minimizes defect size	Immunostaining, if used, is technically demanding and usually requires specialized training
	May lead to simpler repair choice	Insurance coverage variable for truncal sites
	Low complication rate	
	Surgery nearly always completed in 1 day	
	Low complication rate	
	Patient goes home on surgery day knowing margin status	
SE	Lower marginal recurrence rate than WLE, due to rigorous peripheral margin assessment	Always requires two separate surgery days, possibly more, separated by at least 1–2 days
	Minimizes defect size	Higher complication rates reported with delayed closure
	May lead to simpler repair choice	Pathologist's experience and accuracy may not be known
		Requires coordination with a lab capable of rapidly producing difficult (square) or large numbers (radial) of slides
WLE	Surgery nearly always completed in 1 day	Patient must wait for margin status to be known
	Can be performed by any competent skin surgeon	Margin status subject to false-negative error due to inadequate margin sampling
		Pathologist's experience and accuracy may not be known
		Increased complication rate with larger margins
		NCCN margins not always possible due to anatomy
		Minimal evidence for head, neck, and acral sites and very high marginal recurrence in these sites

tates that the excision must fully remove them, but there exists no evidence to show that removing deep fat or fascia provides a benefit to the patient. In fact, recurrence rates of MMS performed on predominantly [24] or exclusively [22] head and neck melanomas have shown nearly identical low recurrence rates when excision is performed either to a level below adnexae [22] or down to fascia [24]. However, if the depth of the melanoma is unknown due to transection in the biopsy, inclusion of deep fat may be reasonable, especially in a WLE or SE specimen that will not be subjected to 100% margin assessment.

The narrow vs wide study arms of the key RCTs have not shown a difference in either local recurrence (between 2 and 3%) or overall survival, though the data is limited in that most excluded head, neck, and acral melanomas, which warrant further mention.Acral melanomas tend to recur more frequently after WLE or amputation, particularly when thicker than 1 mm, with one estimate of 6% (4) [60], though it may be even higher [61]. Head and neck melanomas recur at the margins between 9% and 13% of the time after WLE (1b-4) [42, 62, 63].

The concept of 100% margin control for cutaneous malignancies was pioneered by Dr. Frederic Mohs in the 1930s. The heart of its value lies in its ability to rely on a single physician serving simultaneously as surgeon and pathologist, 100% visualization of the entire three-dimensional surgical margin, and rapid frozen section pathology allowing, if needed, multiple stages of excision targeting residual tumor all in a single day. Since the first report of melanoma treated by Frederic Mohs (4) [64], a substantial body of literature has been generated describing its efficacy for both in situ and invasive disease. Marginal recurrence rates have been reported in a number of studies and generally range from 0% to 6% (2b-4) [21–24, 65, 66] with the most reliable estimates being between 0.2% and 0.7% [22, 24, 58]. Furthermore, all but one of these studies contained at least 80% head and neck melanomas [22–24, 65, 66], which currently only represent about 28% of cases overall (2c) [5] and are strongly associated with increased risk of local recurrence when WLE is performed [54].

Radiotherapy (RT) is rarely considered in treatment of primary melanomas, as melanoma is considered to be relatively radioresistant (4) [67]. Grenz rays or soft x-rays are most commonly used, and only thin invasive melanomas are treatable, since penetration is minimal beyond 1–2 mm. Radiotherapy has been used alone (4) [68] and in combination with surgery (4) [32, 68] for invasive melanoma, though it is more commonly reported as an option for in situ disease. Some studies combine in situ and invasive disease in their statistics (4) [33]. Series of only invasive melanomas are very small (<25 patients) (4) [32, 68, 69] and may include patients with as little as 1 month of follow-up [69], making it difficult to obtain reliable recurrence rates.

Desmoplastic melanomas are often deeply invasive and may recur locally more often than other subtypes, between 17% and 39% (4) [35, 70], but they are rare and more difficult to study. It is not clear whether this propensity for recurrence is due to marginal recurrence or local metastasis. Radiation has been reported as adjuvant therapy after WLE for desmoplastic melanoma (2b-4) [71, 72], but conclusions are difficult to draw due to small sample size. One retrospective cohort seemed to show improved local control in patients who received WLE and RT, though negative resection margin was even more important in preventing recurrence and no survival benefit was seen for irradiated patients [35]. The largest (277 patients) retrospective study showed improved local recurrence in patients who received RT after WLE when surgical margins were positive but no statistically significant benefit when margins were clear unless other high-risk features were present (2b) [73]. Since MMS evaluates 100% of the margin, RT after MMS would not be expected to provide any benefit, though recurrence rate in desmoplastic melanomas treated with MMS has not been defined in the literature.

Cryotherapy sought to exploit the sensitivity of melanocytes to cold thermal injury and had been considered in the past. Available evidence for invasive melanoma is limited to a single report of eight patients who had clinical resolution [36].

Comparative Effectiveness of Common Treatments

The melanoma patient's greatest concern is that the treatment minimizes the chance of relapse [56]. The necessity of wide margins beyond visible tumor to effect complete removal is a by-product of several limitations of traditional excision techniques. First, the margin of excision must be measured from the visible edge of the tumor that is often clinically poorly defined, particularly in sun-damaged skin and on the head and neck. Determination of the edges of any residual lesion after biopsy by visual inspection is inherently subjective, and subclinical, amelanotic extensions compromise the accuracy of tumor delineation between 33% and 62% of the time (2b) [74, 75]. Furthermore, cross-sectional histologic sections sample less than 1% of the true surgical margin [19]. The combination of frequent subclinical extension with subtotal histologic margin assessment will lead to higher recurrence rates for WLE than for excision techniques employing more meticulous histologic margin control; these rates rise with more narrow margins. Consequently, the WLE marginal recurrence rate lies between 2–3% for trunk and extremities and 9–13% for head and neck tumors, with acral tumors likely at least 6% and possibly higher.

Despite WLE's higher marginal recurrence rate, many authors still perpetuate the theory that undetected microsatellite metastases are removed by WLE in addition to the primary tumor, and that their removal provides a benefit to the patient. Although no prospectively controlled comparison exists for WLE vs MMS or staged excision, prospectively maintained databases after MMS treatment have shown that metastasis and long-term survival rates are equivalent or superior to WLE (2b) [21, 22, 58, 65]. Furthermore, WLE RCTs have consistently failed to show a metastasis or survival benefit from excising centimeters of normal skin beyond what NCCN currently recommends for WLE. These data suggest that even if microsatellites can be found in skin beyond the contiguous primary tumor, the theoretical inclusion of nearby metastases does not provide a meaningful, measurable recurrence or survival benefit to the patient. Furthermore, it is exceptionally unlikely to find microsatellites in thin melanomas. Microsatellites are detected in up to 37% in tumors >3 mm thick (2b) [76, 77] but are rare when Breslow depth is <3 mm and exceptionally unlikely under 1 mm (2b-4) [76–78].

WLE marginal recurrence rates do increase as margins are narrowed beyond NCCN guidelines, and the likely explanation is that the primary tumor is not completely removed. 1-cm margins for thick melanomas is inadequate to completely remove an acceptable percentage without 100% peripheral margin evaluation, particularly for 1.01–2-mm [54] and >2-mm melanomas [22, 51]. A logical extension of this data is that 2-cm margins should be advocated for WLE when the original biopsy is partial or when the melanoma is transected, since deeper melanoma cannot be excluded; alternatively, a form of margin-controlled excision may serve the patient better, as complete extirpation does not depend on a predetermined margin. Another notable concept is that of distance between tumor and margin pathologically. Although margin proximity is not universally reported to be a poor prognostic factor (4) [79], others have shown negative consequences such as nodal and distant recurrence associated with <8-mm pathologic margins (2b) [80]. Narrow margins seem to increase the likelihood of subclinical, undetected positive margins.

Both the surgeon and the patient usually desire the most effective therapy, and this is the most important aspect of margin-controlled excision versus its tissue-conserving nature. In addition to greater than 99% chance of complete removal, MMS alone provides additional and important benefits to the patient. MMS is performed in an outpatient setting using local anesthesia and therefore avoids the risks and cost associated with general anesthesia and often a hospital stay. The patient's tumor is completely removed in a single day in all but the rarest occasions, which avoids uncertainty and anxiety while waiting for pathology results. It also eliminates the need to return to repeat surgery in the case of positive margins. This benefit is magnified when compared to the other methods of staged excision, which require the patient to come back on separate days every time an additional stage is performed, as well as for reconstruction. In both MMS and staged exci-

sions, reconstruction is only performed once, whereas WLE is often reconstructed immediately while expecting clear margins, but again in cases with positive margins or clinical recurrence.

Individuals with head and neck melanomas are uniquely poised to benefit from both the tissue-conserving nature and highly reliable local control of margin-controlled excision. Confidence in a negative margin allows the surgeon to consider all available reconstructive techniques without fear of utilizing adjacent tissue containing residual melanoma. A further benefit is the potential for a smaller defect to close. A survey on head and neck melanomas showed patients were significantly more satisfied with primary closure and local flaps versus skin grafts, and smaller defects caused less emotional impairment (4) [81]. Eyelid and nose tumors had a greater emotional impact than other locations. Overall, the degree of appearance alteration was correlated with emotional impairment. Patient satisfaction should not take precedence over patient safety and the cure of melanoma, but given the ample evidence for safety with a smaller defect size and exceptionally low local recurrence with MMS and other forms of margin-controlled excision, these modalities may be preferable to WLE for head and neck melanomas.

Any type of narrow but 100% margin-controlled excision for acral melanoma (AM) has the potential to safely reduce disfigurement or amputation while preserving function, by avoiding the removal of normal skin needed to compensate for the incomplete margin control in WLE. Amputation rates for AM were 21% in one series [60] and reached 34% in another study (4) [82]. By contrast, amputation was never necessary in 20 invasive and 6 in situ primary melanomas treated with MMS in one report [21], neither was it required for the 3 invasive and 25 in situ lesions in another [24]. A recent study examining MMS exclusively on digital melanoma showed 8.2% local recurrence in 62 tumors (35 were invasive with 3 recurrences), which is higher than MMS studies for other locations but comparable to the AM WLE/amputation literature (2b) [83]. Only 2 patients out of the 57 originally referred for primary melanoma required amputation (3.5% amputation rate), which was performed due to recurrent deeply invasive disease. Five- and 10-year melanoma-specific survival rates for AM patients treated with MMS for invasive disease were 91.8% and 67.8%. Reconstruction options are profoundly affected by the size of the defect in this functionally critical area, though directly comparing WLE and MCE with respect to reconstruction is not possible from the current literature. For reconstruction in AM treated by WLE, free flaps were done for the majority of patients in the largest available series [60]. Primary digital melanomas treated with MMS were closed with full-thickness skin graft in more than 3/4 of the cases [83].

While no reports on invasive melanoma have focused exclusively on MMS for trunk and extremity locations, one series had a preponderance of these lesions and showed a lower recurrence rate than WLE [21], despite the lack of immunostaining to aid in melanocyte identification in this cohort. A newer study of in situ melanomas treated with MMS (using immunohistochemistry) showed a 0.5% local recurrence rate for trunk and extremity lesions (2b) [84]; this would be expected to apply to invasive disease, as the largest MMS study to date reported statistically equivalent rates of LR for in situ and invasive melanoma [58]. The increase in average surgical defect size for WLE over MMS on the trunk and proximal extremities may be less problematic than other sites, but other factors still deserve a place in the discussion. As noted above, marginal recurrence carries the risk of deeper invasion [39] and ongoing and increasing risk of metastasis; any increase in efficacy in complete removal of melanoma should be embraced. Given the expense of systemic therapies for melanoma when nodal/metastatic disease develops, vast cost savings might be realized by even a small decrement in metastases requiring systemic therapy, not to mention the potential value to the individual who would develop metastases from persistent melanoma.

Wide local excision without meticulous margin examination is still the most commonly performed surgical procedure for invasive melanoma, but the case for complete margin control and therefore more assured complete excision via Mohs surgery or staged excision is compelling.

Preoperative Evaluation

Biopsy is the first and most important step in the diagnosis and treatment of melanoma, as the decisions made for definitive treatment hinge on an adequate specimen. NCCN and AAD guidelines emphasize the need for complete removal whenever possible, whether it be by saucerization (deep shave), punch, or excisional biopsy [16, 18]. For dermatologists skilled in clinically evaluating pigmented lesions, deep-margin transection after saucerization technique is very rare (4) [85, 86]. Correctly estimating the depth of a melanocytic lesion before biopsy is important if a shave biopsy is chosen, to avoid deep-margin transection. Dermoscopy may be helpful in identifying areas of deeper invasion based on the presence of a blue-white veil, a consistent indicator of depth > 0.75 mm (4) [87]. In tumors that are too large for excisional biopsy, the deepest portion of the lesion should be sought for sampling; areas of ulceration or nodularity should be identified, and, again, dermoscopy may be a helpful adjunct, especially when a blue-white veil is present. During the office visit, a complete HPI and review of systems should be elicited, followed by a full skin exam to identify other concerning lesions (particularly skin metastases and synchronous melanoma), as well as palpation of the lymph node basin(s) draining the biopsy site. Clinically positive nodes identified prior to biopsy are important to document, as post-biopsy lymphadenopathy can be inflammatory in nature.

A great deal of prognostic information can be found in the biopsy report. Breslow depth is the single most important value to note, as it determines WLE margins and has the greatest prognostic impact [88]. Ulceration, and to a lesser extent mitotic rate, also foreshadows a poor prognosis and is factored into the most recent AJCC system (Table 62.2).

Prognostic information can be obtained through one or more ancillary tests. Genetic expression profile (GEP) is a newer technique that uses the genes expressed in a melanoma to identify those with a high risk for metastasis. High-risk lesions originally designated class 2 had 31% 5-year disease-free survival (DFS) versus low-risk class 1 lesions which had 97% DFS (1b) [89]. Since the original report, melanomas are now subdivided into classes 1A, 1B, 2A, and 2B with 5-year recurrence-free survival rates of 92%, 90%, 77%, and 48%, respectively.

Sentinel lymph node (SLN) biopsy can be done in conjunction with or after primary tumor removal for further staging information. NCCN guidelines recommend it be offered in melanomas thicker than 1 mm and recommend consideration when ulceration or mitoses ≥1 per mm^2 are found in those 0.76–1 mm in depth. However, some studies have shown that SLN biopsy has no effect on melanoma-specific or overall survival (1b) [90]. A full review of SLN and subsequent LND is beyond the scope of this chapter, but the primary effect of removing the at-risk nodal basin is the prevention of later recurrence in that nodal basin. Therapeutic benefits, such as reduced rates of distant metastasis and death, have not been confirmed. A potential indirect benefit of clarifying SLN status is the possibility of identifying those who may benefit from systemic therapy. Delineation of its use in early identification of those who may benefit from systemic therapy is under way but has not yet been completed. The use of this procedure as a requirement to obtain potentially beneficial treatments has been questioned (5) [91]. However, as GEP becomes more widely used and its data more refined, this test and other future less invasive tests also hold promise in accurately identifying high-risk melanomas which may benefit from systemic therapy, or as a screen for SLN biopsy. If metastases are suspected by history or exam, referral to the appropriate surgical or procedural service for tissue diagnosis is indicated and appropriate systemic therapy instituted by a medical oncologist. Clinical trial participation should be offered whenever appropriate.

Impact of Patient Preference

Patients who are given complete informed consent may have a variety of reasons for choosing among procedures for melanoma, but most can be summarized in a few categories. The single most distressing aspect of melanoma is the specter of recurrence and ultimately metastasis and

death [56]. Therefore, efficacy will commonly be a key factor in the decision. As described above, MMS has the lowest local recurrence rate of any procedure, and other forms of 100% margin-controlled excision (MCE) can be expected to provide enhanced therapeutic benefit as well.

Surgical risk and morbidity is the other major category most patients consider in choosing a treatment, and the difference between the surgical options varies by body site. Of the surgical options, MMS and other MCE techniques offer the potential for the smallest possible wound. However, delayed reconstruction in MCE is less convenient for the patient and can increase surgical complications such as infection and dehiscence, particularly when the repair is completed more than 1 day after initial excision (3b) [92]. WLE wounds are usually larger than Mohs defects as well as MCE when narrow margins are used as the starting point. Wider margins may require the surgeon to choose between compromising critical anatomic structures or excising smaller than recommended margins which will increase the risk of incomplete removal. Furthermore, the larger defects are more likely to require closure techniques that can involve hospitalization, incur higher cost, carry higher complication rates, and increase risk of disfigurement or dysfunction.

Beyond surgical complications, aesthetic and functional complications are equally worthy of consideration, particularly on head and neck, hands and feet, and where there are specific functional concerns that may be mitigated with more conservative excision. Appearance is a true function of the face, as it allows for recognition of one's identity. This facial function has been ranked by patients as more important than the sense of smell or facial expression (2b) [93]. Congruently, patients were significantly more satisfied with primary closure and local flaps versus skin grafts, and smaller defects caused less emotional impairment [81].

Convenience will play into many patients' decision, though not as importantly as efficacy and risk. Issues to consider include time away from a job or other responsibility, the potential for hospitalization, wound care time and supplies, and the potential for a friend or family member to be needed for transportation to and from the treatment facility. Many studies on radiotherapy use anywhere from 5 to 12 treatments, though up to 30 can be used, making it the most inconvenient option in terms of patient visits. WLE and MMS are typically accomplished in a single day as an outpatient surgery, and other forms of MCE require separate visits for excision and closure. Some WLEs are performed under general anesthesia and occasionally involve hospital stays.

Overall, when patients are offered a procedure that evaluates 100% of the surgical margin and provides the lowest recurrence rate with the smallest surgical wound which is closed on the same day, the authors observe that they usually elect Mohs surgery.

Typical Treatment Plan: Case Narrative

Mr. C is a 68-year-old male with a biopsy-proven 2.8 mm deep non-ulcerated lentigo maligna melanoma of the left medial cheek; the deep margin is negative but lateral margin is positive. He presented for a consult, and a discussion was undertaken to educate him about the various excisional procedures to remove the tumor in its entirety. A 2 cm margin was drawn around the 2.4 × 2.2 cm clinical tumor to show the recommended margins for WLE. The resulting 6.4 × 6.2 cm proposed excision involved part of his nasal ala and upper cutaneous lip. Local recurrence rates were disclosed at roughly 10% for WLE on the head and neck, and less than 1% for Mohs. Removal and reconstruction in a single operative session was discussed for WLE versus potentially multiple stages and repair later in the day for MMS. A delay of 5 days was anticipated for the pathology report after WLE, while the clearance of the tumor was expected to be pathologically confirmed that day with MMS. Due to its ability to achieve 100% margin evaluation with a smaller defect and be repaired on the same day, he chose Mohs surgery. He decided against a SLN biopsy but requested his biopsy specimen undergo GEP for further prognostication. He was educated on self-monitoring his skin for new or changing lesions, as well as periodic lymph node self-examination. He was instructed to return for

examination if a new or changing lesion was identified on his monthly self-exam; likewise, he will return for any new palpable changes in his lymph node exam. Rigorous sun protection was advised. There was no suspicion for nodal or metastatic disease discovered by history or exam. Surgery was scheduled for the next week.

On the day of surgery, visible tumor extent was marked, along with a 6-mm margin of normal-appearing tissue. Local anesthetic was infiltrated into the operative area, and the specimen was excised down to the level of the deep subcutaneous tissue and then inked for mapping. The area was bandaged, and he returned to the waiting room while H&E and MART-1 staining were performed on the frozen sections. One area of residual melanoma in situ was identified at the 12 o'clock position, and a subsequent 3-mm-wide margin of tissue was taken around the positive margin. This second stage was histologically negative using the same stains, and the patient was brought into the room for reconstruction. The defect measured 3.8 × 3.6 cm and primary closure was chosen, oriented along the nasofacial sulcus and melolabial fold. The patient was then bandaged and sent home with instructions for care. Acetaminophen and, if necessary, ibuprofen were recommended for pain control (1b) [94]. The wound was healing well at his 1-week wound check, and regular follow-up skin and node exam was scheduled for 3 months.

Staged excision with en face permanent sections would have been an appropriate third surgical option in this patient. A surgeon may provide staged excision as an option, obviating the need to interpret the pathology oneself if impractical or not preferred. Its virtue over WLE with immediate closure is that more complete histologic clearance is obtained, and a smaller wound is often achieved; however, it requires sending the patient home with an open surgical wound (except in the original description of the square technique, in which residual melanoma at the biopsy site would be allowed to remain until reconstruction). Furthermore, it requires at least one additional surgery date for reconstruction or more if margins prove to be positive. These issues may limit surgeons' willingness to adopt the technique and patients' acceptance of it. However, it should be considered when geography limits access to a Mohs surgeon trained to operate on melanoma.

Safety

Excisional surgery on the skin and subcutaneous tissue can be done with a high degree of safety, but the exact nature and incidence of complications depend heavily on the body site, the type of anesthesia, and the width and depth of the excision, as well as the planned repair. The excision margin RCTs focus on treatment results and many reported no information on complications or how they are affected by margin width. One useful finding from the Intergroup trial (trunk and proximal extremity lesions) was that 11% of defects required skin grafting when a 2-cm margin was removed [41]. Hospital stay was longer when skin grafts were used, and delayed ambulation was implicated in the extended stays. For those who had no LND, patients were hospitalized for an average of 3 days. Wound infections occurred in 5.4% and dehiscence in 4.6% in the 2- cm margin cohort. The UK trial (3 cm vs 1 cm, trunk and limbs excluding palms and soles) reported that 66% of patients in the 3 cm cohort had an inpatient procedure under general anesthesia vs 32% of those in the 1 cm cohort [50]. Complications were reported as a lump sum, with 13.9% vs 7.8% favoring 1-cm margins. The 2011 Swedish trial (trunk and extremity excluding hands and feet) reported primary closure was used in 69% of those with 2-cm margins, while split-thickness skin grafts were used in 12% and flaps in 4% [52]. A quality assurance study for melanoma found that primary closures and flaps were rarely complicated, while 5.9% of skin grafts had more than 20% area of failure, but surgical site was not described (2b) [95]. Grafts are the repair choice associated with the most morbidity in melanoma surgery, and body site affects their success; grafts on the lower limb have failure rates as high as 33% (4) [96], and negative influences include vascular disease, increased body mass index, and immunosuppressant use. All findings were favorable to the smaller margin of excision.

WLE complication data for other sites such as head, neck, and acral sites are less reliably assem-

bled from the melanoma literature, as few RCTs included these sites and none have reported site-specific complication rates. Retrospective studies are complicated by the possibility that some complications were managed by other physicians, or that they were not reported to any physician. A review of desmoplastic melanomas, 62% of which were head and neck, reported an overall 16% complication rate, which most commonly included infection or delayed healing, hematoma requiring evacuation and ligation, and microstomia requiring surgical correction [35]. Regarding repair type, patients with head and neck melanoma treated with NCCN margins will most commonly require a local flap [63]. WLE for acral melanoma necessitates amputation in over a fifth of cases [60], with thicker melanomas treated with amputation more often [82], and repairs are often highly complex with more than half requiring a free flap [60].

The literature describing MMS for melanoma primarily emphasizes efficacy, but many of the same types of complications would be expected regardless of the excisional type, such as infection, bleeding, and tissue distortion. Some WLE literature compares complication and repair statistics between different margin widths, and smaller defect size is universally associated with better outcomes and simpler repairs [41, 50, 52, 63]. With a mean final MMS margin of 7.2 mm in one large report containing both in situ and invasive disease [58], excisional trauma and repair complexity are unquestionably reduced. Digital melanomas treated with MMS had a markedly simpler repair and did not require amputation except in case of two patients with 5-mm-thick recurrent lesions [83]. Since MMS is performed as an outpatient surgery under local anesthesia, eliminating general anesthesia and hospitalization provides a benefit to the subset of patients who otherwise would be subject to these risks. One prospective MMS cohort showed a 2.6% overall complication rate, with bleeding being most common. A significant association was seen between complications and tumor size, postoperative defect size, older age, and choice of repair other than linear closure (2b) [97]. A British review of mostly basal cell carcinomas treated by MMS showed <1% overall complication rate and none were serious (2b) [98]. Further study of surgical complication rates in melanoma treated by MMS would be useful to aid in comparing to WLE, as melanoma defects are often deeper.

Staged excision (SE) techniques add an additional element to the milieu of issues affecting safety. Potentially more narrow tissue excision and therefore lower repair complexity, as well as outpatient setting compare favorably to WLE; however, delayed repair may raise the complication rate as discussed earlier. One series of 51 facial melanomas (9 of which were invasive) treated with SE had a 9.8% overall complication rate, which included partial loss of flap or graft tissue, as well as hypertrophic scars (4) [99]. No functional complications were found, which highlights the importance of tissue-sparing technique on the head and neck. Flaps were used in 44% and grafts in 36%. According to a large study on delayed reconstructions after MMS (primarily in non-melanoma skin cancer), the elapsed time between initial excision and repair correlates with complication risk, with 3 or more days being worse than 1–2 days [92].

Complications in radiotherapy for melanoma are 21% overall according to one study, with 8% being serious (osteoradionecrosis, nonhealing scalp wounds requiring surgical revision, and failure of skin graft) [35]. Less serious issues include hypothyroidism, delayed wound healing, edema, xerostomia, and keratoconjunctivitis sicca. Unlike surgical complications, many radiotherapy complications take months to years to develop, with the median time to development in this study being 19 months. Another report highlights that all patients experience an erosive reaction in the first weeks after treatment [32].

Postoperative Care and Follow-Up

Monitoring patients after melanoma treatment is a complex topic, and little evidence exists to confirm the validity of commonly used schedules. Many sets of guidelines have been presented by various groups, and though this has been succinctly reviewed [100], further research may lead to more uniformity and agreement in these guidelines (Table 62.3). Two categories of monitoring

Table 62.3 Summary of follow-up recommendations

NCCN and AAD guideline summary for following patients with melanoma		
Shared recommendations	NCCN-specific	AAD-specific
At least yearly follow-up (f/u) for life	Stage 0 f/u with physician yearly	Stage 0 f/u every 6-12 months for 1-2 years
3–12-month f/u interval based on clinical details and clinician judgment	Stage IA-IIA f/u every 6–12 months for 5 y	Stage IA-IIA f/u every 6-12 months for 2-5 years
Patients should examine skin and lymph nodes at regular interval	Stage IIB-IV f/u every 3–6 months for 2 y, then every 3–12 months for the next 3 y	Stage IIB-IV f/u every 3-6 for first 2 years, no more than 6 month interval between years 2-5
Asymptomatic stages 0–IIA need no blood work or imaging	Stage IIB-IV without evidence of disease: consider imaging every 3–12 months for 5 years	No baseline studies for asymptomatic stages 0-II
Nodal ultrasound may be considered in certain circumstances	CT chest/abdomen/pelvis with contrast and MRI brain with contrast, and/or PET/CT, are preferred for screening	Lab and imaging only recommended to evaluate signs and symptoms of metastasis

should be considered separately, patient-directed and physician-directed. Patients should be remembered as the most likely entity to detect a recurrence in thicker melanomas (4) [60, 101], and patient education is vital to ensuring the timely identification of disease. The authors routinely instruct patients to perform monthly full-body self-examinations and alert their dermatologist to any new or changing skin lesion. If they have invasive melanoma, they are instructed to examine the regional lymph node basin(s) on at least a monthly basis. Physician-directed surveillance should involve dermatologic history and physical (H&P). The role of imaging is currently not clearly defined [18], but appropriate imaging should be performed for investigating symptoms concerning for metastasis. Imaging asymptomatic patients is controversial and not clearly supported by current evidence. H&P should be performed at least annually for life for two key reasons: the risk for latent disease to manifest as a clinical metastasis never completely disappears, and a melanoma diagnosis identifies a patient as having a much higher risk (probably 8–10% [2b]) [102] of a second melanoma. More frequent visits may be reasonable for invasive melanoma within the first 5 years after diagnosis, since most recurrences occur within this range. Imaging in lower-risk melanoma patients is uniformly discouraged unless there is a specific finding identified on H&P, and imaging higher-risk but asymptomatic patients is controversial. Preferred modalities vary by site, but ultrasonography is the best imaging modality for lymph node staging and surveillance, and PET/CT excels for distant metastasis (2a) [103]. There is no specific blood test for detecting persistent or recurrent melanoma, though surrogate tests include S100β and LDH; neither are uniformly recommended for either staging or surveillance, and they do not offer a reliable opportunity to improve survival.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Findings	GRADE score: quality of evidence
When WLE based on visual inspection is used, NCCN guidelines should be followed	A
Treatment safety is first and foremost related to complete removal of melanoma	A
More thorough tissue exam leads to lower local recurrence	B
When 100% margin control is used, cure rates are less dependent on margin width	B
Treatment options differ enough that complete informed consent is needed	D

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Self-Assessment Questions

1. Recommendations for 1- and 2-cm margins of excision for invasive melanoma are:
   (a) Based on multiple randomized controlled trials
   (b) Based on the Breslow's Thickness of the melanoma
   (c) Based on studies primarily of MM of the trunk and proximal extremities
   (d) Based on RCTs, including the head, neck, extremities, and trunk
   (e) A, B, and C

2. Which of the following techniques are based primarily on visual ID of the melanoma margin:
   (a) Wide local excision
   (b) Mohs micrographic surgery
   (c) Serial excision with curvilinear margins and en face histology sections
   (d) Serial excision with polygonal margins and en face sections (square technique)
   (e) Serial excision with radial sections

3. Components of informed consent include:
   (a) Review of treatment options
   (b) Review of risks
   (c) Review of benefits
   (d) Review of alternative treatments
   (e) All of the above

4. Which of the following is false?
   (a) Recurrence rates decrease with increasing margins, up to 2 cm
   (b) Excision of clinically inapparent satellite metastases likely leads to improved overall survival
   (c) Removing less than recommended margins in WLE results in increased recurrence
   (d) Wider margins of excision result in improved overall survival
   (e) NCCN guidelines for follow-up are based on low-level evidence

5. Which of the following is true?
   (a) LDH should be obtained as surveillance for metastasis in high-risk melanomas
   (b) Imaging plays an important role in discovering recurrence in asymptomatic patients
   (c) A patient with a thin melanoma has a higher risk of a future second primary melanoma than a recurrence from their first primary
   (d) Patients should not be relied upon to perform self-examination of their skin and lymph nodes
   (e) Yearly follow-up visits can be ended after 10 years, since recurrence is exceptionally rare beyond this time

Correct Answers

1. e: Recommendations are based on RCT evidence and vary depending on the Breslow's thickness, but most of the RCTs excluded head and neck locations. In addition, most excluded some or all of the hand/foot.
2. a: WLE is the only method that involves histologic processing that is not standardized and does not always rigorously study the margin. Successful extirpation of the tumor is therefore predicated on using a large clinical margin beyond the visible tumor, to account for subclinical spread and minimize the chance of tumor extending beyond the sparsely sampled margin.
3. e: Informed consent is vital to procedural medical practice yet is often hastily or incompletely performed. Physicians should make an effort to present the evidence for and against each option without injecting opinions to influence the patient's decision. Each patient has their own set of values and thought processes and must be allowed to choose their treatment based on an honest summary of their available options.
4. b: There is no evidence for the benefit of excision beyond removing the primary contiguous tumor; undetected satellite foci, if present, are indicative of metastatic behavior. No evidence suggests these are limited only to the NCCN margin distance from the primary tumor.
5. c: Second primary melanoma occurs in approximately 10% of melanoma patients, which is far higher than the risk of recurrence in thin melanoma. LDH (or any blood test) and imaging are not recommended in asymptomatic patients. Patients should be educated on self-examination of their skin and lymph nodes, as they frequently detect new primary melanomas and recurrences first. Yearly follow-up visits are recommended for life, as recurrence risk never drops to zero.

Prevention and Treatment of Procedure-Associated Infection

63

James V. Twede and Christian L. Baum

Abstract

Procedure-associated and surgical site infections (SSI) in dermatology are rare; however, it is prudent to understand their prevention and treatment. SSI has been variably defined, which may contribute to the broad range of results from studies aimed at quantifying the risk of SSI. The Centers for Disease Control and Prevention (CDC) defines an SSI as a wound that suppurates within 30 days of the procedure, even in the absence of a positive culture (Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. Am J Infect Control 20(5):271–4, 1992). The application of this definition is particularly challenging for dermatologic procedures since wounds may become colonized with organisms, such as *Staphylococcus aureus* (*S. aureus*), and suture granulomas may present with a sterile suppurative exudate within 30 days of the procedure. In this situation, good clinical judgment and the quantity of bacteria (>10^5) (Robson MC, Heggers JP. J Surg Oncol 2(4):379–83, 1970) in the wound can be helpful in differentiating colonization versus a true SSI.

Keywords

Skin · Surgical site infection · Prevention
Treatment · Risk · Dermatology

Introduction

Procedure-associated and surgical site infections (SSI) in dermatology are rare; however, it is prudent to understand their prevention and treatment. SSI has been variably defined, which may contribute to the broad range of results from studies aimed at quantifying the risk of SSI. The Centers for Disease Control and Prevention (CDC) defines an SSI as a wound that suppurates within 30 days of the procedure, even in the absence of a positive culture [1]. The application of this definition is particularly challenging for dermatologic procedures since wounds may become colonized with organisms, such as *Staphylococcus aureus* (*S. aureus*), and suture granulomas may present with a sterile suppurative exudate within 30 days of the procedure. In this situation, good clinical judgment and the quantity of bacteria (>10^5) [2] in the wound can be helpful in differentiating colonization versus a true SSI.

Dermatologic surgery has historically low infection rates ranging from <1% to 4% [3] (2b) [4] (2b), with differing rates based on body site and the specific procedure performed [5] (2b). SSI can result in significant patient morbidity,

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medical costs, lost time from work, flap or graft failure, and a poor cosmetic result. Most current approaches to assessment, prevention, and treatment of SSI are published in the general surgery and surgical subspecialty literature. However, over the past few decades, there has been a renewed focus in dermatology on SSI risk and mitigation. In fact, the bulk of the data related to dermatology procedure-associated infections is derived from excisional surgery and Mohs micrographic surgery (MMS). In an effort to evaluate surgical complications, the American College of Mohs Surgery has created a registry specifically analyzing complications related to MMS. SSI is one important item being assessed in the registry, which may be able to define practices that ameliorate or heighten the risk of SSI [6]. The purpose of this chapter is to systematically review the evidence related to the variables that influence procedure-associated and SSI in dermatology.

Risk Factors for Surgical Site Infection

Multiple variables such as wound quality and size, type of procedure performed, and patient demographics may influence SSI risk. Surgical sites with ulceration, purulence, and/or inflammation have a higher risk of postoperative wound infection due to an increased bacterial load and presence of pathogenic bacteria [7] (2b) [8]. Excision of cutaneous malignancies such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) was identified in one report as independent risk factors for wound infection when compared to the excision of benign lesions such as atypical nevi [9] (2b). Another study demonstrated that individuals undergoing MMS for noninvasive malignant melanoma also had an increased risk of SSI compared to those who had a BCC treated with excision [10] (2b). These particular risk factors may have less to do with the actual tumor than the nature of the procedure. When the time for excision of benign and malignant tumors extended beyond 24 min, there was a significantly higher risk for infection compared to procedures that took less than 24 min [11] (2b). Likewise, this may be why MMS, with its longer duration and intermittent wound care, puts the surgical site at risk for infection compared to a standard elliptical excision [5] (2b). Lastly, the size of the surgical defect tends to be larger with malignant neoplasms than with benign neoplasms, which would increase the amount of time spent on excision and repair.

SSI rates differ significantly from one area of the body to another and the type of procedure performed. An analysis of 5,091 dermatologic procedures revealed rates of infection of 0.73% for curettage, 2.94% for skin flaps, 0.54% for elliptical excisions, 8.7% for skin grafts, and 8.57% for wedge excisions [5] (2b). A subanalysis of these procedures that determined the size of the wound also demonstrated implications for SSI with a 2.24% risk for wounds <11 mm and an 11.6% risk in wounds >11 mm when located below the knee ($p = 0.0001$). On the whole, sites below the knee had a 6.92% infection rate. The groin had a similar high rate of infection at 10%.

Studies assessing the experience of the surgeon and risk for SSI have shown mixed results. One study showed the overall risk for mild and severe infections performed by experienced surgeons was lower than procedures performed by less experienced surgeons (0.6% vs. 3.1%), a finding that may be the result of an experienced surgeon's ability to delicately handle tissue and the speed with which they are able to complete a surgical procedure [7] (2b). Another study evaluating surgical experience showed no difference in adverse events such as bleeding and impaired wound healing between experienced Mohs surgeons and those who had recently completed fellowship [12] (2b).

A patient's age has been shown to influence SSI risk. One study demonstrated infection risk in dermatologic surgery increased with every decade of life and ranged from 2.9% in patients aged less than 40 years to 13.6% in patients aged over 70 years [5] (2b). Another study showed that all patients with severe infections after primarily scalpel-based dermatologic surgery were over the age of 70 [7] (2b). A multicenter prospective cohort study evaluating adverse events

relating to MMS showed the mean age for SSI was 70.8 years [12] (2b). It is well known the aging process leads to a decline in the innate and adaptive immune system [13], and this may influence the increased rate of infection in the elderly.

Patient gender does not appear to influence SSI rate. One prospective study showed no difference in rates between men and women undergoing a variety of scalpel-based dermatologic procedures [5] (2b). To date, there are no data to suggest a link between BMI or ethnicity and dermatology procedure-related infections.

Severity and Duration of Infectious Complications

The vast majority of dermatology procedure-associated infections are not associated with long-term sequelae or mortality. A large multicenter prospective cohort study was performed to quantify adverse events associated with MMS [12] (2b). It showed an overall adverse event rate of 0.72% with SSI reported as the most common event at 61.1% of all complications. Infectious complications that resulted in hospitalization included one case for infection and partial necrosis and two others with cultures positive for methicillin-resistant *S. aureus* (MRSA). None of these patients showed any other temporally related vascular or pulmonary complications, and no deaths were reported.

A multicenter study was conducted analyzing minor and major complications associated with MMS over a 4-week period [14] (2b). Infection was the primary complication with a 0.9% incidence (16 of 1709 patients). There were no deaths during the treatment or in the postoperative period.

A study assessing the severity of infections in primarily scalpel-based dermatologic surgery showed an infection rate of 1.47% (75 out of 5,091 lesions) [5] (2b). Two of the individuals with infected lesions developed serious infections (cellulitis); the third required hospitalization, wound debridement, and intravenous antibiotics.

In another study, the safety of MMS in office-based and hospital-based settings was compared [15] (2c). A total of 3937 cases of MMS were performed with 2397 at an outpatient dermatology office and 1540 treated in a hospital setting. There were no significant differences in patient demographics, tumor types, and repairs. When evaluating the major complications of the two settings, there were no deaths, cardiac or pulmonary complications, deep wound infections, sepsis, or distant infections as a result of the cutaneous surgery.

Isolated, rare cases with severe adverse infectious complications have been reported following dermatologic surgery. A case of toxic shock syndrome occurred after minor dermatologic surgical excision that resulted in multiorgan failure [16]. In another instance, necrotizing fasciitis occurred after excision of malignant melanoma and eventuated into multiorgan failure and death [17].

Laboratory Evaluation

Laboratory values as predictors of SSI are not well defined, but some values may be helpful when stratifying a patient's SSI risk. In a prospective observational cohort study of elderly patients, undergoing a variety of general and orthopedic surgeries, lab values such as hemoglobin, hematocrit, CRP, glucose, AST, ALT, and creatinine showed no influence on SSI risk [18] (2b). Likewise, elderly patients undergoing orthopedic or general surgical procedures often show a blunted febrile response to SSI [19] (2c), making absence of fever an unreliable factor in determining presence or absence of infection.

Serum prealbumin levels as a predictor of complete wound healing has been demonstrated in a number of studies [20] [21] (2b). One particular study assessing skin graft placement in burn patients suggested that prealbumin levels may be a sensitive predictor of successful implantation [22] (3b). Complete graft healing was noted in 93.8% in those with normal prealbumin levels compared to 44.4% in those with low levels. Graft sites in those with normal prealbumin levels showed a preponderance of the less virulent *Pseudomonas aeruginosa* (*P. aeruginosa*) and a relative absence of the more virulent staph-

ylococcus and streptococcus organisms, which may be the reason for enhanced graft survival. One review in the dermatology literature suggested skin infection was one of the most common reasons for skin graft failure [23]. The above evidence suggests low prealbumin levels that may be seen in malnourished and/or elderly patients may be a risk factor for wound colonization with virulent bacterial microorganisms and potential skin graft failure. However, there is currently no data to directly associate prealbumin levels with dermatologic SSI risk.

Patient Behavioral and Medical Risk Factors

Anticoagulants

The use of anticoagulants has increased dramatically over recent decades, and the continuation of these medications for dermatologic surgery is the accepted standard of care [24] (2b). A prospective study evaluating the SSI rate of individuals taking warfarin or aspirin demonstrated a SSI rate of 1.85% and 1.1%, respectively, in patients undergoing a variety of excisional dermatologic procedures [5] (2b). These percentages are in line with the historical infection rate of <4% for dermatologic surgery, but the study had no control group for comparison. Another study examined the effects of antiplatelet and anticoagulant medications on complications related to dermatologic surgery showing a risk of infection of 1.3%, which is not different from the accepted SSI rates for dermatologic surgery [25] (2b). Ultimately, there is no evidence to suggest the use of anticoagulants increases the risk of dermatologic SSI.

Diabetes

The prevalence of diabetes has risen dramatically, and it is currently estimated that the prevalence among Americans is 12.1% [26]. A 5-year prospective observational study evaluating complications after cutaneous surgery in those with known diabetes showed a statistically significant greater risk for SSI in diabetics when compared to those without a history of diabetes (4.2% vs. 2.0%) [27] (2b). Of note, the study subjects were diagnosed with diabetes by a referring provider and the investigators did not quantify the severity of diabetes. There was also no analysis relating HbgA1c levels to rates or severity of SSI. An additional prospective study evaluating patients undergoing aesthetic body surgery demonstrated over double the infectious complications in diabetics compared to those without the condition [28] (2b). Abdominoplasty had the highest rate at 6.1% in diabetic patients versus 3.0% of controls.

Tobacco Use

It is well known that smoking leads to increased risks of myocardial infarction, stroke, deep vein thrombosis, and pneumonia in those undergoing major surgery [29] (2b). A review and meta-analysis assessing the clinical impact of smoking and smoking cessation on wound healing and infection in general surgery demonstrated smoking cessation intervention significantly reduced SSI [30] (1a). Smokers were shown to have a twofold increased risk for infection compared to nonsmokers. Another study from the general surgery literature demonstrated a SSI rate of 12% in smokers compared to 2% in individuals who had never smoked. Other studies have shown no statistical difference, but these randomized controlled trials (RCTs) may have been underpowered [31] (2b) [32], (1b).

Presently in the dermatologic literature, there are conflicting conclusions regarding the impact of smoking on SSI risk. A prospective study evaluating SSI risk between smokers and nonsmokers undergoing a variety of excisional dermatologic surgical procedures showed no statistical difference (2.1% vs. 1.9%) in the risk of SSI [33] (2b). Another study assessing wound complications after biopsies performed on an inpatient dermatology service showed a significant risk for infection in current smokers compared to nonsmokers [34] (4). However, the individuals biopsied suffered from a multitude of medical problems and

the overall infection rate for all biopsies was 27%, which far exceeds other quoted values in dermatologic surgery and therefore may not be applicable to a typical outpatient dermatologic surgery setting. Another study assessing risk factors and outcomes after MMS demonstrated a twofold increase in adverse surgical events (bleeding and wound dehiscence/necrosis) in former smokers compared to current smokers, but there was no association between these risk factors and SSI [12] (2b).

Preoperative Patient Interventions

Preoperative Patient Antisepsis

Numerous preoperative antiseptic interventions have been studied with the purpose of lowering SSI rates. Preoperative bathing or showering with chlorhexidine scrub has long been implemented as a way to reduce bacterial colonization prior to a variety of primarily general, orthopedic, and vascular surgical procedures. A fifth update of a Cochrane review evaluating this practice included seven different trials [35] (1a). It concluded that bathing with chlorhexidine compared to placebo did not significantly reduce SSI and that regular bar soap when compared to chlorhexidine showed no difference in SSI risk. However, one larger study in the review did show a statistically significant difference in favor of bathing with chlorhexidine versus no bathing.

One systemic review of patients undergoing minor skin excision surgery in the primary care setting evaluated the SSI risk for patients who showered or bathed within 48 h of surgery (early bathing) or waited for 48 h after surgery (delayed bathing) [36] (1a). There was no statistical difference in infection rate between the groups with 8.5% in the early bathing group and 8.8% in the delayed group.

There have been no RCTs assessing benzoyl peroxide gel as a topical agent to prevent SSI. However, one prospective study of 673 patients showed that preoperative use of 10% benzoyl peroxide gel may help to decrease SSI. The study compared the application of the gel to the centrofacial area for 7 days to no application prior to dermatologic excisional procedures. The results showed a statistically significant decrease in SSI rate in those using the gel (1.93%) compared to those who did not (3.24%) [37] (2b).

Bleach bathes have often been used in atopic dermatitis to reduce *S. aureus* colonization and may have relevance to those undergoing dermatologic procedures [38] (1b). A retrospective cohort study of children who underwent incision and drainage (I&D) for methicillin-resistant *S. aureus* (MRSA) abscesses, followed by a decolonization procedure with bleach baths and application of intranasal mupirocin ointment, found no statistical difference between individuals undergoing decolonization and those who did not in regard to need for repeat I&D or presence of repeat MRSA-positive cultures [39] (2b). No studies have been performed to date evaluating the use of bleach bathes and SSI risk.

The use of intranasal mupirocin has been advocated as a preventive measure due to its ability to decrease endogenous sources of *S. aureus* [40] (1b). *S. aureus* carriage of the anterior nares is present in 37% of the general population at any given moment [41]. The specific strain of *S. aureus* associated with SSI can be matched through molecular typing with an organism that colonizes a patient's nares 80–85% of the time [42] (1b).

A prospective randomized study evaluated preoperative screening for nasal bacterial colonization and its influence on SSI in patients undergoing MMS [40] (1b). Those with nasal cultures showing *S. aureus* carriage were randomized to receive no treatment or to undergo a decolonization protocol consisting of intranasal application of 2% mupirocin ointment and once daily full body wash with 4% chlorhexidine for 5 days. They reported an infection rate of 4% in carriers who underwent the decolonization protocol and an 11% rate in carriers who did not undergo decolonization. The relative risk of SSI in untreated carriers versus noncarriers was statistically significant. Despite these results, the authors admit that the cost of the decolonization procedure may be a limiting factor when implementing these measures.

A Cochrane review was performed to determine whether mupirocin nasal ointment would reduce *S. aureus* infection rates in individuals with identified *S. aureus* nasal carriage undergoing a variety of general, orthopedic, gynecological, and neurosurgical surgeries and dialysis [43] (1a). The review included nine RCTs and showed a significant reduction in *S. aureus*-associated infections in those who used intranasal mupirocin. When subgroup analysis was performed examining SSI caused by *S. aureus,* the effect disappeared, but the authors conclude this may have been the result of inadequate power.

Given the relatively high cost and inconvenience of intranasal mupirocin, alternative treatments have been sought to treat intranasal *S. aureus* colonization. A prospective, open-label, randomized trial of twice-daily application of intranasal 2% mupirocin ointment ($130 USD) for 5 days prior to surgery compared with two 30-s intranasal applications of povidone iodine (PI) 5% solution ($20 USD) within 2 h of surgical incision was conducted in patients undergoing arthroplasty or spinal fusion [44] (1b). In the intent-to-treat analysis, there was no statistical difference in the *S. aureus* deep SSI rate in the mupirocin group (0.6/100) compared to the PI group (0.1/100). Patient tolerability favored intranasal PI over mupirocin with 3.6% of patients in the PI group rating the experience as unpleasant compared to 38% of patients using mupirocin.

Attire

Much of the evidence for surgical attire is derived from the general surgery and other surgical subspecialty literature. Applying and customizing the available evidence on surgical attire may help to facilitate new and innovative methods in dermatologic surgery making for more efficient processes and improved patient outcomes.

Surgical Face Masks

Surgical face masks have been utilized for over 100 years and have become an intuitive standard amongst most surgical specialties [45]; however, their benefit on decreasing SSI rate is unclear.

A 2016 Cochrane review of three trials demonstrated no significant difference in infection rates between those wearing and those not wearing surgical face masks [46] (1a) for a variety of general, orthopedic, and gynecological surgical procedures.

Despite the lack of conclusive findings that surgical face masks decrease SSI rate, they may continue to serve the purpose of protecting the surgeon from macroscopic facial contamination [47]. A study from the vascular surgery literature showed that 45% of all cases showed blood or body fluid on the protective eye lens of the operator [48] (2b). Additionally, laparoscopic cases showed a 50% blood or body fluid splash on protective lenses, which presumably would have fewer bodily fluid splashes than open surgical cases.

Ultimately, there is no evidence that face masks influence SSI rate. Moreover, there are no well-designed studies demonstrating that face masks protect the surgeon from aerosolized or splash droplet-related infectious diseases. However, given the minor inconvenience, surgical face masks serve the purpose of promoting surgical and sterile discipline and protect the wearer from body fluid exposures.

Head and Feet Covers

Surgical head coverings presumably function to prevent hair fomite contamination of a surgical field. A study of 508 subjects in an emergency department setting evaluating infection rate for uncomplicated sutured wounds showed no difference in infection rates between one group wearing both a head cap and surgery mask and another group wearing no mask nor cap [49] (2b). A 2011 dermatology review of surgical attire concluded surgical head coverings were unlikely to make a difference in SSI risk [50] (2a).

The use of surgical gowns has shown conflicting results in regard to bacterial contamination and SSI, and their utility in dermatologic surgery is uncertain [50].

The use of dedicated footwear (theater shoes) has been advocated by some to minimize bacterial contamination of surgical floors. It is known that outdoor shoes harbor significantly more bacteria compared to theater shoes [51] (2b), but there are no studies to suggest that use of theater shoes decrease the risk for SSI.

The use of shoe covers to prevent bacterial contamination is controversial. One study found no difference in the bacterial contamination of a surgical floor when shoe covers were used and when they were not [52] (2b). At the same time, shoe covers are considered by some to be inconvenient while they also incur cost. Furthermore, their removal and replacement may increase the risk of bacterial contamination of the hands [53].

Jewelry and Nail Polish

The wearing of finger rings and use of nail polish have been implicated as factors that decrease the efficacy of surgical scrubs, subsequently leading to potential increase in bacterial counts and SSI. To date, there have been no RCTs investigating infectious complications comparing the wearing of finger rings and not wearing them [54] (2b). Furthermore, there have been no trials evaluating the impact of wearing nail polish versus no nail polish. Despite this lack of evidence, the advisory committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force continue to recommend that surgical team members remove rings, watches, and bracelets before surgical hand scrub and avoid the wear of artificial nails [55] (5).

Intraoperative Interventions

There are a number of dogmatic principles and some evidence-based practices to guide the dermatologic surgeon in the preoperative and intraoperative routine. The choice of surgical antisepsis, use of sterile vs. clean surgical gloves, employment of hair removal techniques, utilization of prophylactic antibiotics, choice of surgical instruments, and other intraoperative techniques are just a few items where evolving evidence has positively influenced dermatologic surgical behaviors and practices.

Surgical Drapes

Use of surgical drapes is a common method to avoid fomite contact outside of the surgical field. Interventions to augment surgical draping systems include iodine-impregnated and non-iodine-impregnated adhesive drape systems, as well as impermeable and permeable adhesive drapes. Systematic reviews on the superiority of one system over another show mixed conclusions [56] (1a). One prospective randomized trial in patients undergoing cardiac surgery showed a more rapid recolonization of bacteria in groups using adhesive drapes versus no drapes [57] (2b). Another prospective randomized study assessing drape permeability and its effect on SSI during breast reconstruction surgery showed a statistically significant higher SSI rate when reusable sterile woven drapes were used compared to disposable drapes [58] (1b). An additional study showed elevated bacterial counts in operative fields with permeable linen drapes (664 CFU/50 cm^2) compared to impermeable nonwoven drapes with self-adhesive edges (393 CFU/50 cm^2). A similar difference in CFU counts between the two draping systems was also noted in the wound itself (164 CFU/sample vs. 12 CFU/sample, respectively) [59] (2b).

Gloves

The use of sterile versus nonsterile gloves in dermatologic surgery has been investigated quite extensively. The first randomized prospective trial to compare the infection rates of wounds with clean versus sterile gloves was performed during the repair of simple lacerations in an emergency room setting [60] (1b). The study of 816 subjects showed no statistical difference in infection rates between sterile gloves (6.1%) versus clean, nonsterile gloves (4.4%). The first dermatologic study examining this topic was a retrospective chart

review of 1,810 consecutive patients performed in 2006 evaluating the tumor extirpation with MMS. The results showed no statistical difference in SSI rate between the use of sterile and clean nonsterile gloves [10] (2b). A 60-subject, prospective, patient-blinded, pilot study showed no difference in SSI rates when using clean, nonsterile gloves versus sterile gloves for reconstruction after MMS. The authors noted considerable financial benefit to the institution with estimates ranging from $17,580 to $23,440 in annual cost savings [61]. (2b). A prospective trial of 3,491 patients undergoing flap or graft reconstruction found a significantly higher rate of SSI when nonsterile gloves were used compared to sterile gloves (14.7% vs. 3.4%), but no difference was noted for simple excisions and closure (1.7% vs. 1.6%) [62] (2b). Lastly, a systemic review and meta-analysis of multiple high-quality studies to include multiple randomized clinical trials and prospective or retrospective comparison studies evaluating the use of sterile versus nonsterile gloves for MMS, laceration repair, and mucosal dental procedures showed no difference in SSI or other adverse events [63] (1a).

Surgical Site Scrub

The use of preoperative surgical site scrub is routinely performed to reduce transient and resident microorganisms prior to surgical intervention. The most common agents used in the United States are iodophors (mainly povidone-iodine (PI)) and chlorhexidine gluconate (CHG) (with and without alcohol).

A Cochrane review assessing the ability of topical antiseptics to prevent SSI applied immediately prior to incision in clean surgery was performed [64] (1a). Thirteen studies were included in the review containing 11 different comparisons between various antiseptics. The comparisons included iodine in alcohol and alcohol alone, and various products containing iodine versus products containing CHG. One study suggested that 0.5% CHG in methylated spirits led to a reduced risk of SSI compared with an alcohol-based PI solution. This particular study has gained traction in support of CHG as a preoperative surgical scrub in dermatologic surgery. All the other studies in the review showed no significant differences in SSI rates between the various antisepsis regimens.

One prospective randomized clinical trial compared 2% CHG and 70% isopropyl alcohol (ChloraPrep®, Cardinal Health) and 10% PI aqueous solution (Scrub Care Skin Prep Tray®, Cardinal Health) [65] (2b). The overall rate of surgical site infection (superficial, deep and organ space) was significantly lower in the CHG-alcohol group than in the PI group (9.5% vs. 16.1%, respectively).

Surgical Team Preoperative Scrub

Preoperative surgical scrub of the hands, fingernails, and forearms of the operative team is a well-established method to decrease SSI. A Cochrane review of the effects of surgical hand antisepsis on preventing SSI and diminishing number of bacterial CFU was performed [66] (1a). The review included fourteen RCTs: four trials with SSI as the primary outcome and ten trials assessing CFU quantities (not SSI rate). In the trials covering SSI risk, various antiseptic solutions were compared. The comparisons included basic hand hygiene (soap and water) and antiseptic alcohol rubs and aqueous scrubs. There was no firm evidence that any of these scrubs were superior to one another. For the trials covering CFU growth, some key findings included the evident superior ability of CHG to lower CFUs immediately after scrubbing, 2 h after initial scrub, and 2 h after subsequent scrub when compared to PI. Additionally, alcohol rubs with added ingredients may reduce CFUs when compared to aqueous scrubs.

There are a number of RCTs and reviews that have been conducted on preoperative surgical personnel scrub techniques. A systemic review of preoperative hand scrubbing protocols on skin integrity and SSI rates that included eight RCTs and two nonrandomized controlled studies (NRS) was performed [67] (1a). Of the trials reviewed,

two assessed SSI within 30 days of surgery. The first compared a traditional hand scrub of 7.5% PI or 4% CHG and water for 3–5 min prior to surgical procedures and a similar hand scrub technique prior to the first procedure followed by alcohol hand rub for subsequent procedures. The second study compared a 5-min hand scrub with 4% PI or 4% CHG and with an alcohol-based solution. The pooled analysis showed no statistical difference in SSI rate between the groups. Ultimately, alcohol rubs appear to be as effective as traditional scrub techniques, and they appear to have superior skin tolerability for operative personnel.

Hair Removal

Preoperative hair removal is commonly performed to increase surgical site visualization and decrease impairment of surgical technique. Various methods have been employed, but there is currently a lack of data to support the efficacy of this intervention and the degree to which each technique influences SSI risk. A Cochrane review of 14 trials assessing hair removal prior to surgery was performed in 2011 [68] (1a). The trials compared hair removal (shaving, clipping, or depilatory cream) with no hair removal as well as the use of depilatory cream and shaving, showing no statistical difference in SSI rates in any of the comparisons. Three trials found a greater SSI risk with shaving when compared to clipping, although the comparison was underpowered to detect a statistically significant difference. One trial compared individuals who either shaved or clipped their hair the day prior to surgery or the day of surgery. The trial found no statistically significant difference in SSI rate between the two groups. Another more recent meta-analysis showed similar findings with no difference in SSI rates between various hair removal methods [69] (1a). The authors of both studies conclude there is insufficient evidence to determine if one technique increases SSI risk over the other and if hair removal, in general, affects SSI rate. Given the available evidence, if it is necessary to remove hair, it seems prudent to gently clip hair with scissors or electric clippers rather than shave the area with a razor.

Electrocautery

It is well known that electrocautery creates necrosis and inflammation of treated skin. This alteration has been postulated as a cause of a suboptimal healing environment that potentially increases SSI. A study of the effect of electrocautery on MMS wound outcomes showed that excess use impaired wound healing (partial necrosis, dehiscence, or full necrosis), but an effect on SSI could not be concluded [12] (2b).

The use of electrocautery scalpel for skin incisions versus a cold scalpel has been assessed by a systematic review and meta-analysis of randomized controlled trials (RCTs). The study found no statistical difference in SSI between the two modalities. At the same time, the electrocautery scalpel was faster and patients experienced less postoperative pain [70] (1a).

A randomized, controlled, clinical pilot study in patients undergoing Caesarean sections evaluated the use of electrocautery for coagulation versus nonintervention and found similar rates of infection 7–10 days after the surgery (10% and 8.7%, respectively) [71] (1b). Of note, this study lacked statistical power to demonstrate significant statistical difference.

Surgical Instruments

In many clinical practices, when performing MMS, it is common to use one set of instruments for tumor extirpation and another set of sterile instruments for reconstruction. One prospective study of 338 subjects undergoing MMS used a single set of sterile instruments for both surgical phases and found an overall infection rate of 2.1%, which is in line with the reported average SSI rate for dermatologic surgery [72] (2b). Some limitations to the study included a lack of control group, and all skin grafts were treated

postoperatively with a 7-day course of antibiotics, which may have falsely decreased the true SSI incidence.

Wound Closure Materials

Antimicrobial sutures have been developed with the intent of inhibiting bacterial colonization and, ultimately, reducing SSI. A meta-analysis of patients undergoing primarily general, pediatric, vascular, and cardiac surgeries found that triclosan-coated polyglactin 910 sutures (Vicryl Plus) significantly reduced SSI when compared to regular polyglactin 910 sutures (Vicryl) [73] (1a). Other studies have failed to demonstrate a protective effect of these sutures after elective colorectal surgery and in head and neck reconstruction [74] (1a) [75] (2b).

Materials used for wound closure as well as closure technique and their effect on SSI have been evaluated by various surgical subspecialties with some implications for dermatologic surgery. A systemic review and meta-analysis of 13 studies comparing SSI incidence with staples versus sutures for skin closures after orthopedic surgery showed no significant difference in infection risk [76]. In contrast, another meta-analysis of RCTs that included primarily general, obstetric/gynecological, and head and neck operations (excluding orthopedic operations) found a statistically decreased risk of SSI with staple versus suture closure [77] (1a).

2-Octyl-cyanoacrylate is a commonly used adhesive for rapid, simple closure of surgical wounds. In a prospective randomized clinical trial comparing 2-octyl-cyanoacrylate to subcuticular suture closure for maxillofacial wounds, there was no significant difference in wound complications or patient satisfaction [78] (2b). The time for closure was also significantly less for 2-octyl-cyanoacrylate. Another cohort study of individuals undergoing spinal surgery was performed comparing 2-octyl-cyanoacrylate versus staples for wound closure, which demonstrated a statistically significant decreased risk of SSI in the 2-octyl-cyanoacrylate group [79] (2b). The authors also conclude that use of 2-octyl-cyanoacrylate is more cost effective and requires less time to perform.

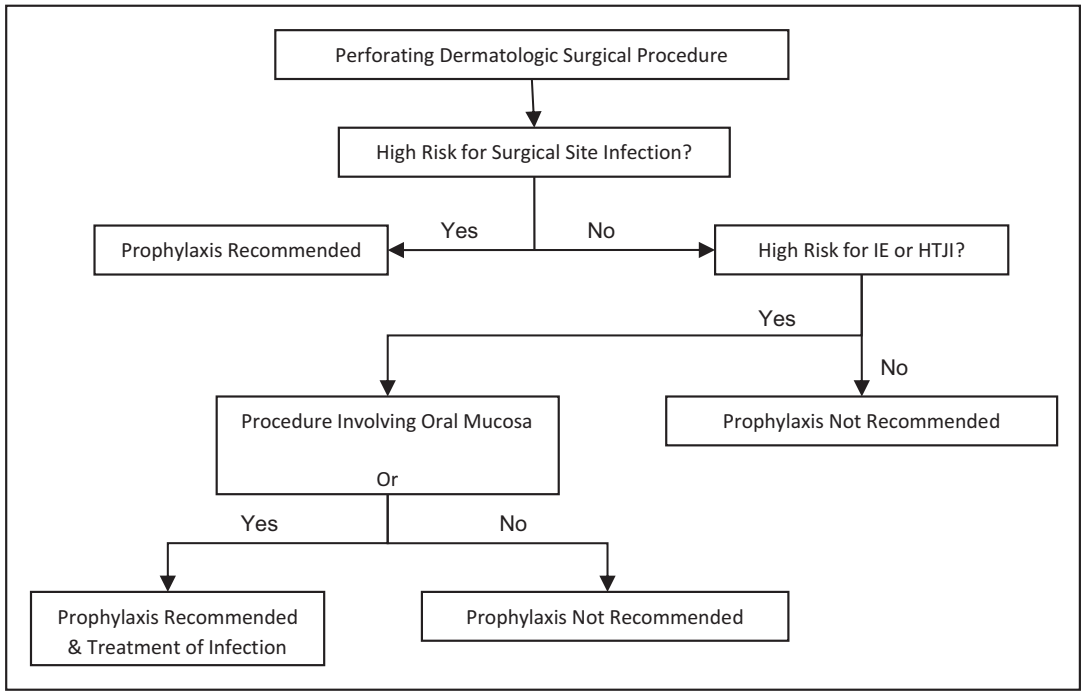
The use of simple interrupted and running epidermal closure are both commonly performed in dermatologic surgery. A Cochrane review that included five RCTs assessing the benefits and harms of continuous running suture versus single interrupted suture closure in nonobstetric surgery found no statistical difference in SSI between the two techniques, but a lower risk of dehiscence was noted with running subcuticular sutures [80] (1a).

Prophylactic Antibiotics

Antibiotic prophylaxis in dermatologic surgery remains controversial, and our current understanding relies primarily upon expert consensus and extrapolation of data from other specialties due to the lack of RCTs in dermatologic procedures. The incidence of bacteremia in immunocompetent individuals undergoing dermatologic surgery on non-infected skin is <1% [81] (2b). The 2008 dermatologic surgery antibiotic prophylaxis advisory statement provides direction on the indications for prophylactic antibiotic use and reflects guidelines given by the American Heart Association, the American Dental Association, and the American Academy of Orthopaedic Surgeons [82] (5). These recommendations are based on preventing hematogenous total joint infection (HTJI), infective endocarditis (IE), and SSI prevention of specific high-risk sites and/or procedures (Table 63.1.). The algorithm has recently undergone a small update from the original 2008 statement within the Mayo Clinic dermatologic surgery division to remove levofloxacin as an alternative treatment for prophylaxis for surgery done on the lower extremity. The change was made after the US Food and Drug Administration (FDA) increased warnings in 2016 regarding permanent adverse events related to the use of fluoroquinolone antibiotics.

Performing dermatologic surgery without the use of prophylactic antibiotics has the benefit of decreasing healthcare costs, avoiding the emergence multidrug-resistant bacterial clones, and eliminates the possibility of allergic drug reac-

Table 63.1 Recommendations for antibiotic prophylaxis in dermatologic surgery



IE = Infective Endocarditis, HTJI = Hematogenous Total Joint Infection

***IE* infective endocarditis, *HTJI* hematogenous total joint infection**

tions. One study evaluating 1,000 patients with 1,204 lesions demonstrated an infection rate of 0.91%, using only clean surgical technique (without oral antibiotic use) for all steps of MMS including wound reconstruction [83] (2b). There were no infections with skin grafts, wedges of the lips or ears, or wounds healing by second intent. Primary closure showed an infection rate of 0.78%, and for skin flaps, which have been known to be at an elevated risk for infection, the rate was 2.67%.

One RCT was performed evaluating the effect of preoperative oral antibiotics versus topical decolonization measures in patients with positive nasal cultures for *S. aureus* undergoing MMS [84] (1b). Patients were separated into two groups: swab negative (no *S. aureus*) and swab positive (presence of *S. aureus*). They were subsequently randomized into two cohorts: one receiving topical nasal mupirocin and 4% CHG body wash to be used for 5 days preoperatively and the other receiving 2 g of cephalexin 30–60 min prior to surgery and 1 g 6 hours after surgery. The results showed a disproportionate infection rate in cases receiving oral antibiotics compared to the topical regimen (9% versus 0%, respectively), and the study was prematurely terminated based on ethical grounds.

The optimal application of prophylactic antibiotics in dermatologic procedures is influenced by multiple factors and is an opportunity for well-designed, prospective research. The current guidelines (with a few minor modifications) set out by the 2008 advisory statement aim to mitigate HTJI, IE, and SSI of specific high-risk sites. There is some evidence suggesting that antibiotic prophylaxis for some high-risk indications and procedures, such as site (lower extremity) and type of closure (skin graft, skin flap and wedge closure), may not be always necessary [83] (2b). The evidence also suggests that topical mupirocin may be preferable to oral cephalexin for preoperative decolonization in patients with *S. aureus* nasal carriage.

Finding ways to mitigate the risk of SSI in patients undergoing cutaneous surgery is of paramount importance. Preoperative antibiotics have important value, but their use also exposes the patient to potential health consequences to include multidrug-resistant bacteria, drug reactions, and disruption to the patient's gut microbiome [85] (2a). To illustrate this point over 140,000 annual visits to the emergency room in the United States are attributable to adverse effects from antibiotics [86] (2c). The strong emergence of MRSA can be partially attributable to antibiotic overuse, with estimated costs to the US healthcare system ranging from $478 million to 2.2 billion dollars every year [87] (2c). Moreover, the dreaded complication of *Clostridium difficile* colitis, commonly caused by clindamycin and second- and third-generation cephalosporins, is on the rise [88] (2c). These circumstances highlight the need for judicious and responsible application of antibiotics in dermatologic surgery.

Intraincisional Antibiotics

Huether and colleagues described a unique approach to reduce SSI by using intraincisional clindamycin mixed with an injectable lidocaine-based anesthetic preparation [89] (1b). They performed a prospective, blinded, placebo-controlled study of 1030 subjects undergoing MMS comparing an anesthetic solution containing clindamycin to standard local anesthetic. The results showed a statistically significant reduction in SSI rate with the clindamycin containing solution (0.2%) compared to standard local anesthetic (2.5%). There were no allergic reactions in either group. Four patients experienced nausea in the clindamycin group, and no diarrhea occurred in either group. The same authors performed another study using intraincisional nafcillin [90] (1b), but given the high rate of stated penicillin allergy, injectable clindamycin was found to be a more suitable alternative with similar reduction in SSI rate. The authors conclude that intraincisional antibiotics decrease systemic exposure to the medication, provide immediate delivery to the surgical site, and are relatively less expensive compared to oral antibiotics.

Enhanced Infection Control Practices

Despite the already published low infection and complication rates of MMS, one study performed showed heightened infection control practices could lower the rate even further [91] (2b). This study demonstrated an infection rate of 2.5% using a standard sterile surgical tray setup and chloroxylenol 3% surgical patient prep. When the infection control practices were introduced, this rate dropped to 0.9%. The interventions included adding surgical caps and hair containment, use of sterile towels, limitations on jewelry, use of sterile gloves during Mohs stages, changes to patient antiseptic and surgeon hand rubs, and use of surgical gowns. The cost of these measures equaled $10.76 per case and in a practice performing approximately 1,000 cases a year added up to a cost of $10,760. Based on the percent reduction in SSI, this would cost the practice $672.50 to prevent one infection. The authors make the point, in their particular situation, that these measures may be cost effective when considering the physician time in managing the infection and the associated costs of wound cultures and antibiotics. A follow-up on analysis to this study was performed by one of the coauthors showing infection-control costs could be reduced by eliminating sterile gloves during Mohs stages and sterile gowns and half-sheet drapes during reconstruction [92] (2b). These changes did not demonstrate a significant change in the SSI but reduced the infection control cost from $678.75 to a more cost-effective $136.67 per infection.

Managing Postoperative Wound Infections

There are a number of general principles regarding the use of wound care and therapeutic antibiotics when dealing with postoperative wound

infections. Most interventions are based on dogmatic principles from other surgical specialties with minimal evidence from RCTs.

Topical Antibiotics

The use of topical ointments after dermatologic procedures is a common, highly accepted practice. A systematic review and meta-analysis of topical antibiotics used in dermatologic surgery of four different trials did not show a statistically significant difference in postoperative surgical wounds between topical antibiotics and topical petrolatum/paraffin with the ultimate conclusion that topical antibiotics should not be used as prophylaxis in dermatologic surgery [93] (1a). There is also a lower risk of contact dermatitis when using white petrolatum compared to bacitracin [94] (2b).

An RCT compared the SSI rate of no ointment, paraffin ointment, and mupirocin ointment to sutured wounds prior to application of wound dressings [95] (1b). The respective infection rates between the groups (1.4%, 1.6%, and 2.3%) were not statistically different. Moreover, there was no variation in postoperative pain, wound perception, or patient satisfaction with either intervention.

Topical application of acetic acid has long been advocated as a way to reduce *P. aeruginosa* colonization on superficial burn wounds [96]. The efficacy of 1% acetic acid compared to normal saline on the treatment of burn and other chronic wounds infected with *P. aeruginosa* was determined, showing the use of acetic acid eliminated *P. aeruginosa* on average 7 days faster than the saline group [97] (1b). There was no evidence to show that this sped up the wound healing or improved patient comfort.

Wounds on the ear are commonly encountered in dermatologic surgery, and second intent wound healing is frequently utilized. The uses of topical or oral antibiotics are often advocated given the elevated risk of inflammatory chondritis and suppurative chondritis with a variety of organisms, most prominently *P. aeruginosa* [4] (2b). A prospective study of 142 patients undergoing MMS was performed comparing wounds treated with gentamicin ointment or petrolatum ointment showing no statistical difference in the prevention of postoperative auricular suppurative chondritis [98] (2b). The study was not powered statistically to show a difference in inflammatory chondritis, but there were a disproportionate number of patients affected in the gentamicin group compared to petrolatum (11.90% versus 3.33%, respectively). This study suggests that gentamicin ointment shows no benefit for ear wounds healing by second intent and may potentially increase the risk of inflammatory chondritis. Gentamicin may also be a source of allergic contact dermatitis [99], which could further compromise wound healing.

Systemic Antibiotics

Empiric treatment of dermatologic SSI should be based on clinical suspicion and community sensitivity patterns. Microorganisms causing cutaneous abscesses are often related to more virulent strains of MRSA [100] (2a). Microorganisms related to dermatologic SSI, on the other hand, are often derived from endogenous strains of bacteria [42] (1b), which may or may not originate from virulent strains of *S. aureus*. Therefore, the recommendations for abscesses cannot be completely applied to the treatment of all dermatologic surgical wounds. For treatment of an SSI in communities with low risk for MRSA, empiric treatment for methicillin-sensitive *S. aureus* (MSSA) with a first-generation cephalosporin such as cefadroxil or cephalexin is reasonable. When MRSA is the likely etiology, guidelines have been established by the CDC and Infectious Diseases Society of America (IDSA) for antibiotic treatment of cutaneous abscesses [101] (1a), which include clindamycin, tetracycline (doxycycline, minocycline), and trimethoprim-sulfamethoxazole (TMP-SMX). Empiric use of these antibiotic choices would be the same for dermatologic SSI in cases with high suspicion for MRSA. Linezolid can be considered if the above antibiotics fail and the CDC recom-

mends it be administered in conjunction with infectious disease consultation. For simple abscesses, the IDSA recommends treatment with incision and drainage alone (without antibiotics). Many uncomplicated wound infections on the trunk or extremities that develop after dermatologic surgery fall into this category and will respond to drainage and removal of sutures alone. Conversely, concomitant antibiotic therapy and incision and drainage should be considered in patients with wounds of the head and neck and those with associated comorbidities to include extremes of age and immunosuppression [101] (1a).

The duration of antibiotic treatment after SSI has been debated. A randomized noninferiority trial was performed assessing the duration of treatment with TMP-SMX after surgical drainage of uncomplicated skin abscesses in pediatric patients [102] (2b). The patients were randomized to either 3- or 10-day courses. Among the individuals with positive cultures, 87% grew *S. aureus* (55% MRSA). Patients receiving 3-day courses showed a 10.7% higher recurrence rate when compared to 10-day courses if the patient was infected with MRSA. There was no difference between the groups when the patients were infected with MSSA. When other potential confounders were resolved, there was almost a sixfold greater risk of recurrent infection in the 3-day group when compared to 10-day group. The authors suggest the option of giving patients a 3-day supply of TMP-SMX (to limit longer term exposure to antibiotics) for all patients and adding an additional 7-day supply if their cultures grow MRSA. This is a reasonable option but may be logistically difficult to coordinate.

Initial choice of empiric antibiotic therapy after SSI is often made based on physician preference and local sensitivities. A randomized, double-blind, superiority trial at five US emergency departments was conducted evaluating clindamycin versus TMP-SMX for uncomplicated wound infections primarily caused by MRSA or MSSA [103] (1b). Both antibiotics had similar cure rates for the infections; however, there was a significantly lower rate of recurrence in the clindamycin group when compared to TMX-SMP at 7–14 days (1.5% vs. 6.6%) and 6–8 weeks (2.0% vs. 7.1%).

Excellent clinical judgment, antibiotic stewardship, and adherence to prescribing guidelines for dermatologic SSI are imperative to avoid the emergence of multidrug-resistant bacterial clones and patient complications. The temptation to prescribe empiric postoperative antibiotics for noninfected wounds without evidence-based SSI risk factors should be resisted and is not a sustainable practice.

Wound Packing

Packing of wounds is a common practice in many surgical fields, but there is currently no evidence to support its benefit over second intent healing without packing. A Cochrane review on the use of wound cavity packing after perianal abscess drainage was performed. The review concluded there is insufficient evidence this practice decreased healing time, pain, development of fistulae, or recurrence of abscesses [104] (1a). Furthermore, packing and repacking of a wound may lead to excess cost and time expenditures and potentially increase patient discomfort. Given the limited depth and size of most dermatologic surgical defects, the utility of wound packing is uncertain.

Postoperative Care

Wound Dressings

Application of wound dressings is a dogmatic part of the postoperative phase of surgical site care. A Cochrane review that included 11 studies evaluated the use of antiseptic and topical antibiotics for wounds healing by second intention [105] (1a). The review concluded that no high-quality RCT has adequately answered the question, but there was some low- and moderate-quality evidence that a few interventions relevant to dermatologic surgery may provide some benefit. These include the following: (1) sucralfate cream increased wound healing after hemorrhoidectomy when compared to petrolatum [106] (2b), (2) honey-soaked gauze decreased healing times after abscess excision compared to stan-

dard gauze [107] (2b), and (3) Dermacyn (a superoxidized disinfectant solution) increased postoperative wound healing in diabetic foot ulcers when compared to iodine [108] (2b). These options may be considered in wounds healing by second intent or as post-treatment skin care after resurfacing procedures.

A systemic review and meta-analysis that included 20 RCTs evaluating the impact of various dressings on the infection rate of surgical wounds closed by a primary repair found no clear evidence that any particular dressing offered a clear advantage over others in regard to SSI incidence [109] (1a). Similarly, another systemic review and meta-analysis found no difference in SSI between various dressing types and also showed no increased risk of infection in exposed surgical wounds [110] (1a). Despite these findings, properties such as containment of odor and/or exudate as well as autolytic ability and patient comfort offered by the various wound dressings may still offer advantages in the postoperative phase of wound healing.

The current guidelines given by the CDC recommend that postoperative surgical wounds be covered for 24–48 h after surgery [111] (5). A review was performed evaluating early (<48 h) versus delayed (>48 h) dressing removal after primary closure of clean and contaminated surgical wounds [112] (1a). The review concluded there was no difference in serious adverse events, to include SSI, between the two dressing removal times.

Negative-pressure wound therapy (NPWT) has been advocated as an intervention for nonhealing pressure ulcers and other chronic wounds. A Cochrane review found no rigorous RCT evidence that NPWT offers any benefit over standard wound care in the treatment of pressure ulcers [113] (1b).

Special Situations

Laser Resurfacing

Laser resurfacing and other resurfacing procedures are common in the United States, but there is currently no set standard for patients regarding antiviral, antibiotic, and antifungal prophylaxis.

Of the three methods of prophylaxis, the use of antibiotics is most in question. One retrospective study of 133 patients comparing the use of a variety of prophylactic antibiotic regimens to no prophylaxis in individuals undergoing CO_2 laser resurfacing showed an infection rate of 24% versus 0%, respectively [114] (2b). Surprisingly, the group with the highest infection rate was exposed to the longest courses of antibiotics, which consisted of intraoperative cephalexin and postoperative azithromycin for 5 days.

Another retrospective study analyzed infection rates in 395 patients undergoing laser resurfacing for facial rhytides [115] (2b). The study found an overall infection rate of 4.3% with over half of patients demonstrating microorganisms similar to what is commonly found on burn patients, which included *P. aeruginosa*, *S. aureus,* and *Staphylococcus epidermidis.* All study patients were given oral preoperative antibiotics, and interestingly, when in addition to the standard antibiotic regimen (250 mg/d of azithromycin for 7 days), the application of an occlusive dressing and the use of topical prophylaxis (intranasal mupirocin and gentamicin sulfate otic solution) were employed, the infection rate increased seven-fold from 1.35% to 9.82%.

One study compared prophylactic ciprofloxacin and mupirocin antibiotic regimens to no prophylaxis [116] (2b). Those receiving ciprofloxacin had a post-treatment bacterial infection rate of 4.3% compared to 8.2% in those without prophylaxis. The study also demonstrated only those using intranasal mupirocin went on to develop *S. aureus* infections. Despite some evidence that prophylactic ciprofloxacin may decrease post-treatment infections, its routine use should not be uniformly recommended given the knowledge of potential serious adverse effects.

The use of antifungal prophylaxis has been advocated by some in patients undergoing full-face laser resurfacing (FFLR) procedures. One study showed that fluconazole significantly increased re-epithelialization and decreased healing time after facial resurfacing [117] (2b). Another study compared oral ketoconazole and fluconazole prophylaxis to no prophylaxis demonstrating zero yeast infections in the prophylaxis group and 6/356 patients (1.7%) developing

yeast infections in those without prophylaxis [116] (2b). Given the demonstrated low risk of yeast infections in those undergoing FFLR, the use of antifungals for the prevention of yeast infections may not be necessary, and, even though there is accelerated healing with fluconazole, it is uncertain if use of the medication has any long-term cosmetic consequences.

Reactivation of herpes simplex virus-1 (HSV-1) can be a devastating complication for individuals undergoing FFLR and prophylactic use of antiviral medications has been strongly encouraged. One study evaluating antiviral prophylaxis with famciclovir 125 mg–250 mg twice daily starting 1–2 days prior to laser resurfacing and continued for 5 days afterward compared to no prophylaxis showed a reactivation rate of 1.1% and 9.4%, respectively [118] (2b). Another study assessing valacyclovir 10- or 14-day regimens showed no difference HSV-1 reactivation in either group [119] (2b). Another randomized study showed no difference in reactivation in patients given valacyclovir either the day before or the day of the resurfacing procedure [120] (1b). Another prospective study evaluated the difference in HSV reactivation between using famciclovir 250 mg and 500 mg twice daily prior to FFLR [121] (2b). They noted a higher incidence of reactivation in those with a clinical history of herpes labialis (33.3%) compared to those without a clinical history (5%). The authors emphasize the importance of eliciting a clinical history of herpes labialis in those undergoing resurfacing procedures and recommend a prophylactic dose of 500 mg twice daily in those with a strong history and 250 mg twice daily in those without a history of herpes labialis.

In conclusion, many questions remain regarding the optimal prophylaxis regimen for those undergoing FFLR. The use of antiviral prophylaxis is a low-risk and accepted technique and should be highly considered for all patients. The evidence suggests the use of prophylactic antibiotics may increase risk for infection by selecting out and tipping the balance away normal skin flora toward organisms more resistant to antibiotics [114] (2b). Antifungal prophylaxis should not be routinely recommended given the already low risk for fungal infection with resurfacing procedures. Ultimately, responsible use of antimicrobial medications, employment of meticulous technique, thorough wound care, and close patient observation should be the focus of the laser surgeon.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Summary of the prevention and treatment of procedural-related infections
Risk factors for surgical wound infection
Surgical sites with ulceration, purulence, and/or inflammation have a higher risk of SSI (B)
Surgical sites of the groin and below the knee have higher infection rates compared to other areas (B)
Skin flaps, skin grafts, wedge excisions of the ear and lip, wounds >11 mm in size, and procedures >24 min are at increased risk for wound infection (B)
Surgical site infection rates increase with every decade of life after the age of 40 and severe infections are more common over the age of 70 (B)
Laboratory values, patient behavioral factors, and medical risk factors
Warfarin and other antiplatelet and anticoagulant medications have no impact on wound infection rates (A)
Diabetics have an increased risk of surgical site infection (A)
Evidence suggests smoking is associated with an increased risk of SSI (B)
Preoperative interventions
Preoperative body wash with chlorhexidine and bathing with bar soap are associated with equivalent SSI (A)
Benzoyl peroxide 10% gel applied to the centrofacial area may decrease SSI if used around the surgical site 7 days prior to surgery (C)
The use of preoperative intranasal mupirocin in patients with *S. aureus* nasal carriage decreases postoperative infection rate (A)
Intranasal mupirocin is superior to oral cephalexin when decolonizing patients with intranasal *S. aureus* prior to surgery (B)

Summary of the prevention and treatment of procedural-related infections
Surgical attire
Face masks do not influence SSI rate (A)
Surgical head coverings, gowns, dedicated theater shoes, and shoe covers do not influence SSI risk (B)
Wearing of finger rings and nail polish increases wound infection risk (D)
Intraoperative interventions
Adhesive drapes increase the rate of bacterial recolonization of surgical fields compared to no drapes (B)
Reusable woven drapes have a higher wound infection rate compared to disposable draping systems (B)
Use of impermeable drapes results in lower bacterial counts in the surgical field than permeable linen drapes (B)
Clean, nonsterile gloves may be used for laceration repair and tumor extirpation of Mohs surgery, including reconstruction, with no difference in infection rate (A)
Chlorhexidine isopropyl alcohol solution is superior to povidone iodine scrub in reducing SSI rates (B)
Chlorhexidine 0.5% in methylated spirits has a reduced risk of SSI compared with an alcohol-based povidone iodine solution (B)
Preoperative surgical personnel scrub with traditional chlorhexidine and povidone iodine shows similar abilities in reducing infection rates (A)
Chlorhexidine surgical scrub demonstrates residual activity to lower bacterial CFU beyond the time of application (A)
Alcohol-based rubs are as effective as traditional povidone iodine and chlorhexidine aqueous hand scrubs in preventing surgical site infection (A)
There is no evidence that hair removal decreases SSI (A)
If hair removal is necessary, it is prudent to clip the hair with scissors or an electric razor (A)
There is currently no evidence to suggest that the use of electrocautery increases SSI rate (C)
Use of a single set of instruments for tumor extirpation with Mohs micrographic surgery and reconstruction does not increase the overall infection rate (B)
Use of triclosan-coated polyglactin 910 sutures reduces SSI compared to regular polyglactin 910 sutures (B)
Staple skin closure has a lower SSI risk when compared to a sutured wound closure (B)
2-Octyl-cyanoacrylate has a decreased risk of surgical site infection compared to staple closure (B)
Subcuticular skin closure and interrupted suture closure have similar surgical site infection risks (A)
Prophylactic antibiotics should be given when there is a risk of hematogenous joint infection or infective endocarditis (A)
Skin grafts, wedges of the lips or ears, and skin flaps have a low infection rate and may not require prophylactic antibiotics (B)
Intraincisional administration of clindamycin or nafcillin mixed with an anesthetic solution decreases surgical site infection risk (B)
Postoperative interventions
White petrolatum ointment is recommended over topical antibiotics for clean and clean contaminated wounds
Early bathing (<48 h) and delayed bathing (>48 h) after minor skin surgery have no effect on SSI (A)
The use of ointment on sutured wounds shows no reduction in wound infection compared to no ointment (B)
The use of gentamicin ointment for ear wounds does not decrease SSI and may increase the risk of inflammatory chondritis and allergic contact dermatitis (B)
Packing of surgical wound abscesses does not reduce rate of recurrence or decrease healing time (C)
Short 3-day courses of antibiotics are preferable over longer 10-day courses unless the wound is infected with MRSA (B)
There is no clear evidence that one wound dressing is superior to another in reducing infection rates (A)
There is no difference in infection rates for early (<48 h) versus delayed (>48 h) dressing removal (A)
Negative-pressure wound therapy offers no benefit over standard wound care in the treatment of chronic wounds (B)
Antiviral prophylaxis should be given to all patients undergoing ablative fractionated facial laser resurfacing (A)
Prophylactic systemic and/or topical antibiotics may increase the risk for infection in patients undergoing laser resurfacing procedures(B)

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Self-Assessment Questions

1. Which one of the following preoperative interventions has been shown to decrease surgical site infection (SSI)?
   (a) Surgical face mask
   (b) Waiting to bathe 48 h after surgery
   (c) Intranasal mupirocin
   (d) Bleach baths

2. Which intervention has been shown to prevent postoperative wound infections?
   (a) Iodoform packing strip for deep wounds allowed to heal by second intent
   (b) Intraoperative injectable mixed lidocaine and clindamycin solution.
   (c) Dedicated operating room footwear
   (d) Gentamicin ointment for wounds on the ear with exposed cartilage

3. What statement best explains the current recommendations for prophylaxis prior to full-face laser resurfacing?
   (a) Treatment with prophylactic antibiotics, antiviral agents, and antifungal agents are recommended for the majority of patients
   (b) Postoperative intranasal mupirocin, gentamicin otic solution, and an occlusive dressing decrease post-treatment infection risk
   (c) Ciprofloxacin is the antibiotic of choice for prophylaxis
   (d) Prophylactic antibiotics should be discouraged

4. What statement best explains the current recommendations for hair removal prior to dermatologic surgery?
   (a) Shave the area with a razor the day of surgery
   (b) Use a depilatory cream the day before surgery
   (c) Clip the area with scissors or an electric razor just prior to surgery
   (d) Hair removal should never be attempted prior to surgery

5. A patient is undergoing preoperative workup for Mohs surgery. What factor is true in regard to surgical site infection risk?
   (a) Surgical site infection risk increases with every decade of life
   (b) Men are at a statistically higher risk for wound infection compared to women
   (c) Use of warfarin has been shown to increase dermatologic surgery infection risk
   (d) Skin flaps and elliptical excisions have approximately equivalent infection rates
   (e) Duration of surgery has shown no impact on surgical site infection rate

Answers

1. c: Intranasal mupirocin. The use of intranasal mupirocin in patients with *S. aureus* nasal carriage decreases postoperative infection rate and is superior to oral cephalexin when decolonizing patients with intranasal *S. aureus* prior to surgery.
2. b: Intraoperative injectable lidocaine and clindamycin solution. Intraoperative clindamycin anesthetic solution has been shown to significantly reduce the surgical site infection rate with minimal side effects and low cost
3. d: Prophylactic antibiotics should be discouraged. Prophylactic antibiotics have shown no benefit in reducing postprocedure infection risk, and in many instances, they increase the risk of bacterial infection. Likewise, their use carries the risk of antibiotic resistance and allergic reactions. The use of antiviral prophylaxis is a low-risk and accepted technique and should be highly considered for all patients undergoing resurfacing procedures.
4. c: Clip the area with scissors or an electric razor just prior to surgery. There is currently insufficient evidence to determine if one technique of hair removal is superior to another. Hair removal should be done only if it hinders proper surgical technique or surgical field visualization. It is generally accepted that hair should be gently clipped hair with scissors or electric clippers rather than shave the area with a razor.
5. a: Surgical site infection risk increases with every decade of life. Surgical site infection rate increases with every decade of life after the age of 40, and severe infections after dermatologic surgery were more common over the age of 70. This increase may be related to the decline in the innate and adaptive immune systems seen with age.

64 Prevention and Treatment of Bleeding Complications in Dermatologic Surgery

Bryan Sofen and Isaac Neuhaus

Abstract

In general, the rate of complications in dermatologic surgery is extremely low. A single-center prospective analysis of 1343 cases of Mohs micrographic surgery (MMS) reported an overall complication rate of 1.6% (22/1,343 cases), including wound infection, postoperative hemorrhage, hematoma, wound dehiscence, and flap or graft necrosis (Cook JL, Perone JB. Arch Dermatol 139(2):143–52, 2003) [4]. A recent multicenter, prospective study of 23 centers revealed an even lower complication rate of 0.72% (149/20,821 cases) (Alam M, Ibrahim O, Nodzenski M, Strasswimmer JM, Jiang SI, Cohen JL, et al. JAMA Dermatol 149(12):1378–85, 2013) [2a]. This chapter reviews the available evidence regarding the prevention of bleeding complications of cutaneous surgery. Information regarding treatment options after the bleeding has occurred is discussed elsewhere. Although much of the data will be generated from the collective dermatologic experience with Mohs micrographic surgery, the conclusions drawn will be applicable to standard excisional surgery, as well as other common procedures of the dermatologist and dermatologic surgeon. Not only is perioperative bleeding the most common complication associated with cutaneous surgery, but it is also the subject for which the most robust evidence exists. The decision as to whether or not to discontinue anti-coagulation is important as it is estimated that 35–38% of patients undergoing cutaneous surgery are taking an antithrombotic agent (Callahan S, Goldsberry A, Kim G, Yoo S. Dermatol Surg 38(9):1417–26, 2012) [3a]. It is additionally important to note that complications involving dehiscence, necrosis, poor wound healing, and infection often occur after difficulties with hemostasis.

Keywords

Bleeding · Hematoma · Anticoagulants
Surgery · Complication

Introduction

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hemorrhage, hematoma, wound dehiscence, and flap or graft necrosis [1] [4]. A recent multicenter, prospective study of 23 centers revealed an even lower complication rate of 0.72% (149/20,821 cases) [2] [2a]. This chapter reviews the available evidence regarding the prevention of bleeding complications of cutaneous surgery. Information regarding treatment options after the bleeding has occurred is discussed elsewhere. Although much of the data will be generated from the collective dermatologic experience with Mohs micrographic surgery, the conclusions drawn will be applicable to standard excisional surgery as well as other common procedures of the dermatologist and dermatologic surgeon. Not only is perioperative bleeding the most common complication associated with cutaneous surgery, but it is also the subject for which the most robust evidence exists. The decision as to whether or not to discontinue anticoagulation is important as it is estimated that 35–38% of patients undergoing cutaneous surgery are taking an antithrombotic agent [3] [3a]. It is additionally important to note that complications involving dehiscence, necrosis, poor wound healing, and infection often occur after difficulties with hemostasis.

Consensus Documents

A review of the websites of the American Academy of Dermatology (AAD), the American Society for Dermatologic Surgery (ASDS), the American College of Mohs Surgery (ACMS), and the Association of Professors of Dermatology (APD) reveals no published consensus documents regarding complications in dermatologic surgery. Similarly there are no relevant documents published by Cochrane.

Bleeding

The first step in the prevention of bleeding complications occurs through preoperative assessment of an individual patient's risk. A complete and directed preoperative history is the first step in assessing potential risk for bleeding in a patient undergoing a dermatologic surgery procedure. Common medical problems such as hypertension and anxiety can contribute significantly to bleeding, especially intraoperatively, and every effort should be made to adequately manage these medical problems in the pre- and perioperative periods. History taking should also include medical conditions that can contribute to altered platelet function and coagulation. This includes, but is not limited to, liver disease, renal dysfunction, and both hematologic and solid malignancies. For example, one paper reported a case of disseminated intravascular coagulation and persistent postoperative bleeding in a patient with metastatic prostate cancer unmasked by Mohs micrographic surgery for a relatively small basal cell carcinoma on the forehead [4] [5]. In another case, persistent postoperative bleeding unmasked an extremely rare form of acquired autoimmune hemophilia A, with autoantibodies targeting factor VIII [5] [4]. Poor nutritional status must also be considered a risk factor for excessive bleeding. This is especially relevant in the elderly population, the most common group of patients undergoing surgery for cutaneous malignancy. Many mild forms of bleeding disorders go undiagnosed, so clinicians should specifically assess for any prior history of significant bleeding during low-risk surgical procedures (i.e., dental extractions), episodes of epistaxis, menorrhagia, or extensive bruising. Though a patient's description of prior operative bleeding is often very subjective, a previous history of excessive bleeding in this setting may indicate an inherited bleeding disorder such as hemophilia or von Willebrand disease, the most common hereditary bleeding disorder. Peterson and Joseph have provided an excellent review on inherited bleeding disorders in dermatologic surgery patients [6] [5], as have Bunick and Aasi [7] [3a]. Both reviews emphasize the importance of working in conjunction with an experienced hematologist when dealing with this patient population.

Much more common than inherited bleeding disorders are acquired abnormalities in coagulation or platelet function secondary to medications and ingested products. It is well known that ethanol consumption contributes to bleeding via

decreased vasoconstriction and impaired platelet and coagulation function [8] [5]. Though this effect is difficult to quantify, patients who routinely consume alcoholic beverages may be advised to abstain for several days before and after cutaneous surgery. Alternative medicines and therapies may also effect bleeding, and the use of such modalities has dramatically increased in recent years. A 2007 National Health Interview Survey found that four out of ten adults had used some form of complementary alternative medicine during the past years [9] [4]. Another report found that 22% of presurgical patients take various herbs and 51% consume vitamin supplements [10] [5]. Looking at MMS patients specifically, Collins and Dufresne reported in a 2002 study that 49% of MMS patients were actively taking dietary supplements [11] [4]. Vitamins and herbal supplements are also often overlooked in the preoperative history. Patients frequently do not readily reveal their alternative medications to their physicians, and physicians frequently do not specifically ask patients. One report found that over 35% of patients on alternative therapies did not inform their doctor during the medical history [12] [3b]. In the report by Collins and Dufresne, of those patients taking dietary supplements, 65% neglected to report them on preoperative questionnaires [11] [4]. Similar results are seen in the anesthesiology literature, with one study showing that 89% of patients consuming herbal plant products did not consider them to be a medication and that 91% would not have told an anesthesiologist about them on routine interview [13] [5]. Dinehart and Henry published an excellent comprehensive review on dietary supplements and altered bleeding and coagulation [14] [1]. They report that many dietary supplements can alter coagulation and platelet function, with many effects on platelets being irreversible. Therefore, the recommendation is for patients to stay off all vitamins and supplements for 7–10 days prior to surgery. The exceptions are vitamin E and ginkgo, which can be discontinued several days prior to surgery [14] [4]. Nonetheless, for the sake of simplicity, the authors typically advise patients to discontinue all of their supplements and herbals for the full 7–10 days.

While most patients can easily discontinue their alternative therapies or alcohol consumption in the perioperative period, discontinuation of nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulant and antiplatelet medications such as warfarin and aspirin is a much more complex issue that continues to be debated among dermatologic and other surgeons. A large percentage of patients are on NSAIDs for musculoskeletal aches and pains as well as other chronic inflammatory conditions. A significant proportion of the US population takes aspirin for primary prevention of cardiac and cerebrovascular events, with primary prevention being defined as treatment aimed at preventing vascular events in patients who currently have no evidence of vascular disease. Furthermore, a variety of anticoagulants and blood-thinning agents are currently utilized in patients as secondary prevention for thromboembolic events. Secondary preventative efforts focus on identifying and treating those with established disease or those at very high risk for developing thromboembolic disease. Common indications for secondary prevention include patients with artificial heart valves or valvular heart disease, history of stroke or myocardial infarction, atrial fibrillation, underlying coagulopathies, and a history of pulmonary embolism and/or deep venous thrombosis (DVT) [15] [5].

Table 64.1 summarizes the currently utilized antiplatelet and antithrombotic agents, with brief explanations of their mechanisms of action [15] [5]. It is important to note that the various anticoagulants act at different levels in the process of coagulation and are therefore theoretically predicted to result in problems at different times in the perioperative period. Antiplatelet agents such as aspirin interfere with primary hemostasis: platelet aggregation and activation at the site of blood vessel injury. These agents are therefore predicted to cause more difficulty in the initiation of hemostasis intraoperatively. This is distinct from that which might be expected from warfarin, which interferes with secondary hemostasis, the enzymatic activity of coagulation factors that leads to the formation of a fibrin clot. These agents might therefore be expected to cause more

Table 64.1 Blood-thinning agents and their mechanisms of action

Class	Subclass/mechanism	Chemical (brand) name
Antiplatelet	Block formation of thromboxane A2 via inhibition of cyclooxygenase	Aspirin
		Ticlopidine hydrochloride (Ticlid)
	Inhibitors of ADP-induced activation of platelets	Clopidogrel (Plavix)
	Glycoprotein IIb/IIIa inhibitors (block platelet adhesion)	Abciximab (Reopro)
		Eptifibatide (Integrilin)
		Tirofiban hydrochloride (Aggrastat)
Antithrombin	Unfractionated heparin (binds antithrombin III and rapidly inactivates coagulation enzymes)	Heparin
		Hirudin (Refludan)
	Direct thrombin inhibitors	Agatroban (Novastan)
		Dabigatran (Pradaxa)
	Low molecular weight heparins (similar mechanism to unfractionated heparin)	Enoxaparin sodium (Lovenox)
	Factor Xa Inhibitor	Rivaroxaban (Xarelto)
		Apixiban (Eliquis)
	Coumarins (antagonists of vitamin K which decrease vitamin K dependent clotting factors II, VII, IX, X, and protein C and S)	Warfarin (Coumadin)
Thrombolytic	Plasminogen activators (activate plasminogen and hence cause fibrinolysis)	Streptokinase (Streptase)
		Alteplase (tPA)

Adapted from Alam and Goldberg [44]

problems postoperatively since they handicap the terminal portion of the coagulation process. Similar to warfarin, newer antithrombotic agents also interfere with secondary hemostasis by blocking other components of the coagulation cascade such as factor Xa (rivaroxaban [Xarelto®, Janssen], apixaban [Eliquis®, Bristol-Myers Squibb]), or thrombin itself (dabigatran [Pradaxa®, Boehringer Ingelheim]).

The decision of whether or not to discontinue anticoagulant therapy in patients with significant thromboembolic risk has been subject to significant study and debate in dermatologic surgery and other fields. The deliberations center around balancing the possible increased risk of bleeding and hemorrhage with the low, but potentially life-threatening, risk of a thrombotic event if anticoagulant therapy is temporarily discontinued. The vast majority of published literature involves the use of warfarin and aspirin. The effects of perioperative discontinuation of other blood-thinning agents are not well studied, with few studies examining the effects of clopidogrel or the new direct thrombin and factor Xa inhibitors.

In order to provide guidelines regarding anticoagulant use in dermatologic surgery, several factors need to be taken into consideration:

- What is the overall rate of hemorrhagic complications in dermatologic surgery?
- Is the risk of hemorrhagic complications in patients taking blood-thinning agents higher than this overall risk?
- Does temporary perioperative discontinuation of blood-thinning agents significantly decrease the risk of hemorrhagic complications?
- Are there objectively measurable adverse operative effects of warfarin and aspirin?
- What is the risk of thromboembolic events following temporary perioperative discontinuation of blood-thinning agents?
- What is the relative magnitude of bleeding vs. thrombotic complications?

As previously mentioned, there is a very low baseline risk of hemorrhagic complications in dermatologic surgery. One prospective study investigating immediate and delayed dermatologic surgery complications demonstrated an overall complication rate of 1.64%. Many of these complications (postoperative hemorrhage, hematoma formation, flap or graft necrosis, wound dehiscence, and infection) were either directly or indirectly related to problems with hemostasis [16] [4]. In this series, none of the

patients required hospitalization or the assistance of another specialist. This demonstrated 1.64% rate of complications is comparable to two additional reports estimating 2% rates of significant hemorrhage or hematoma in control patients undergoing dermatologic surgical procedures in the absence of blood-thinning agents [17, 18] [3]. A recent multicenter, prospective study of 23 centers revealed an even lower overall complication rate of 0.72% (149/20,821 cases), of which 22 (15.4% of all complications) were related to bleeding [2]. The majority of the complications were mild, with only four serious adverse events noted (0.02% of all procedures). While there are no randomized controlled studies on the subject, the question of continuing or discontinuing anticoagulants lends itself to a study design where rates of hemorrhagic complications are compared between patients who underwent surgery on anticoagulants and those who underwent surgery without. While the study of this kind cannot control for the possible contribution of the underlying indication for anticoagulation to a patient's risk of bleeding, the data are relatively consistent across studies and therefore lend themselves to making confident recommendations. Numerous studies have compared the rate of hemorrhagic complications in patients on vs. off of blood-thinning agents. A review of these published reports reveals the near-unanimous conclusion that there is no increased risk of severe hemorrhagic complications in anticoagulated patients. Furthermore, the literature suggests that perioperative discontinuation of anticoagulants does not significantly decrease the risk of bleeding complications [19] [4]. Several of these studies even focused specifically on Mohs surgical procedures, during which difficulties with hemostasis would have been expected to be tested by increased defect size, extensive undermining, and relatively more complex repair methods. Sufficient data exist to support that blood-thinning agents may be safely continued in dermatologic surgery without exposing the patient to a significant increase in risk for bleeding complications (see Table 64.2).

Billingsley and Maloney published one large prospective study regarding anticoagulant use in dermatologic surgery [17] [2b]. The authors reported no significant increase in severe adverse events in MMS patients on blood-thinning agents (12 patients on warfarin and 97 on either aspirin or NSAID) compared with controls. There was also no significant difference between these groups in the complexity of repair performed. Thirty-three percent of the aspirin/NSAID group and 8% in the warfarin group underwent flaps or grafts, compared with 34% in the control group. The only statistically significant finding noted was that 5/12 (42%) of warfarin patients had "excessive intra-operative bleeding," defined as excessive if the time required to achieve hemostasis during closure was greater than 3 min [17].

Another larger prospective study by Bordeaux and Maloney looked at the complication rates following dermatologic surgery in a cohort of 1911 patients [20] [2b]. The overall rate of hemorrhagic complications was 0.89% (18/1911 cases). Of those, 11 cases had persistent bleeding perioperatively and 2 postoperatively, and 5 developed hematomas. All were sufficiently mild to be handled in an office setting without hospitalization. The authors found a statistically significant increased risk of bleeding with patients taking warfarin ($P < 0.0001$) and to a lesser degree clopidogrel ($P = 0.03$). Patients on both clopidogrel and warfarin were 40 times more likely to have a hemorrhagic complication. Of note, in this study aspirin, anatomic location and closure type did not increase bleeding risk.

In the multicenter study by Alam and colleagues, of the few (22/202,821 cases) occurrences of hemorrhagic complications, all but one patient was on some form of anticoagulation [2]. Regarding the specific agent, 22.7% were taking clopidogrel, 18.0% warfarin, 9.1% aspirin plus warfarin, 4.6% aspirin plus clopidogrel, and 4.6% other anticoagulants. Most bleeding did occur in patients receiving anticoagulants, but the majority of the complications were mild and all were easily controlled. While the majority of bleeding complications in this study were in patients on some form of anticoagulation, this difference was not seen in other studies. Liu et al. looked at 423 MMS procedures in 383 anticoagulated patients and found no significant difference

Table 64.2 Summary of studies examining the incidence of dermatologic surgical complications in patients on blood thinners

Drug and study	No. of patients	Controlled study	Increased severe complications[a]	Evidence level
Aspirin and NSAIDs				
Otley et al. [18]	286	Yes, retrospective	No	IV/B
Billingsley and Maloney [17]	97	Yes, prospective	No	III/B
Lawrence et al. [19]	61	Yes, prospective	No	IV/B
Bartlett [29]	52	Yes, prospective	No	V/B
Shalom and Wong [28]	41	Yes, prospective	No	III/B
Kargi et al. [18]	37	Yes, prospective	No	III/B
Warfarin/multiple agents				
Otley et al. [18]	26	Yes, retrospective	No	IV/B
Billingsley and Maloney [17]	12	Yes, prospective	No	III/B
Lam et al. [25]	13	Yes, prospective	No	IV/B
Alcalay and Alkalay [22] and Alcalay [23]	16	Yes, prospective	No	III/B, V/B
Kargi et al. [30]	21	Yes, prospective	Yes	III/B
Syed et al. [26]	47	Yes, prospective	No	IV/B
Lewis and DuFresne [31]	1373	Meta-analysis	Yes	IV/B
Shimizu et al. [40]	760	Yes, retrospective	Yes	III/B
Eichorn et al. [54]	650	Yes, retrospective	No	IIb/B
Alam et al. [2]	20,821	Yes, prospective	No	IIa/A
Bordeaux et al. [20]	1911	Yes, prospective	Yes	IIb/B
Cook-Norris et al. [32]	363	Yes, retrospective	Yes	IIb/B
Dhiwakar et al. [55]	974	Yes, retrospective	Yes	IIb/B
Kimyai-Asadi et al. [56]	3937	Yes, retrospective	No	IIIa/B

[a]Excessive bleeding (>1 h despite pressure), hematoma, flap/graft necrosis, wound dehiscence, or infection

in the relative risk of bleeding complications between groups where the pre-existing anticoagulation was either stopped or continued during surgery [21] [2b].

Otley et al. published another large retrospective study of warfarin, aspirin, and NSAID use in cutaneous surgery patients [18] [2a]. In this study, the incidence of severe complications was reported for 653 patients undergoing MMS and excisional surgical procedures. Severe complications were defined as significant intraoperative or postoperative hemorrhage, wound bleeding greater than 1 h and not stopped with pressure, acute hematoma, necrosis of flap or graft, or dehiscence greater than 2 mm. Of the 26 patients who continued warfarin, only 1 experienced a severe complication, compared with the control group of 101 patients in whom warfarin was held, where there was also only one severe event. Similarly, four severe events were reported in the 286 patients continuing aspirin or NSAID compared to three out of the 240 patients who discontinued these medications perioperatively. On the basis of these results, the authors concluded that continuation of warfarin or platelet inhibitors is associated with a very low risk of severe complications and that the rate of complications is not statistically significantly increased compared to patients in whom the same medications are discontinued. It is worth noting that only 54 (8%) of the 653 patients underwent flap or graft repairs, with 2 out of the 5 severe events in patients on warfarin or blood thinners occurring in these more complex repairs [18].

Other smaller prospective studies have also supported the safe use of blood-thinning agents in cutaneous surgical procedures. Alcalay and Alkalay reported no significant adverse events in 68 consecutive patients undergoing Mohs micrographic surgery while on warfarin, including those with therapeutic INR [22, 23] [4]. Another retrospective review by Ah-Weng et al. looked at 68 patients on warfarin who underwent a variety of dermatologic procedures and found no

instances of hemorrhagic complications or necrosis, even at a maximum INR of 3.5 [24] [4]. Similarly, Lam et al. found no difference in adverse events in a small group of dermatologic surgery patients continuing warfarin therapy during the procedure as compared to those patients who had their warfarin stopped and were treated with perioperative heparin [25] [4]. In contrast, Syed et al. published a prospective study of 47 patients on warfarin undergoing cutaneous surgery, noting significantly more minor bleeding in patients on warfarin compared with controls [26] [4]. In this report, nine patients experienced minor bleeding, but there were no major adverse events. Of those cases of minor bleeding, three had an intraoperative international normalized ratio of 3.5 or greater. Of note, only 5 out of 47 patients had intraoperative INRs of 3.5 or greater, with 60% of those experiencing the minor bleeding episodes [26]. A more recent study has prospectively addressed the potential correlation between INR values and bleeding complications in patients undergoing excisional surgery while anticoagulated on warfarin. While very few patients were noted to have INR values greater than 3, no correlation was found between increased INR value and intraoperative or postoperative bleeding [27] [3]. One can conclude that perioperative INRs may only serve to identify the small subset of patients with supratherapeutic values who may be at particular risk for bleeding complications, postoperative, or otherwise. Shalom and Wong reported a statistically increased incidence of intraoperative suture ligation for hemostasis in 41 patients on aspirin compared with 212 controls undergoing excisions of cutaneous and subcutaneous lesions [28] [5]. However, the authors did not find any increased risk of significant bleeding events in those patients taking aspirin. Barlett et al. reported no increased incidence of minor, severe, or overall bleeding complications in 52 patients undergoing minor dermatologic surgery while on aspirin compared with 119 patients who were not taking aspirin [29] [3]. Only one group has published data suggesting significantly increased major bleeding complications in patients undergoing minor cutaneous surgery while on warfarin [30] [4]. Of 21 patients on warfarin, 5 (24%) experienced a major bleeding complication, which was defined as persistent bleeding, wound hematoma, loss of skin graft, or wound infection. This number was significantly higher than that in the 37 patients on aspirin and the 44 controls. This study did not report on INR values or monitoring in the warfarin-treated patients. No significant difference between the aspirin and control groups with regard to bleeding complications was observed [30].

A recent meta-analysis increases the power of many of the aforementioned small studies [31] [1]. Somewhat surprisingly, there was a statistically significant sixfold increased risk of bleeding complications for patients taking warfarin vs. controls (12.3% vs. 2.1%, respectively). A similar but much less robust trend was observed for patients taking aspirin; however, this distinction failed to meet statistical significance. The reliability of this meta-analysis is somewhat compromised by virtue of summing data from several small heterogeneous studies. It is also important to note that additional medical comorbidities were not controlled for in any of the aforementioned anticoagulation studies. It is likely true that anticoagulated patients tend to be older and have greater number and severity of medical problems. If the risk of bleeding complications is somewhat higher in anticoagulated patients, the question of acceptable risk persists. As pointed out by Alcalay, the observed complications have never been reported as life-threatening, while there are numerous reported cases of life-threatening complications potentially attributable to the discontinuation of anticoagulants perioperatively [22] [5].

While multiple studies in the dermatologic surgery literature have addressed NSAID, aspirin, and warfarin use, there are few published reports addressing bleeding complications in patient on clopidogrel (Plavix®, Bristol-Myers Squibb), and fewer still of the newest anticoagulants, dabigatran (Pradaxa®, Boehringer Ingelheim), rivaroxaban (Xarelto®, Janssen), and apixaban {Eliquis®, Bristol-Myers Squibb). Clopidogrel is a selective inhibitor of platelet adhesion to fibrinogen and aggregation via inhibition of ADP-induced platelet activation. Its use

continues to increase as a component of secondary prevention among cardiac and cerebrovascular patients, and it is often used in combination with aspirin, as they have synergistic antiplatelet effects. In a study by Cook-Norris et al., patients taking clopidogrel monotherapy were 28 times more likely to have severe bleeding complications after Mohs micrographic surgery than controls on no anticoagulation and 6 times more likely than patient on aspirin monotherapy [32] [3b]. In contrast, in a prospective study by Kramer et al. comparing anticoagulant use, there was no significant difference in complication rate in 32 patients on clopidogrel monotherapy or clopidogrel vs aspirin as compared to 2329 other patients taking no anticoagulants, aspirin monotherapy, or warfarin monotherapy [33] [3b]. Reports from the nondermatologic picture further suggest an increased risk of perioperative bleeding with clopidogrel. A 2006 prospective study from the pulmonology literature found that clopidogrel significantly increased the bleeding risk in patients undergoing transbronchial biopsy, with the effect exacerbated by concomitant aspirin use [34] [3]. A paper from the cardiology literature also found that combination therapy with clopidogrel and aspirin led to an increased perioperative bleeding risk, in this case comparable to that of warfarin [35] [2a]. The multicenter study by Alam and colleagues did not show much increased risk of the aspirin-clopidogrel combination, but the numbers of such patients were too low to draw concrete conclusions [2]. As this agent continues to be utilized in more patients, studies regarding its effects on dermatologic surgery complications will be beneficial.

There are a number of newer antithrombotic agents that have been developed and approved in the past several years targeting other portions of the coagulation cascade, including direct thrombin inhibitors such as dabigatran (Pradaxa®, Boehringer Ingelheim), direct factor Xa inhibitors such as rivaroxaban (Xarelto®, Janssen), apixaban {Eliquis®, Bristol-Myers Squibb), and several others in various stages of development. Even more agents targeting these and other components of the coagulation cascade are currently in development. These new oral anticoagulants are increasingly used as they have more predictable pharmacokinetics, do not require routine monitoring, and have fewer severe life-threatening hemorrhagic complications as compared to warfarin [36] [2b]. Despite their widespread popularity amongst cardiologists, these drugs often remain prohibitively expensive for many patients. An antidote to dabigatran has been approved for patients with life-threatening perioperative bleeding, but antidotes to the factor Xa inhibitors rivaroxaban and apixaban are still in development. Unlike with warfarin, the lack of effective reversal agents to these drugs has caused considerable debate for recommended practice with more invasive surgical procedures, but with dermatologic surgery, the risk of severe bleeding is much less. With these new agents, there is only one study of bleeding rates in cutaneous surgery and two case reports of complications during cutaneous surgery with dabigatran. There are no reports of bleeding complications during cutaneous surgery with rivaroxaban or apixaban. Chang and colleagues retrospectively looked at surgical outcomes for patients on these newer agents undergoing Mohs micrographic surgery and found a hemorrhagic complication (mild, intermittent postoperative bleeding that resolved after 3 days) in only one of 27 patients on dabigatran [36] [2b]. Of four patients taking rivaroxaban, there were no bleeding complications. Regarding the case reports, one described an elderly patient on dabigatran who developed a subarachnoid hemorrhage following dermabrasion for scar revision [37] [4] and another who developed a hematoma following a melanoma excision [38] [5]. The half-life of these drugs is relatively short (dabigatran 13–18 h, rivaroxaban 7–13 h, apixaban ~12 h) [39] [2a], suggesting that cessation 2–3 days prior would eliminate most hemorrhage risk. However, initial data is in line with past studies of other antithrombotics (e.g., aspirin, warfarin, and clopidogrel) demonstrating that continued use during cutaneous surgery is safe. Moreover, these newer agents are currently used predominantly for secondary vs. primary prevention, i.e., in patients with established cardiac disease and increased risk of a devastating event with cessation. Further studies are necessary to

draw more definitive conclusions regarding these new agents, but at this time, we recommend continuing the use of these medications during surgery.

An increasingly relevant subject for which there is little published has to do with patients on multiple anticoagulants. Patients are increasingly put on multiple anticoagulants as a number of studies demonstrate the efficacy of combination therapy [20]. There are many frequent combinations of both prescription and nonprescription agents that may or may not act synergistically in terms of enhancing the risk of bleeding, especially when there are agents interfering with both primary and secondary hemostasis as described above. This subject is difficult to study since the number of patients on any particular combination is much less than the total number of dermatologic surgery patients on any one particular agent. Nonetheless, one report attempted to address the subject retrospectively through a chart review [40] [5]. There were no significant bleeding complications in 227 patients undergoing Mohs surgery on one anticoagulant (ASA, warfarin, clopidogrel, dipyridamole/ASA, vitamin E, or fish oil). There were three cases of significant bleeding in a total of 58 patients on 2 or more blood thinning agents. While the authors did show statistical significance for these findings, they are somewhat limited by the very low number of adverse events. Furthermore, none of the patients exhibited any significant morbidity associated with their bleeding complications. This is consistent with the absence in the literature of any life-threatening or lethal bleeding complications after cutaneous surgery. The subject deserves more study with larger numbers to better quantify the increased risk potentially associated with multiple agents. Regardless, it seems difficult to justify modifying a patient's multiple anticoagulant regimen on the basis of this study alone.

Despite the belief by many surgeons that they can predict anticoagulant or blood thinner status intraoperatively, one study of dermatologic surgeons demonstrated that physicians at all levels of training were equally unable to assess blood thinner status based on visual inspection of intraoperative oozing [41] [5]. This is similar to findings reported in coronary artery bypass patients, in which surgeons' impressions of aspirin status were unreliable [42] [2].

There have been several documented reports of serious thromboembolic events occurring in patients who discontinued warfarin or aspirin therapy for dermatologic surgery. Kovich reported data from a survey of 504 members of the American College of Mohs Micrographic Surgery and Cutaneous Oncology, and 168 respondents reported 46 patients who experienced thrombotic events [43] [4]. These were all serious events and included 24 strokes, 3 cerebral emboli, 5 myocardial infarctions, 8 transient ischemic attacks, 3 deep venous thromboses, 2 pulmonary emboli, 1 retinal artery occlusion leading to blindness, and 3 deaths were reported. Of the 46 patients who experienced thrombotic events, 54% had an event when warfarin was held, 39% occurred when aspirin was held, and 4% of events happened when both medications were held. Alam and Goldberg presented two additional cases and reviewed the above data, calculating an estimated thrombotic risk of one event per ~12,800 operations, and suggested that at least one event would occur per career in half of all dermatologic surgeons [44] [3a]. A meta-analysis of 50,000 patients demonstrated a three-fold higher risk of cardiac events associated with preoperative cessation of aspirin [45] [2a]. A systematic review of published cases from the dental literature found that in 542 cases of preoperative discontinuation of warfarin, there were 5 thrombotic complications, 4 of which were fatal [46] [3a]. There are other documented case reports in the dermatologic surgery literature of stroke, pulmonary embolus, and clotted prosthetic valve occurring in patients in whom anticoagulation or antiplatelet medications were discontinued perioperatively [44, 47] [5].

Anticoagulation is often critical given the profound morbidity and mortality of thromboembolic events. The risk of ischemic stroke increases 1.5-fold for every 10 years of age increase, with estimated incidence of 14 per 1000 person-years for people aged 75 to <85 years and 29 per 1000 person-years for people 85 years and older [48] [2a]. A review in the *New England Journal of*

Medicine highlights the potential gravity of thromboembolic complications. A patient who experiences a recurrent episode of venous thromboembolism has a 6% mortality risk and 2% risk for serious permanent disability [49] [1]. Arterial thromboembolism morbidity and mortality rates are higher, with 20% of events being fatal and 40% resulting in serious permanent disability. The risk of these grave complications varies somewhat depending upon the circumstance and indication for anticoagulation. Patients with older mechanical cardiac valves or a mechanical mitral valve are at higher risk than those with newer or aortic mechanical valves. Patients with DVT are at much greater risk if the DVT was diagnosed within 1 month of the perioperative period. In addition, patients with stable, lone atrial fibrillation who have no history of stroke or other risk factors for stroke are at much lower risk than those atrial fibrillation patients who do have such a history [50] [5].

For two of the common indications for warfarin or the newer anticoagulants, (atrial fibrillation and artificial heart valve replacement), the estimated risks of thromboembolism are 1–20% per year and 8–22% per year, respectively [50] [4]. For the third most common indication, DVT, the estimated clotting risk is 1% per day for patients who have had a DVT within 1 month, and 0.2% and 0.04% for patients with DVTs within 2–3 months and over 3 months, respectively. Using these numbers, the estimated 2-day risk of a thrombotic event in a patient taken off warfarin for a dermatologic procedure is 0.01–0.3% in the setting of atrial fibrillation and 0.08–0.4% for a patient with an artificial heart valve replacement. For DVT patients, the 2-day risk is 4–6% in those less than 1 month after a DVT, 0.8–1.2% in those 2–3 months after DVT, and 0.16–0.24% in those more than 3 months after DVT [50].

The majority of studies support the continued use of existing anticoagulation during dermatologic surgery, but providers do have variable practices. A 2005 ACMS survey of Mohs surgeons found that 87% discontinue prophylactic aspirin, 37% medically necessary aspirin, 44% discontinue warfarin, 77% discontinue NSAIDs, and 77% discontinue Vitamin E [51] [2c]. These numbers are down from an earlier 2002 survey of Mohs surgeons reporting that rather than 44%, fully 80% of surgeons discontinued warfarin preoperatively, marking a notable shift in the paradigm of anticoagulant use during cutaneous surgery [52] [3b]. With continued, mounting evidence to support the continuation of anticoagulation, those numbers are likely even lower today.

These data lend themselves to the clinical recommendations summarized below with their accompanying evidence levels. The literature overall supports the continuation of anticoagulants given the ease of managing the potential minimally increased risk of bleeding given that thrombotic complications are potentially devastating and life-threatening. While it is generally clear that patients should be maintained on anticoagulants for secondary prevention, some cases inevitably merit further discussion. It is important to remember that these guidelines have not necessarily been adopted by other surgical fields who often extrapolate data from more invasive surgeries in considering the risk of continuing an anticoagulant during surgery. Therefore, communication with our colleagues in the other surgical disciplines is critical if, for example, the dermatologic surgeon anticipates referral to a plastic or head and neck surgeon for repair of a Mohs surgery defect in an anticoagulated patient. Our consulting colleagues may wish to hold anticoagulants for large defects, defects involving the scalp or eyelids, or any reconstruction that is expected to require extensive and/or deep undermining. Though the data in the dermatologic surgery literature is quite clear, and even other specialty groups such as the American College of Chest Physicians have recommended continuing anticoagulation for minor dermatologic procedures [53] [3a], it is important to remember that the decision to withhold anticoagulants preoperatively depends upon numerous clinical factors and assessment of risk must be conducted on a case-by-case basis. This decision depends not only upon a critical appraisal of the relevant literature but also on the clinical acumen of the surgeon performing the procedure. Furthermore, while it seems common to consult with a patient's cardiologist or primary care physician regarding

perioperative anticoagulants, the value of this practice is limited by these physicians' lack of familiarity with the above reviewed literature and dermatologic surgery procedures in general.

Cutaneous surgery is performed commonly on patients taking medically necessary blood-thinning medications such as warfarin and aspirin. Available data suggest that the risk of severe hemorrhagic complications is not increased if these medications are continued. Importantly, brief perioperative discontinuation does NOT lower this already minimal hemorrhagic risk. Life-threatening thromboembolic complications have been related temporally to perioperative discontinuation of both warfarin and aspirin. In general, the risks of stopping anticoagulants far outweigh the risks of continuing them for most dermatologic surgery procedures. As the use of these agents increases, the onus is on the dermatologic surgeon to help prevent bleeding complications through careful preoperative assessment, meticulous intraoperative hemostasis, effective use of pressure dressings, and excellent postoperative care and follow-up.

Observations and Recommendations

Findings	GRADE score: quality of evidence
Recommendations regarding perioperative use of blood-thinning agents	
All vitamin supplements and herbal medications should be discontinued 7–10 days preoperatively and resumed 1 week following surgery. For practical purposes, and since many supplements and over-the-counter vitamins can affect bleeding, we do not distinguish between various agents with regard to recommending patient discontinuation	C
Nonsteroidal anti-inflammatory medications (NSAIDs) should be stopped 3 days prior to surgery, with recommended resumption 1 week following the procedure. Because of their reversible effect on platelet aggregation via cyclooxygenase inhibition and the relatively short drug half-life, 3 days of preoperative discontinuation is sufficient for resumption of platelet function, and we find that most patients can tolerate being off NSAIDs for that period of time	B
Primary preventative aspirin, which irreversibly inhibits platelet function, should be discontinued 10–14 days prior to surgery and restarted 1 week after the procedure	B
Medically necessary warfarin and aspirin should be continued, with an INR value recommended within at least 1 week of surgery. Care must be taken to assess the preoperative history whether or not the warfarin doses and INR measurements are stable. In addition, a careful medication history assessing for new medication additions that may affect warfarin levels is crucial	A
We currently recommend that patients continue clopidogrel in the perioperative period, although further studies regarding this medication and complications are warranted	B
Regarding current use of thrombin inhibitors dabigatran, rivaroxaban, and apixaban, we currently recommend that medically necessary use should be continued, but further studies are needed	B

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Self-Assessment Questions

1. Which of the following conditions assessed in a preoperative evaluation of past medical history does not contribute to altered platelet function and coagulation?
   a. Liver disease
   b. Renal dysfunction
   c. Hematologic and solid malignancies
   d. Hypertension
   e. All of the above can promote bleeding

2. What is the consensus recommendation for stopping over-the-counter supplements prior to surgery?
   a. Stop supplements 1–3 days prior
   b. Stop supplements 7–10 days prior
   c. Stop supplements 2 weeks prior
   d. Stop supplements 4 weeks prior
   e. It is not necessary to stop supplements prior to surgery

3. Which of the following complications is least likely to be related to complications with hemostasis?
   a. Wound infection
   b. Wound dehiscence
   c. Flap or graft necrosis
   d. Hematoma
   e. All of the above can be related to bleeding complications

4. Based on consensus guidelines, it is necessary to stop which of the following antithrombotic agents before surgery?
   a. Warfarin
   b. Aspirin
   c. Clopidogrel
   d. Dabigatran
   e. Rivaroxaban
   f. None of the above

5. Circle all correct answers: For which class of anticlotting medications is there a known reversal agent?
   a. Thrombin inhibitors (dabigatran [Pradaxa])
   b. Factor Xa inhibitors (rivaroxaban [Xarelto], apixaban [Eliquis])
   c. Inhibition of vitamin K-dependent clotting factors (warfarin [Coumadin])
   d. Platelet inhibitors [aspirin, clopidogrel [Plavix])
   e. All of the above have known reversal agents

Correct Answers

1. e: All of the above can promote bleeding. Explanation: All of the above answers can contribute to dysfunction of coagulation. Hypertension increases systemic pressure and thus increases bleeding from vessels cut during a procedure, while hepatic and renal disease can lead to an abnormality of normal levels of clotting factors. Malignancies as well can stress the system and lead to an excess of factors that inhibit normal clotting.
2. b: Stop supplements 7–10 days prior. Explanation: Common anticoagulant supplements such as vitamin E and Gingko have shorter half-lives and could be stopped only 3 days prior to surgery without causing much problem. However, many other supplements are less well studied, and to be safe, consensus practice suggests 7–10 days of discontinuation.
3. e: All of the above can be related to bleeding complications. Explanation: Without proper hemostasis, bleeding complications can lead to hematoma and possible wound breakdown and dehiscence. A resolving clot can also serve as a nidus for infection in that scenario.
4. f: None of the above. Explanation: Consensus guidelines have shown through a multitude of studies that it is not necessary to stop any antithrombotic agents prior to dermatologic surgery. The risk of thrombotic events (myocardial infarction or cerebrovascular accident) is of much greater concern than bleeding in cutaneous surgery, as the bleeding is typically controlled with relative ease. It is recommended for those on warfarin to have a stable INR, but studies have shown that even with an elevated INR, bleeding during cutaneous surgery is minimal. The majority of providers discontinue use of prophylactic aspirin in patients with no history of cardiovascular disease prior to surgery, but this has not been shown to be necessary in the literature.
5. a and c: Explanation: Vitamin K or prothrombin complex concentrate are known reversals for inhibitors of vitamin K-dependent clotting factors (warfarin [Coumadin]), with IV administration working in less than 24 h. There is also a new reversal agent for the direct thrombin inhibitor dabigatran [Pradaxa]. There are no known reversal agents for the platelet inhibitors aspirin and clopidogrel [Plavix] or factor Xa inhibitors rivaroxaban [Xarelto] or apixaban [Eliquis]. Particularly for the newer factor Xa inhibitors, the lack of an antidote has led to concerns over an inability to stop surgically induced bleeding in a life-threatening situation. No such situations have been reported during dermatologic surgery thus far in the literature.

Prevention and Treatment of Perioperative Pain and Anxiety

65

Kristina Navrazhina, Cerrene N. Giordano, and Kira Minkis

Abstract

A rise in skin cancer incidence alongside the increasing popularity of dermatologic procedures necessitates continued advances in dermatologic surgery. Unlike other types of surgeries, the majority of patients are conscious during dermatologic surgery, and thus it is critical for physicians and the medical team to minimize pain and anxiety levels associated with the procedure. Perioperative anxiety can lead to elevated blood pressure, syncope, and increased risk of intraoperative and postoperative bleeding (2b, 3a) (Ravitskiy et al, J Am Acad Dermatol 64:310–322, 2011; Kreicher and Bordeaux, JAMA Facial Plast Surg, 2016). Importantly, a negative surgical experience may hinder the patient from seeking dermatologic care in the future. This chapter assesses the current evidence regarding prevention and treatment of perioperative pain and anxiety.

Keywords

Perioperative anxiety · Perioperative pain
Anxiolytics · Analgesia · Topical anesthetics
Infiltrative anesthetics · Regional nerve blocks · Pain management

Introduction

A rise in skin cancer incidence alongside the increasing popularity of dermatologic procedures necessitates continued advances in dermatologic surgery. Unlike other types of surgeries, the majority of patients are conscious during dermatologic surgery, and thus it is critical for physicians and the medical team to minimize pain and anxiety levels associated with the procedure. Perioperative anxiety can lead to elevated blood pressure, syncope, and increased risk of intraoperative and postoperative bleeding (2b, 3a) [1, 2]. Importantly, a negative surgical experience may hinder the patient from seeking further dermatologic care in the future. This chapter assesses the current evidence regarding prevention and treatment of perioperative pain and anxiety.

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Preoperative Pain and Anxiety Management

Administration of Preoperative Anxiolytics

The diagnosis of skin cancer and the subsequent surgical treatment can be a daunting and overwhelming experience for patients. A thorough preoperative evaluation is necessary to establish an understanding of the patient's anxiety level. Anxiety directly impacts cardiovascular physiology and can lead to syncope and increased risk of bleeding (2b) [1]. These adverse effects may hinder patients from seeking future surgical treatment for cutaneous malignancies. Preoperative anxiolytics can mitigate anxiety and decrease pain perception, ultimately resulting in a more positive surgical experience.

An optimal anxiolytic for dermatologic surgery would have a rapid onset, a short half-life, and a large safety margin, thereby enabling appropriate outpatient administration [1]. Benzodiazepines provide anxiolytic, hypnotic, and anterograde amnestic effects that are dose dependent (2b, 4) [1, 3]. Midazolam, which is a short-acting benzodiazepine, has an elimination half-life of 1.5–3 hours and can be administered intravenously, intramuscularly, or orally [1]. The most common side effects include nausea, coughing, vomiting, and hiccoughing, with rarer adverse effects including cardiac arrhythmias and allergic reactions (2b, 5) [1, 4]. Several studies have examined the role of preoperative oral midazolam in patients undergoing dermatologic surgery. Otley and colleagues analyzed a cohort of pediatric patients who received oral midazolam prior to dermatologic procedures. The authors concluded that oral midazolam is a safe and effective anxiolytic and that the provided anxiolysis, in combination with local anesthetics, was sufficient without intravenous sedation or general anesthesia [3].

A randomized double-blind placebo-controlled study led by Ravitskiy and colleagues examined the efficacy of single-dose oral midazolam in anxiolysis during Mohs surgery [1]. Patients were randomized to receive either preoperative 5 cc of 2 mg/mL of midazolam, or color and texture matched placebo. A subset of the patients chose to receive midazolam in a prospective manner. The authors used a ten-point visual analog scale (VAS) to assess anxiety levels 60 minutes following administration of midazolam or placebo. Additionally, adverse effects associated with each study arm were evaluated. Patients in the randomized arm that received midazolam showed a tenfold mean decrease from baseline anxiety at 60 minutes compared to the control cohort. Patients that received midazolam prospectively were more than three times less anxious than at baseline. The decreased anxiety in these patients was accompanied by decreased alertness at 60 and 120 minutes. Midazolam was associated with a statistically lower systolic and diastolic blood pressure at 60 minutes. There was only one self-limited minor respiratory event in the cohort of patients who received midazolam. The group of patients choosing to receive midazolam prospectively had almost threefold higher levels of anxiety at baseline than patients who were willing to be randomized, suggesting that there is a subpopulation of patients who may particularly benefit from receiving an anxiolytic [1].

Although limited in sample size, both studies promote the utility of oral midazolam as an effective anxiolytic in patients undergoing dermatologic surgery. This can be of particular utility in the subpopulation of patients with higher baseline anxiety levels. While there is currently a dearth of reports examining the efficacy of other benzodiazepines in anxiolysis prior to cutaneous surgery, other randomized controlled studies showed the efficacy of several benzodiazepines including clonazepam, diazepam, alfentanil, and midazolam in patients undergoing same-day non-cutaneous surgeries (2b) [5–7].

Paradoxical reactions to benzodiazepines, characterized by increased talkativeness, restlessness, excessive movement, excitement, agitation, and aggressive behavior, have been documented in <1% of patients (5) [8]. Pediatric and the elderly populations are at a higher risk for paradoxical reactions to benzodiazepines [8]. Although these paradoxical reactions are exceedingly rare, physicians using benzodiazepines

should remain cognizant of these potential effects and be prepared to either cease benzodiazepine use or counter the effects in serious cases with the benzodiazepine antagonist flumazenil.

Preoperative Education

With the majority of dermatologic surgeries taking place in outpatient facilities, it is essential that patients are comfortable taking on a key role in their own postoperative care at home. Preoperative education allows physicians to adequately prepare patients regarding postoperative wound care, expected level of pain, both pharmacological and non-pharmacological pain control, and any relevant management regarding their postoperative recovery. Adequate understanding of the surgical procedure as well as postoperative care may decrease anxiety levels in patients undergoing dermatologic surgery.

While there are no studies specifically addressing the benefit of preoperative education on anxiety and pain levels of patients undergoing dermatologic surgery, O'Donnell and colleagues implemented a quality improvement project to assess the value of preoperative pain management education on the reported pain levels in patients undergoing same-day laparoscopic cholecystectomy. During the preoperative visit, subjects in the intervention group received written and verbal education on postoperative pain management, including proper use of medications, potential side effects and their management, non-pharmacological ways to subdue pain, and the overall importance of timely pain management (3b) [9]. Patients who received detailed preoperative education about pain management reported less severe pain during the first 24 hours postoperatively. This clinically significant result suggests that preoperative education can decrease the severity of pain that patients experience after their operation and thus allow patients to return to regular activities sooner [9].

Sobanko and colleagues conducted a clinical trial of 53 patients randomized to receive same-day consultation versus 51 patients randomized to receive both same-day consultation and preoperative phone call 1 week prior to Mohs surgery. Interestingly, there were no statistical differences in anxiety levels or overall satisfaction with the surgery between patients who received a phone call and those who did not (2b) [10]. Sharon and colleagues retrospectively surveyed 97 patients who underwent Mohs surgery regarding whether patients preferred separate or same-day preoperative consultation. While having a separate-day consultation may decrease anxiety levels by allowing patients to have more time to establish a relationship with the dermatologic surgeon, become better informed regarding the procedure, and allow the surgeon to better understand the patient's concerns, attending a separate appointment may present both a financial and a time burden on the patients and delay the time to removal of the neoplasm. In the cohort of patients studied by Sharon et al., 67% of the patients preferred same-day preoperative consultation. When analysis was accounted for other covariates, the authors showed that higher education level was associated with predilection for same-day consultation. Furthermore, the authors suggest that patients with a more difficult surgical history may benefit from advanced preoperative consultation (3b) [11].

Studies by O'Donnell, Sobanko, Sharon, and colleagues highlight a clear role of preoperative education on pain and anxiety levels of patients undergoing same-day surgery [9–11]. While same-day preoperative education may be sufficient, physicians must balance patient preference with urgency for the procedure.

Intraoperative Pain Management

Perioperative pain remains a leading concern for patients. When disregarded or inappropriately managed, pain may lead to decreased patient satisfaction and an increase in postoperative complications including inferior wound healing, insomnia, substance abuse, cardiovascular sequelae, transition to chronic pain, and other psychological disorders (5) [12]. However, even patients who report continuous pain maintain a higher overall satisfaction when the staff

attempted to appropriately manage their pain (4) [13]. Dermatologic surgery is unique in its outpatient basis and complete patient consciousness throughout the duration of the operation. Therefore, intraoperative pain control is imperative for the comfort of the patient and the safety of the procedure.

Postoperative pain in dermatology has been widely studied (3b) [14, 15]; however, the literature remains sparse on intraoperative pain assessment and control. In one recent study by Connolly et al., 270 patients undergoing Mohs micrographic surgery were queried on their pain level (on a scale of 1–10) between each layer (3b) [16]. Participants reported pain during 32.8% of procedures, with a majority of patients demonstrating a mild degree of pain with an average score of 3.7 out of 10. Younger patients, those requiring three or more layers, periorbital and nose anatomic locations, more complicated tissue rearrangement repairs, and total elapsed time of at least 6.6 hours, were all associated with a higher likelihood of pain intraoperatively. Interestingly, the authors concluded that patients were less likely to report pain unless prompted by the staff, suggesting that intraoperative pain may be more prevalent than previously reported.

The most efficient approach at reducing pain due to dermatologic surgery is through adequate anesthesia prior to procedure initiation. A majority of dermatologic surgeries are conducted with the use of local anesthesia due to the reduced recovery time, decreased cost, and improved safety relative to procedures performed under general anesthesia or intravenous sedation (3b) [17]. However, while this modality is ultimately safer in practice, this requires the patient to remain awake through the duration of the procedure, which may increase the possibility for pain and/or anxiety intraoperatively. In addition, the process of anesthetizing a patient, while successfully eliminating intraoperative pain, may in turn evoke pain and anxiety itself (5) [18]. There are many described procedural, behavioral, and communication techniques, as well as anesthetic additives, which can ease the process and reduce patient-perceived pain.

Procedural Techniques

Patient expectation, needle phobia, and suboptimal injection technique may all lead to patient intraoperative anxiety and discomfort (5) [19]. The perception of pain associated with local anesthetic injection occurs in a two-part phenomenon. The first sensation is related to the physical insertion of the needle tip, leading to a rapid, sharp pain (5) [20]. Infiltration and rapid tissue expansion cause both chemical and physical stimulation of tissue nociceptors responsible for the second more prolonged and intense portion (3b) [21]. Various injection techniques have been studied with the goal of optimizing anesthesia and easing the burden for both the patient and surgeon.

One of the simplest and most important basic techniques involves proper patient positioning to establish patient and provider comfort. Ergonomics is an applied science concerned with designing and arranging a space to improve the efficiency and safety of human-environment interactions and is becoming an increasing focus in medicine to maintain provider health and longevity. One study surveyed members of the American College of Mohs Surgery and suggested that 90% of surgeons reported some types of musculoskeletal symptoms or injuries, including neck (65%), lower back (63%), upper back (53%), and shoulder (61%) pain (3b) [22]. Even more concerning evidence exists that musculoskeletal pain occurs early in the careers of Mohs surgeons, with 69% of young surgeons reporting musculoskeletal ailments within their first 5 years of training. Similar evidence exists in the dental literature as well, with 90.2% of dental practitioners surveyed reporting musculoskeletal pains, with shoulder pain and lower back pain significantly related to years of experience (3b) [23]. This is likely due to the improper positioning, frequent reaching, and repetitive bending during procedures. Proper positioning can ensure provider comfort and minimize surgeon error from accidental slips as well as allow patient stability and reduction in unexpected movements. Bhatia et al. suggest frequent breaks to

stretch, core strength training, and early posture improvement to combat these issues early on in training (5) [24]. Data from other fields suggests that ergonomic interventions may improve and prevent musculoskeletal disorders (3b–4) [25, 26]. Additionally, workers who receive training in ergonomics in addition to workspace redesign have fewer symptoms compared to those who receive training only without available supportive equipment (2b–3a) [27, 28]. Formal studies are indicated in the field of dermatology and dermatologic surgery in order to validate interventions that promote and improve ergonomics for our specialty.

Smaller needle sizes, particularly 32 gauge, may reduce pain perception upon needle entry (1b) [29]. This has shown benefit for cosmetic procedures; however, it may be extrapolated to anesthetic injections as well. In addition, needles should be frequently replaced to reduce injection-associated pain [29] and where possible, injection through a large pore or follicle has been demonstrated to minimize discomfort with anesthesia as well as cosmetic injections (2b) [20, 30]. Anecdotal evidence exists for additional techniques such as pinching or stretching the skin through the duration of injection and slow infiltration with initial depot aimed below the dermal-subcutaneous junction with slow advancement into the dermis, where a majority of nerve fibers are located (3a–5) [20, 21, 31]. Injection at a 90-degree angle can minimize the number of transected nerve fibers as well [20], and anterograde injection in a fanlike manner may minimize the number of needlepoint injections while maintaining the anesthetic wheal before the needle tip to avoid further needle-related pain (3a) [31].

Local external cooling has shown benefits in reducing postoperative pain and edema, and attempts have been made to capitalize on this evidence perioperatively (1b–2b) [21, 32–37]. Some suggest that cooling can substitute for the injection of local anesthetics with minor cutaneous procedures [21]. However, more practical uses involve the application of cryoanalgesia to lessen the pain of injectable anesthesia, not to replace it. A randomized trial examined the effect of ice application on pain reduction prior to anesthetic infiltration for eyelid surgery (2b) [38]. The authors concluded that the ice application prior to anesthesia reduced the level of perceived pain by 24.6%. The method of cryoanalgesia has also been examined in a split-hand study for botulinum toxin injections for palmar hyperhidrosis, comparing ice packs to dichlorotetrafluoroethane spray for 5 seconds prior to injection (3b) [39]. Authors concluded that 36 out of 40 patients reported at least a mild decrease in intensity of pain associated with the dichlorotetrafluoroethane spray compared to the ice packs. This has also previously been demonstrated (2b–5) [40–44].

In one small prospective split-arm study, 60 healthy volunteers were treated with lidocaine and epinephrine buffered with sodium bicarbonate in one arm and injection of an unbuffered solution after ice application for 2 minutes to the other arm [21]. Subjects rated the pain immediately after each injection, and while investigators found a trend toward improved anesthesia with the buffered solution (60% of subjects reporting less pain compared to the ice application), there was no significant difference noted between the two methods, suggesting that cryoanalgesia shows equivalent benefit. A number of theories have been postulated in an attempt to explain the mechanism behind skin cooling and pain reduction. Postulates range from vasoconstriction and reduced tissue metabolism in lessening inflammatory mediators and edema to local cooling directly retarding pain signal or neuromuscular transmission, with the activation of A-delta fibers and inhibitory pain pathways (4, 5) [21, 45, 46]. Additionally, the "counterirritant" theory has been postulated, where a temperature stimulus overrides a painful stimulus in the same region, thereby reducing the perceived painful sensation [39]. However, caution must be taken as prolonged application of ice or cooling may in turn cause a burning discomfort. While duration of ice application has been studied (3b) [38, 47, 48], randomized trials are necessary to determine the most appropriate time threshold for ice application.

Behavioral/Communication Techniques (Table 65.1)

Physical distraction methods such as vibration, slight pinching of the skin, and tapping alternate body areas are fairly common, also utilizing the concept of counterirritation or the "gate control" theory where the activation of dermal mechanoreceptors leads to the stimulation of large-diameter A-beta fibers, thereby "closing the gate" and reducing spinal cord transmission of signals produced by pain fibers (5) [20, 31, 49]. Various vibration stimulation devices have been reported in small series to decrease injection-related pain, when applied at or near the injection site (3b–4) [50, 51]. In one small survey-based, split-faced study, 86% of individuals reported mild to no pain with coordinated use of vibration with dermal filler injections, compared to only 12% of those without vibration (4) [52].

Pain interpretation is subjective and individualized; therefore, behavioral interventions are often successful in minimizing pain and anxiety. Distraction or "talkesthesia" is a simple and popular modality that involves talking with the patient about their occupation, hobbies, family, etc. to focus their mind elsewhere during a painful procedure [20]. Often a calming voice, an unhurried attitude, and an anticipatory warning prior to the injection can significantly reduce pain and anxiety [20]. In addition, a soothing and relaxed atmosphere through guided imagery and/or listening to music can be beneficial for the patient and physician (2a–2b) [53–55], each showing benefits in anxiety reduction intraoperatively (1a–1b) [56, 57]. Interestingly, in one randomized study by Alam et al., patients undergoing cutaneous excisions were not significantly impacted by short-contact imagery or music; however, surgeon anxiety was significantly lower when compared to the control group (1b) [58]. Presumably, patient distraction of any method allows the surgeon the freedom to focus on the technical aspects of the procedure, while minimizing the peripheral struggle of limiting patient awareness of the intraoperative proceedings such as cautery, sounds of instruments, etc. In general, music or guided imagery is a favorable technique with growing popularity given its low cost, efficiency, and relative ease of application in daily practice.

More limited evidence exists for the use of hypnosis or meditation (3b–5) [53, 59–61] or additional distraction techniques such as breathing modalities (3b) [62] or physical visual barriers, particularly in the pediatric literature (5) [63].

Table 65.1 Techniques for minimizing pain on injection

Type	Technique	Clinical considerations	Quality of evidence
Procedural	Proper positioning and ergonomic equipment [22, 24]	Patient and provider comfort	C
	Smaller gauge needle with frequent replacement [29, 31]	32 gauge > 30 gauge	B
	Injection through a pore/follicular orifice [30]		C
	Slow, deeper infiltration, injection at 90-degree angle [29, 31]	Fewer nerve fibers transected	D
	Local external cooling—ice, dichlorotetrafluoroethane spray [38–39]		C
	Warming the solution [31, 69–70]		C
Behavioral	Vibration, pinching, tapping, stretching skin [31, 50–51]	Counterirritation theory	C
	"Talkesthesia," music, guided imagery [56, 58]	Distraction	B
	Hypnosis, meditation [53, 59–61]		D
Anesthetic additives	Bicarbonate [64, 67]	Generally 9 or 10:1 mixture	B
	Epinephrine [20, 31]	Vasoconstriction. 1:200,000 adequate	B
	Hyaluronidase [71]	Enhanced diffusion	D

Anesthetic Additives

Additions to injectable anesthetics such as bicarbonate, epinephrine, and hyaluronidase can enhance efficacy and/or improve patient comfort during procedures. The pH of the solution, duration of action of the anesthetic agent, diffusion capabilities, and temperature can all impact the anesthetic effect and degree of patient comfort.

Lidocaine solutions are often acidic, which contributes to pain upon initial infiltration. Commercial preparations of lidocaine generally have a pH of around 6.6–7.0 with the addition of epinephrine decreasing the pH further closer to 3.5–4.6 in order to promote epinephrine stability (1a–3b) [20, 64, 65]. Epinephrine is often added for its vasoconstrictive property. The vasoconstriction provides multiple benefits including minimization of bleeding at the operative site and minimizing systemic absorption. A dual effect is achieved, reducing the potential for systemic toxicity while simultaneously concentrating the anesthetic agent at the target nerves. The addition of epinephrine prolongs the duration of anesthesia by a factor of at least 2 (5) [66]. However, epinephrine increases the acidity of the solution thereby increasing pain with infiltration [20].

To counteract the acidity, bicarbonate is commonly added to increase the pH of the solution, thereby reducing the pain with product infiltration. In a recent Cochrane review, pain associated with the infiltration of a buffered lidocaine solution was significantly less than the pain of unbuffered lidocaine [64]. As expected, the difference in magnitude of the decrease in pain intensity was greater when the solution contained epinephrine, given the lower pH of the unbuffered epinephrine-containing solution compared to plain lidocaine (1a–3b) [64, 67]. Additionally, patient preference results were homogeneous across multiple studies within the meta-analysis with patients universally preferring buffered solutions [64]. A study by Al Shahwan *et al.* noted no significant difference when comparing bicarbonate-buffered lidocaine with preoperative cooling for 2 minutes with ice [21]. While no significant difference existed between the two methods, 60% of subjects reported more pain after the skin cooling compared to the buffered method.

Additional methods have been attempted to reduce the pain of anesthetic infiltration. One small prospective, double-blind study evaluated the difference between a buffered, premixed 1% lidocaine with epinephrine solution and 1% lidocaine freshly mixed with epinephrine on the day of the procedure, both commonly used methods in dermatology offices to reduce anesthetic-associated pain (2b) [68]. Subjects received an intradermal injection of each solution and rated the pain of each injection immediately after using a visual analog scale. While 65% of subjects reported less pain with the buffered solution, results did not achieve statistical significance. Additionally, warming the solution to 98.6–130 °F, particularly when combined with buffering, has been shown to reduce injection-related discomfort (1b–5) [31, 69, 70]. Hyaluronidase is another potential anesthetic additive that promotes diffusion of the anesthetic through digestion of the extracellular matrix. While hyaluronidase has no known properties to reduce pain directly, it has been shown to enhance analgesic efficacy over a larger surface area with a mixture of lidocaine and hyaluronidase when compared to lidocaine alone, requiring lower volumes of anesthetic solution to achieve proper local anesthesia (2b) [71]. No increase in onset or duration was observed [71].

Topical Anesthesia (Table 65.2)

Topical anesthetic agents encompass a wide variety of non-invasive, painless products, which are commonly used prior to minimally invasive cosmetic procedures, such as soft tissue augmentation and laser procedures (2a–3b) [72–77]. They have also shown success with use prior to injections in order to minimize the pain associated with needle stick or venipuncture (1b) [78]. Topical lidocaine and Eutectic Mixture of Local Anesthetics (EMLA, Astra Pharmaceuticals, Westborough, MA) are the two most widely studied and commonly used topical agents in dermatology. Lidocaine is available in many

Table 65.2 Topical anesthetics for cutaneous surfaces

Anesthetic	Onset	Duration	Clinical considerations
EMLA cream (2.5% lidocaine and 2.5% prilocaine hydrochloride)	60–120 minutes [132–133]	3 hours	Applied under occlusion for a recommended minimum of 1 hour, risk of methemoglobinemia [133]
Ela-Max Cream (4% liposomal lidocaine)	Not Defined [133]	Not defined	Over-the-counter. Multiple formulations available, including spray, patches, ointment, and jelly [133]

formulations including cream, viscous solution, jelly, ointment, spray, and patches [77]. Due to its unique liposomal delivery system to enhance penetration through the stratum corneum, lidocaine 4% cream (LMX-4, Ferndale Laboratories, Ferndale, MI, USA) has the advantage of ease of application without occlusion, more rapid onset compared to EMLA, and availability without a prescription [78]. EMLA consists of a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine hydrochloride and is applied to intact skin, under occlusion, for a minimum of 1 hour to facilitate absorption through the stratum corneum.

In one small, randomized pediatric study, a 30-minutes application of 4% liposomal lidocaine without occlusion was shown to be equally as effective as a 60-minute application of EMLA with occlusion prior to venipuncture in children [78]. Further studies exist documenting the success in pain reduction associated with topical anesthetic use prior to minor invasive procedures such as venipuncture or intravenous catheterization (2b) [79–82]. An additional study in children compared the use of an EMLA patch versus placebo prior to local anesthetic infiltration followed immediately by a skin biopsy (1b) [83]. The authors concluded that the EMLA patch did significantly reduce the degree of pain associated with the local anesthetic injection according to verbal pain scores, as assessed by both the patients and physicians. As venipuncture and intravenous catheterization are not synonymous with dermatologic cutaneous procedures, more studies in the dermatologic setting are warranted to truly determine product efficacy.

Additional formulations for topical therapy continue to arise. Friedman *et al*. assessed the efficacy of four commonly used topical agents (EMLA, 4% liposomal lidocaine, tetracaine gel, and Betacaine-LA ointment) with the use of a Q-switched Nd:YAG laser [75]. EMLA and liposomal lidocaine 4% emerged superior and the authors concluded that all four agents achieved adequate anesthesia 90 minutes after initial application. One systematic review concluded that topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine are all equally as efficacious as EMLA [74]. This same systematic review compared topical formulations with infiltrated anesthetic during minor superficial instrumentation such as venipuncture, cannulation, or lumbar puncture. While results were largely mixed, some studies demonstrated non-inferiority or superior results with topical formulations over infiltrative anesthesia. While this data may be extrapolated to advocate the use of topical agents prior to local anesthetic injection, the additional time delay due to the necessary incubation time makes consistent use of this technique impractical for the average busy dermatology practice. However, use should be considered prior to certain pre-planned dermatologic procedures, including treatment of anxious patients and children.

New Longer-Acting Agents (Table 65.3)

The ideal local anesthetic would be nontoxic, relatively painless to inject, have a rapid onset, and a lengthy duration of action, providing adequate intraoperative pain relief throughout the duration of the procedure without the need for frequent injections. Lidocaine is the mainstay for achieving local anesthesia in dermatologic surgery due to its rapid onset and moderate duration. However, for a lengthy, multi-hour procedure such as Mohs micrographic surgery, multiple series of injections are often required to maintain adequate anesthesia through the duration of the multi-step procedure. To combat this issue, some

Table 65.3 Local infiltrative anesthetics

Class	Anesthetic	Onset (minutes)	Duration (hours) with epinephrine	Duration (hours) without epinephrine	Clinical considerations
Amide	Bupivacaine [84]	2–10	2–4	4–6	High concentrations in blood may cause re-entrant arrhythmias that are refractory to treatment; increased cardiac toxicity in pregnant patients [86]
	Etidocaine [84]	3–5	3.3	4–6	High concentration in blood can lead to cardio-toxicity
	Levobupivacaine [86, 88]	2–10	2–4	4–6	
	Lidocaine [101]	<1	0.5–2	1–6.6	Most commonly used local anesthetic in dermatology. Pregnancy category B
	Mepivacaine [101]	3–20	0.5–2	1–6.6	
	Ropivacaine [88–91, 101]	1–15	2–6	Not defined	Safer and longer-acting than bupivacaine
Ester	Procaine [101]	5	0.25–0.5	0.5–1.5	
	Tetracaine [101]	7	2–4	2–8	Longest acting of the ester anesthetics

surgeons are supplementing with a longer-acting agent to ease the burden of multiple injections between layers.

One commonly used agent is bupivacaine. Bupivacaine is a slower-acting agent, with a 2–10 minutes onset; however, it has one of the longest durations of action, lasting 120–240 minutes without epinephrine. Due to the longer duration of action, bupivacaine is commonly used in lengthy surgical procedures. In one randomized, double-blind trial comparing local infiltration of intradermal etidocaine 1%, bupivacaine 0.5%, and lidocaine 2%, each with and without epinephrine, it was concluded that adrenalized bupivacaine lasted 27% longer than lidocaine and 45% longer than etidocaine (1b) [84]. However, it was more painful to inject when compared to lidocaine. Some practitioners will use lidocaine and bupivacaine concurrently to combine the more rapid onset of lidocaine with the longer duration of bupivacaine. One small study investigated intradermal injections of 0.25% bupivacaine, 1% lidocaine, 0.125% bupivacaine mixed with 0.5% lidocaine, and 0.25% bupivacaine mixed with 1% lidocaine, with all solutions also containing epinephrine, although the concentrations of epinephrine differed with each solution (2b) [85]. The authors concluded that there was no statistical difference in time to onset for all four solutions. The mean duration of effect was longer in the bupivacaine groups compared to plain lidocaine, with the longest mean duration noted in the 0.125% bupivacaine with 0.5% lidocaine group which was statistically significant compared to plain lidocaine but not to the other groups. Concentrations of epinephrine differed based on the commercially available formulations and may have played a role in the observed clinical durations. The risk of bupivacaine causing cardiac and neurologic toxicity remains a concern (2b) [86]. However, adverse event data is lacking in the dermatologic literature for local cutaneous procedures suggesting that these toxicities should not preclude its use if staying well below the maximum suggested dosage (5) [87].

Ropivacaine and levobupivacaine are two newer amide anesthetics that have a similar duration of action to bupivacaine with fewer cardiotoxic and central nervous system effects and less pain on injection when compared to lidocaine with epinephrine (2b) [86, 88]. In one prospective randomized study comparing lidocaine 2% to ropivacaine 0.75% for digital nerve blocks, ropivacaine had a longer time to onset for pain control (4.5 minutes) but a longer duration of action (21.5 hours) with less patient requirement for analgesics during the first 24 hours postoperatively (2b) [89]. There have been various reports citing the vasoconstrictive properties of ropivacaine (2b–3b) [88, 90, 91]. While clinical

cutaneous blanching was observed, free blood flow was established with removal of the tourniquet, and no harmful effects were observed in the ropivacaine group suggesting comparable safety profiles to lidocaine even with digital blocks. Moffitt *et al.* compared intradermal injections of four different concentrations of ropivacaine (1, 2, 5, and 7.5 mg/mL) and lidocaine 2% with epinephrine 1:80,000 [88]. Pain of ropivacaine increased with increasing strength, and lidocaine with epinephrine was significantly more painful than 7.5 mg/mL of ropivacaine. Ropivacaine had a fairly rapid onset and long duration of action, with the 7.5 mg/mL concentration having the most rapid onset (51 s) and longest duration of action (773 minutes) compared to the lower concentrations. Compared to prilocaine 1% with epinephrine 1:100,000 for upper blepharoplasties, ropivacaine with epinephrine resulted in significantly less intraoperative bleeding and postoperative edema in a split-faced study (2b) [92]. Additionally, plastic surgery groups have compared the use of ropivacaine 0.375% and levobupivacaine 0.25% for acute postoperative pain relief after septorhinoplasty and found similar postoperative analgesic effects between the two agents [86]. Evidence for the use of levobupivacaine in local cutaneous procedures is lacking and more data is needed.

Regional Nerve Blocks (Table 65.4)

Some of the pain associated with local infiltrative anesthetics involves the volume used and degree of tissue distention during infiltration. Regional nerve blocks involve the anesthesia of small selective nerves for the regional elimination of pain. Nerve blocks hold the advantage of utilizing less total volume of medication, thereby minimizing significant tissue distortion and limiting toxicity, while ultimately causing less patient discomfort (4) [93]. However, they are more challenging to administer and require a thorough knowledge of locoregional anatomy in order to be effective. Regional nerve blocks have an excellent safety profile, with one retrospective study of 135 patients with 816 nerve blocks undergoing a laser procedure demonstrating complications in 1.1% of patients, including vasovagal syncope, swelling, and transient neuropraxia (4) [94]. Most evidence surrounding nerve block anesthesia in dermatology is for facial laser procedures or botulinum toxin injection for hyperhidrosis of the palm. One study found significantly lower pain scores in patents receiving peripheral nerve blocks for facial laser treatments compared to topical anesthesia (3b) [95]. In addition, patients undergoing fairly aggressive treatment with a fractional ablative carbon dioxide laser for rhinophyma tolerated the procedure well with regional paranasal nerve blocks (4) [96]. Multiple clinicians have discovered the advantage of nerve blocks prior to acral injections for hyperhidrosis, (2b–4) [97, 98] with one study showing superiority of nerve blocks to cutaneous cooling (2b) [99] and another showing comparable anesthetic results and high safety profile for peripheral nerve blocks compared to Bier's block (intravenous regional anesthesia) (2b) [100]. Nerve blocks have also demonstrated clinical benefit in more sensitive anatomic locations such as the digits, eyelids, nose, and lips with the added benefit of minimized tissue distortion during cutaneous procedures, which aids with improving reconstruction results, postoperative edema, and ecchymosis (1a, 5) [101].

Management of Postoperative Pain and Anxiety

The pathophysiology of acute postoperative pain is multifactorial, involving the stimulation of nociceptive fibers by direct surgical manipulation, postoperative inflammatory pathways that result in downstream modulation of afferent and cortical networks, and previously established psychosocial and neurologic factors that influence cortical pain modulation (5) [12]. Previous studies have demonstrated that failure to properly manage acute postsurgical pain increases the rate of complications including bleeding, poor wound healing, insomnia, chronic pain, substance abuse, and various psychological disorders [12]. Thus, understanding the nature of pain experienced by patients undergoing

Table 65.4 Regional nerve blocks

Nerve block	Clinical indication	Nerve involved	Technique	Area anesthetized
Supratrochlear/ Supraorbital	Laser resurfacing or other laser procedures, local surgery [93, 95]	Supratrochlear, supraorbital	Supratrochlear at medial eyebrow and nasal root junction Supraorbital foramen in midpupillary line at orbital rim	Supratrochlear-medial brow, central forehead/ frontal scalp Supraorbital- middle/ lateral brow and lateral forehead/frontal scalp
Infraorbital		Infraorbital	Percutaneous or mucosal approach Infraorbital foramen in midpupillary line Mucobuccal fold over the second premolar	Lower eyelid, medial cheek, nasal ala, upper cutaneous lip [101]
Mental		Mental	Percutaneous or mucosal approach Foramen midway between the upper and lower edges of the mandible in a direct line with the second bicuspid Gingival-buccal fold at the base of the first bicuspid and directed parallel to the bicuspid in the direction of the foramen [135]	Soft tissues of lower lip and chin
Regional paranasal	Mohs surgery, rhinophyma correction, rhinoplasty [96]	Dorsal nasal branches	Where the nasal bone meets cartilage about 0.6–1.0 cm lateral to midline	Dorsal/lateral nose and tip
Digital	Local surgery, nail procedures	Digital nerves (fingers or toes)	Lateral finger/toe on each side Interweb injections generally less painful. Single volar subcutaneous block is another option [134]	Digit distal to area of anesthesia
Wrist	Hyperhidrosis botulinum toxin injections, local acral surgery [97–98]	Median and/or ulnar nerves	Median insertion between the palmaris longus and flexor carpi radialis at the most proximal wrist crease Ulnar—same level, between the ulnar artery (pulse) and the flexor carpi ulnaris tendon	Median—majority of palm, digits 2–3, and partial anesthesia of digits 1 and radial side of 4 Ulnar—hypothenar eminence, digits 5, and ulnar side of 4

dermatologic surgery and the proper treatment of such postoperative pain is critical in the successful management of postsurgical patients.

Predicting Postoperative Pain

Patients undergoing dermatologic surgery typically experience mild to moderate postoperative pain (4) [14, 102]. Several studies have examined how preoperative and perioperative factors influence postoperative pain levels following Mohs surgery (2B, 4) [14, 15, 103]. The highest pain levels occur on the day of surgery, being most prominent 4 hours postoperatively, and decrease with each successive postoperative day. There has been no reported significant difference between pain levels in the morning and in the evening [15, 103].

Several studies have demonstrated that younger patients have higher levels of postsurgical pain [14, 15]. Firoz *et al.* prospectively analyzed the relationship between postoperative pain levels and

surgical and patient characteristics of 433 patients undergoing Mohs surgery [15]. The authors reported that patients younger than 66 years (the mean age of the cohort) had significantly higher pain levels than patients older than 66 years. There were no statistical differences in pain levels between men and women. Conversely, a study by Merritt and colleagues entailing 1550 patients undergoing Mohs surgery showed women had significantly higher levels of postoperative pain [100]. Multiple studies have shown that patients undergoing Mohs surgery for more than one lesion at a time report higher pain levels than those with only one lesion treated [14, 15, 102].

Although there is clear evidence that having multiple same-day lesions removed and being younger correlate with higher postoperative pain, the significance of location, lesion size, and modality of repair requires further elucidation. While Firoz and colleagues did not find significant differences in postoperative pain levels when separating lesion locations by head and neck versus trunk and extremities [15], several studies associated scalp lesions [14]; lip, nose, and ear lesions [103]; and genital lesions [102] with higher postoperative pain levels among patients. There is no clear consensus regarding the type of closure and mean pain scores. Firoz *et al.* showed that full-thickness skin grafts and flaps (rotation, advancement, transposition, and island pedicle) correlated with the highest pain scores on the day of the surgery, followed by linear closures and secondary intention healing [15]. However, Limthongkul and colleagues did not find any statistical differences in pain scores among patients who underwent different closure techniques in their cohort [14].

These conflicting reports suggest that there are additional factors responsible for pain levels following Mohs surgery other than repair type and lesion site. Studies of non-dermatologic procedures report that obesity, depression, history of hyperalgesia, opioid, and anxiolytic use may be associated with higher postsurgical pain [12]. While it is difficult to predict which patients are more likely to experience pain, surgeons should discuss the spectrum of postoperative pain patients may experience in order to establish appropriate expectations and create a proper management plan.

Postoperative Pain Management

There is no universally accepted treatment for postsurgical pain following dermatologic surgery [12]. As such, balancing successful postoperative analgesia with potential side effects of pain medications is a challenging but crucial step for any dermatologic surgeon. Successful pain management can not only increase patient's comfort and overall satisfaction of the surgery but ensure the surgical experience will not hinder the patient from seeking further dermatologic care.

Evidence for Pain Management with NSAIDs and Acetaminophen (Table 65.5)

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation by selective or nonselective inhibition of the pro-inflammatory enzyme cyclooxygenase (COX), which facilitates the metabolism of phospholipid-derived arachidonic acid into prostaglandins in response to tissue injury. Non-selective NSAIDs inhibit both COX-1 and COX-2, while selective NSAIDs are specific for COX-2. It is hypothesized that inhibition of COX-2 is responsible for decreased pain and inflammation, while inhibition of COX-1 may impair renal perfusion as well as lead to gastric perforation [12]. The benefit of NSAIDs in postoperative care can be attributed not only to pain control but also to decrease in postoperative opioid consumption (2B; 5) [104–106].

While the effect of NSAIDs in postoperative pain management, specifically in dermatologic surgery, has not been well studied, previous trials examined the efficacy of ibuprofen versus acetaminophen with codeine in mitigating postoperative pain in patients undergoing cosmetic facial surgery. Chen *et al.* performed a prospective, double-blind randomized trial where patients received either 400 mg of oral ibuprofen or 600/60 mg of acetaminophen/codeine four times a day through the third postoperative day [107]. There were no significant differences in pain levels or the amount of bruising or hematomas between two groups; however, the group

Table 65.5 Non-opioid management for postoperative pain following dermatologic surgery

Chemical class	Drug	Half-life (hours)	Recommended oral dose	Maximum oral dose per 24 hours	Clinical considerations
P-Aminophenol derivative	Acetaminophen [103, 107, 112, 137]	1–4	650–1000 mg every 4–6 hours	3000 mg	Higher doses may lead to hepatic toxicity and renal damage; avoid in chronic alcohol consumers and known liver disease
Salicylate	Aspirin [108, 136–137]	0.3	325–1000 mg every 4 hours	4000 mg	Long-term usage may lead to gastric ulcers and bleeding
Cox-2 selective NSAID	Celecoxib [136, 137]	11	50–100 mg every 12 hours	400 mg	Special consideration in the elderly population as peak plasma concentrations can be up to 40% higher than in younger population
Propionic acid class of NSAIDs	Ibuprofen [107, 136, 137]	2–4	200–800 mg every 4–6 hours	2400 mg	Elderly (>60 years), smokers, patients with previous history of peptic ulcers, patients receiving corticosteroids or anticoagulants, or patients with renal, cardiac, or liver disease may be at a higher risk for GI side effects and renal failure
Acetic Acid class of NSAIDs	Ketorolac [104, 106, 136–137]	5–6	10 mg every 4–6 hours	40 mg	Treatment should be limited to 5 days; dose should be reduced by 50% in patients over 65 years
Anticonvulsant	Gabapentin [114, 137]	5–7	100–300 mg every 24 hours	3600 mg	May lead to dizziness, drowsiness, peripheral edema
	Pregabalin [123, 137]	6–11.5	25–75 mg every 12 hours	600 mg	

receiving ibuprofen had significantly less side effects [107].

Given that NSAIDs inhibit platelet aggregation, thus potentially prolonging bleeding time, there is a concern that postoperative NSAID use may lead to bleeding complications including dehiscence, hematoma formation, or cutaneous hemorrhage. In a series of case studies, Lawrence *et al.* showed that intraoperative bleeding complications during dermatologic surgery only occurred in patients who are taking aspirin and have prolonged bleeding times, suggesting that patients who have normal bleeding times may continue NSAIDs prior to surgery (4) [108]. Similarly, in their cohort of patients, Chen and colleagues did not find evidence of ibuprofen increasing bruising or rates of hematoma compared to non-NSAIDs [107].

For certain patients, acetaminophen may be more advantageous than NSAIDs as it does not impede platelet function and is safer to use in patients with a previous history of peptic ulcers. Firoz and colleagues prospectively evaluated 433 patients undergoing Mohs surgery with the Wong-Baker pain scale [15]. Patients recorded their perceived pain levels up to postoperative day 4. Only 52% of 433 patient cohort took any medications on the day of the surgery, with the majority of patients managing their pain with 500 mg of acetaminophen. 7.1% of patients took narcotic medications on the day of surgery, with a steadily decreasing usage seen on each successive postoperative day. Postoperative defect size was not a significant predictor of the medication type preferentially used by patients. Thus acetaminophen is an effective analgesic following cutaneous surgery. Additionally, considering albeit limited studies, that ibuprofen is as effective at managing postoperative pain as acetaminophen and codeine, with fewer side effects and without increased rates of bruising or hematoma, eligible patients may receive ibuprofen for pain control rather than prescribed narcotics for treatment of postoperative pain.

Pain Management with Narcotics

Opioids are reserved for patients with moderate to severe pain. Oral opioids, such as codeine, oxycodone, and hydrocodone, may be used alone or can be prescribed in combination with acetaminophen or NSAIDs. Opioid analgesia is often limited by the adverse side effects including vomiting, constipation, nausea, pruritus, and more rarely respiratory depression. Special attention must be given while prescribing narcotic medications to the geriatric population, who make up a significant portion of patients undergoing dermatologic surgery for malignancies. As such, choosing opiates as the analgesic of choice in postoperative pain control must be weighed against their adverse effects.

In a retrospective review of 233 charts, Harris and colleagues showed that 82 patients (35% of the cohort) received postoperative opioid prescription following dermatologic surgery (4) [109]. A different study by Harris and colleagues showed that 86% of patients who filled a prescription for opioids had left over pills (49 out of 57 patients). Additionally, 26 of these 49 patients reported that they considered the possibility of not discarding the excess medication (4) [110]. As such, there may be a tendency for dermatologic surgeons to over-prescribe opioids following dermatologic surgery. Since opioids carry a high side effect profile and previous studies have shown that acetaminophen and NSAIDs provide satisfactory analgesia following dermatologic surgery, acetaminophen and NSAIDs should be recommended as first-line analgesics and opioids should only be prescribed if pain control with non-opioids is insufficient.

Evidence for Pain Management with Dual Therapy

Multimodal analgesia can be an effective treatment for postoperative pain due to combining differing mechanisms of the multiple drugs. A Cochrane review analyzed three trials that compared the postoperative efficacy of ibuprofen 400 mg plus 5 mg oxycodone versus placebo (603 subjects), 400 mg ibuprofen plus 5 mg oxycodone versus 400 mg ibuprofen monotherapy (717 subjects), and 400 mg ibuprofen plus 5 mg oxycodone versus 5 mg oxycodone monotherapy (471 subjects). The authors concluded that combining 400 mg ibuprofen with 5 mg oxycodone produced longer pain relief than oxycodone alone but not ibuprofen alone (1A) [111]. A meta-analysis conducted by Ong and colleagues examined the multimodal therapy of NSAIDs with acetaminophen for postoperative pain management. Of the 21 human trials analyzed, the multimodal combination of acetaminophen and NSAIDs was more effective than paracetamol or NSAIDs alone in 85% and 64% of the studies, respectively (1A) [112]. In a systematic review of 60 trials, Maund *et al.* showed that when paracetamol, NSAIDs, and COX2 inhibitors were added to patient-controlled analgesia morphine, all produce a postoperative morphine-sparing effect, with a mean cumulative reduction of morphine usage of 6.34–10.92 mg compared to placebo (1A) [113].

A randomized, double-blind study led by Sniezek and colleagues examined the efficacy of analgesia between 1000 mg acetaminophen monotherapy, 1000 mg acetaminophen plus 400 mg ibuprofen, and 325 mg acetaminophen plus 30 mg codeine in 210 patients undergoing Mohs surgery for solitary head and neck skin cancers [103]. Patients received a mandatory dose immediately following surgery and additional doses every 4 hours as needed. Postoperative pain levels were analyzed at postoperative hours 0, 2, 4, 8, and 12 using a 100-mm visual analog scale. The group randomized to receive acetaminophen and ibuprofen had the smallest change in pain scores from baseline at 2, 4, 8, and 12 hours postoperatively. There were no statistical differences in pain levels among patients in the three cohorts who underwent surgery for lesions larger than $10cm^2$ [2]. Interestingly, although both acetaminophen plus ibuprofen and acetaminophen plus codeine groups provided adequate analgesia, the former cohort reported no adverse side effects, while the latter cohort reported increased bleeding episodes, which is contrary to the commonly held belief that postoperative NSAID use causes

an increase in bleeding complications [103]. Importantly, this study highlights that the use of non-opioid analgesics for small dermatologic defects may be superior to the use of opioids.

Given the high efficacy and minimal complication rate of acetaminophen and ibuprofen, patients should be offered this combination as the first-line analgesic regimen for Mohs surgery. In cases where patients are more likely to experience higher levels of postoperative pain, such as those patients undergoing multiple procedures in a day, or procedures in sensitive regions, such as the scalp or lips, this subset of patients may be offered narcotic medications. However, they should be prescribed a limited number of pills to minimize dependency, as well as to improve interval follow-up rates for refractory pain.

Evidence for Pain Management with Gabapentin/Pregabalin

Gabapentin, a structural analog of γ-aminobutyric acid, is an FDA-approved anticonvulsant for the treatment of seizures and post-herpetic neuralgia (5) [114]. While the exact mechanism of gabapentin-mediated neuropathic pain mitigation is unclear, one plausible explanation entails nerve injury leading to redistribution of calcium and sodium channels, causing neurons to fire spontaneously or at higher frequencies (5) [113–115]. It has been suggested that gabapentin may employ its antihyperalgesic effects by counteracting the hyperexcitability of these pathological channels (5) [115].

Gabapentin possesses a relatively benign side-effect profile, the most common adverse effects being dizziness and somnolence [116]. However, cases of gabapentin-induced ataxia, myoclonus, diplopia, nausea, rhinitis, and Stevens-Johnson syndrome have been reported (5) [116, 117]. The antinociceptive properties combined with a relatively mild side effect profile make gabapentin an attractive candidate for managing postoperative pain. A Cochrane meta-analysis analyzing double-blind trials comparing a single dose of preoperative gabapentin versus placebo in patients undergoing either dental or orthopedic surgeries demonstrated that gabapentin is superior in controlling acute postoperative pain. However, the number needed to treat is inferior to routinely prescribed analgesics (1A) [116].

Gabapentin's role in the postoperative pain management of dermatologic surgeries has not been explored in detail. One case report illustrated the efficacy of gabapentin in a 52-year-old woman who presented with diffuse left cheek pain radiating to the neck and ear following a face-lift procedure. The pain, while refractory to previously administered analgesic medications, responded to a 2-week course of 300 mg gabapentin administered three times daily (5) [118]. Gustorff and colleagues examined the efficacy of gabapentin compared to opioid remifentanil following UVB-induced inflammatory hyperalgesia (2b) [119]. In a double-blind, placebo-controlled study, a patch of skin on 16 healthy volunteers was irradiated with UVB light prior to treatment with either placebo, oral gabapentin, IV remifentanil, or a combination of IV remifentanil and gabapentin. Hyperalgesia in these spots was measured via heat pain perception threshold and heat pain tolerance threshold. Gabapentin did not affect these thresholds, suggesting that gabapentin may not be an effective analgesic for hyperalgesia due to inflammatory skin conditions. Taken together, this evidence suggests that while gabapentin may be a potential avenue for treatment of neuropathic pain, it does not play a role in inflammatory cutaneous conditions where there is no nerve injury [116].

Pregabalin has a similar mechanism of action to gabapentin but with faster oral absorption (5) [120]. In a prospective, randomized, placebo-controlled, double-blind trial involving 52 patients, Wei and colleagues examined the efficacy of 150 mg pregabalin administered 15–60 minutes prior to eyelid surgery compared to placebo (3b) [121]. Subjects were given postoperative acetaminophen for pain control and were asked to evaluate their pain levels using a visual analog scale at time intervals up to 48 hours postoperatively. Throughout the evaluation, patients who were randomized to receive pregabalin reported a 5.5-point lower pain score on average (in a scale of 0–100) compared to

those receiving placebo. Additionally, subjects that received preoperative pregabalin required less postoperative acetaminophen for pain control [121]. However, in a similar randomized study entailing 110 women undergoing same-day cosmetic surgery, Chaparro *et al.* found no statistical difference in the postoperative opioid or anti-inflammatory requirements between those receiving either 75 mg of oral pregabalin every 12 hours for 5 days prior to surgery or placebo (2b) [122]. A systemic review analysis involving 55 studies which assessed the analgesic efficacy of various doses of perioperative pregabalin showed that pregabalin was associated with opioid sparing 24 hours following surgery (1a) [123].

Both gabapentin and pregabalin are potentially effective options to control neuropathic pain following cutaneous surgery. However, further research is warranted to identify whether gabapentin and pregabalin could control non-neuropathic pain following cutaneous surgery and whether the abovementioned studies can therefore be extrapolated to dermatologic surgery.

The excellent safety profile and often expedient postoperative recovery after dermatologic surgery often preclude a detailed discussion about pain control as many patients require minimal to no postoperative pain management. However, patients should be aware of the sequela of postoperative healing, including bruising, swelling, and proper management of pain should they encounter it. Acetaminophen and ibuprofen are a common and efficient treatment for pain in minor dermatologic procedures [15, 103]. However, in a subset of patients who are more likely to encounter more severe pain, they may be offered narcotic pain medication [103]. The side effects of narcotics should be disclosed to the patient, such as constipation and nausea, as these may negatively influence the patient's adherence to the medication—leading to inadequate pain control. Additionally, dermatologic surgeons should remain cognizant of potential for abuse of prescribed narcotics, especially in the setting of the high volume of dermatologic surgeries performed. Therefore, for all the abovementioned reasons, non-opioid alternatives should be considered as first-line analgesics in patients undergoing cutaneous surgery.

Current Evidence on Postsurgical Wound Care

A moist wound environment increases the healing rate of cutaneous lesions by preventing cellular dehydration and subsequent cell death, fostering growth factor release by viable cells, and promoting angiogenesis, ultimately reducing pain during healing and improving cosmetic results (5) [124, 125]. While many dermatologic surgeons achieve this by advising patients to apply topical emollients for 1–2 weeks following surgery, there is no universally accepted standard of care regarding wound care following cutaneous surgery (4) [126].

The risk of infection after dermatologic surgery is low, with previous studies reporting infection rates of 2.45% in Mohs surgery and 2.13% following excisions (2c) [127]. Despite these low infection rates, a previous study demonstrated that dermatologists were more likely to prescribe topical prophylactic antibiotics (6.5%) compared to non-dermatologists (3.5%) (4) [128]. A randomized, double-blind, prospective trial of 922 patients undergoing dermatologic surgery showed that postoperative use of white petrolatum carried the same infection rate as bacitracin but with a lower risk of allergic contact dermatitis (2b) [129]. Campbell and colleagues prospectively randomized patients undergoing auricular Mohs surgery to receive either gentamicin ointment or petrolatum postoperatively. The authors showed that there was no statistical difference in the rates of infection among both cohorts. However, 11.9% of patients using gentamicin, and only 3.33% of patients using petrolatum, developed inflammatory chondritis (2b) [128]. This data suggests that prophylactic topical antibiotics are not necessary following Mohs surgery. Indiscriminate use of such treatment may not only cause dermatitis but can ultimately lead to bacterial resistance.

A 2013 survey of practicing Mohs surgeons reported that petroleum jelly (53.1%) was the most common topical emollient applied immediately post-surgery, followed by Aquaphor (19.4%) and bacitracin (8.2%) [126], with topical antimicrobial treatment being used by 17.7% [124]. For postoperative wound care at home,

the majority of surveyed surgeons recommended petroleum jelly (69.4%), Aquaphor (38.4%), and bacitracin (10.0%). It is important to note that petroleum jelly has a low risk of allergic dermatitis, while Aquaphor, which contains lanolin, may cause a positive reaction in a subset of patch-tested individuals [124]. The successful trend of dermatologic surgeons educating patients regarding the use of topical emollients, rather than antimicrobial agents, may ultimately lead to lower rates of antibiotic resistance and allergic dermatitis.

Postoperative Cold Analgesia

The use of ice packs to reduce pain and swelling is a common household practice. Cooling causes vasoconstriction, thus decreasing blood flow and resulting in reduced tissue metabolism and oxygen consumption, inflammation, and muscle spasms of the treated region (5) [130]. However, the evidence behind the use of ice packs following dermatologic surgery is limited.

Previous studies demonstrate that cold-pack application immediately following surgery reduces postoperative pain levels. Koc *et al.* enrolled 40 patients undergoing inguinal hernia repair in a double-blind, randomized study (4) 131]. Either ice or room temperature water in a plastic bag was applied postoperatively over the incision for 20 minutes, and pain levels were assessed using a VAS scale. There was a decrease in pain levels associated with postoperative ice treatment. Pool *et al.* enrolled 38 subjects undergoing bilateral upper blepharoplasty to study the effect of local ice-pack application on postoperative pain (4) [131]. One eyelid per patient was randomized to receive an ice pack for 30 minutes immediately after surgery, 15–20 minutes upon returning home, and three times for 15–20 minutes on the first postoperative day. The authors used a VAS to assess pain levels at 1 hour and 1 day postoperatively. While the pain levels did not differ between each eyelid on the day of surgery, there were significantly lower pain levels in cooled eyelids on the first postoperative day. However, while statistically significant, the reported pain-level differences were not found to be clinically relevant, nor did ice-pack application reduce hematoma, erythema, or edema between the two groups. Based on these findings, the authors concluded that postoperative cooling following blepharoplasty should not be recommended.

While some studies suggest cold-pack application may potentially decrease postoperative pain, further research is needed to validate the clinical utility of this affordable and simple way to reduce pain following dermatologic surgery.

Conclusions

Management of perioperative and anxiety levels is critical in dermatologic surgery. Preoperative education plays a critical role not only in ensuring the patient's understanding of the procedure and post-procedural care but also in helping the physician assess the patient's baseline anxiety level. Studies show that same-day preoperative education is sufficient to counsel patients regarding their care. Current evidence supports the utility of preoperative oral benzodiazepines to ease patients' anxiety throughout the surgery, particularly in a subset of patients that have a higher baseline anxiety level. Multiple perioperative measures may be utilized to reduce pain and anxiety of conscious surgery and local anesthesia administration. These range from perioperative music and intraoperative distraction techniques to various methods of limiting pain associated with anesthesia including buffered solutions of local anesthesia, warmed solutions, and longer-acting local agents. Dermatologic surgery has an excellent safety profile, often associated with minimal postoperative pain. Nontheless, it is important to prospectively address patient concerns regarding potential for postoperative pain, and establish a clear plan between the medical team and the patient. Multiple studies support the efficacy and favorable side effect profile of ibuprofen and acetaminophen in postoperative pain reduction; thus, prescription of narcotics should be reserved for a subset of patients with increased risk factors for higher

postoperative pain. Finally, larger-scale and controlled trials are needed specifically in dermatologic surgery in dermatologic surgery to further validate optimal peri- and postoperative pain control to allow dermatologic surgeons to continue to provide excellent, evidence-based care for our patients.

Observations and Recommendations

Evidence-Based Summary for Management of Perioperative Pain and Anxiety

Level of Evidence	Conclusions
B	Oral midazolam reduces perioperative anxiety during dermatologic surgery
C	While there is a clear role of preoperative education in management of pain and anxiety, same-day preoperative education may be sufficient in dermatologic surgery
C	Smaller-gauge needles with frequent replacement, and needle insertion into a pore/follicular opening, can minimize injection pain
B	Sodium bicarbonate is often added to local anesthetic mixtures to increase the pH of the solution and reduce pain with product infiltration
B	The use of longer-acting agents such as bupivacaine, ropivacaine, or levobupivacaine is recommended in lengthy, multi-step procedures
C	Regional nerve blocks are useful in anesthetizing large areas (i.e., full face), and anatomically sensitive areas (i.e., eyelid, nose, lip), to minimize tissue distortion and limit toxicity
C	Patients undergoing same-day surgery for multiple lesions as well as younger patients may have higher postoperative pain levels
C	Postoperative use of topical petrolatum carries the same rate of infection as postoperative use of topical bacitracin
B	Individual or multimodal use of acetaminophen and ibuprofen may be sufficient in management of postoperative pain following dermatologic surgery and can be used as first line in place of opioids

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Self-Assessment Questions

1. Based on current evidence, what is the recommended topical ointment following dermatologic surgery for most anatomic locations?
   (a) Gentamicin ointment
   (b) White petrolatum
   (c) Bacitracin ointment
   (d) Aquaphor

2. Which of the following local infiltrative anesthetics has the longest duration of action?
   (a) Ropivacaine
   (b) Bupivacaine
   (c) Tetracaine
   (d) Lidocaine

3. Which of the following statements regarding postoperative pain is correct?
   (a) Older patients typically have higher levels of postoperative pain
   (b) Men in general experience higher pain levels then women
   (c) Having multiple lesions removed on the same day correlates with higher postoperative pain
   (d) Patients should expect the highest pain levels on the second postoperative day

4. Based on current evidence, which of the following benzodiazepines has shown promise in the treatment of preoperative anxiety in patients undergoing dermatologic surgery?
   (a) Oral midazolam
   (b) IV diazepam
   (c) Oxazepam
   (d) IV midazolam

5. Which of the following anesthetic additives has the strongest evidence to support its use in reducing pain on infiltration?
   (a) Epinephrine
   (b) Hyaluronidase
   (c) Sterile saline
   (d) Bicarbonate

Answers

1. b: White petrolatum. Evidence suggests that wounds receiving white petrolatum had the same infection rates when compared to wounds treated with bacitracin or topical gentamicin. White petrolatum had the same infection rate when compared to bacitracin or topical gentamicin. Additionally, petrolatum had a lower risk of allergic contact dermatitis and inflammatory auricular chondritis compared to the antibiotic ointments.
2. a: Ropivacaine. Ropivacaine has been shown to last an average of 2–6 hours without epinephrine, with studies demonstrating a duration of 21.5 hours when used in a nerve block and 12.9 hours when combined with epinephrine.
3. c: Having multiple lesions removed on the same day correlates with higher postoperative pain. Younger patients and those undergoing same-day multiple site surgeries tend to have higher levels of pain. The highest pain is generally within the first 24 postoperative hours.
4. a: Oral midazolam. An optimal anxiolytic for dermatologic surgery would have a rapid onset, a short half-life, and a large safety margin, thereby enabling appropriate administration in an outpatient setting. Several studies have examined the role of preoperative oral midazolam in patients undergoing dermatologic surgery. The authors concluded that oral midazolam is a safe and effective anxiolytic and that the provided anxiolysis, in combination with local anesthetics, was sufficient without intravenous sedation or general anesthesia.
5. d: Bicarbonate. To counteract the acidity of lidocaine, bicarbonate is commonly added to increase the pH of the solution, thereby reducing the pain with product infiltration. In a recent Cochrane review, pain associated with the infiltration of a buffered lidocaine solution was significantly less than the pain of unbuffered lidocaine. Additionally, patient preference results were homogeneous across multiple studies within the meta-analysis with patients universally preferring buffered solutions.

Prevention of Undesirable Outcomes

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Nicholas Golda, Brandon Brown, Alison Basak, Kathryn Potter, and Nita Kohli

Abstract

When performing reconstructions in cutaneous surgery, there are several potential pitfalls that can lead to suboptimal outcomes. The most common of these issues include wound edge necrosis, trapdoor deformities, flap or graft necrosis, nasal valving, and free margin distortion. In this chapter, the causes of these issues are explored, and evidence-based techniques for minimizing or preventing inferior outcomes related to these factors as well as techniques that can be used to address these outcomes should they arise are discussed.

Keywords

Wound edge necrosis · Ectropium · Eclabium Pincushioning · Trapdoor deformity · Graft necrosis · Nasal valving

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Wound Edge Necrosis

Epidemiology

The incidence of skin edge necrosis has not been described, though, anecdotally, this is a more or less common occurrence in dermatologic surgery depending on patient and technique factors existent in different surgeons' offices.

Severity and Duration

Wound edge necrosis can result in a more obvious scar where wound edges have been brought together. While the cosmetic impact of this may be important to some patients, it may be less so to others. The furrowing along the wound edge that can be present in the setting of resolved wound edge necrosis is typically permanent though some improvement may be noted during the first 6–12 months postoperatively during which time collagen remodeling and wound maturation occur.

Preoperative Evaluation

As most known causes of wound edge necrosis are technique-dependent, there are no significant preoperative factors to consider in an effort to

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prevent this complication. One of the most significant patient factors associated with wound edge necrosis is smoking. A meta-analysis of several cohort studies including thousands of patients found a significantly increased risk of wound necrosis, healing delay, dehiscence, and infection in smokers when compared with nonsmokers. With respect to smoking cessation, a meta-analysis of studies of complications following elective general surgical and orthopedic procedures showed a significantly lower rate of overall complications, wound healing complications, and infections in patients on smoking cessation programs with the benefit increasing with every week of smoking cessation up to 6 weeks (2a) [1]. A prospective study focusing on skin surgery, however, showed no significant difference between smokers and nonsmokers with respect to infection, bleeding, wound dehiscence, and total complication rate. A significant difference was, however, found with respect to scar contour distortion with smokers having a greater risk of this result. This may be attributable to wound edge necrosis, but that attribution is not certain with the information collected in the study (3b) [2].

Effect of Wound Edge Necrosis on Patients

Scars, especially on the head and neck, can change physical appearance and negatively impact psychosocial functioning (2a) [3]. For some patients, their satisfaction with skin cancer treatment correlates significantly with the final aesthetic outcome of their surgery. The impact of flap and graft necrosis on patients has not been studied specifically, but common sense dictates that this complication is likely to distress patients about the future cosmesis and functionality of their repair. Infection, multiple office visits, and supplementary surgeries may be additional worries. For most patients, knowing that their surgeon takes their concerns seriously and stands behind their work goes a long way toward assuaging their worries. Most patients can be reassured that they will heal without the need for further significant intervention. If further interventions are needed, then a repeat surgical procedure should not be feared. If either the surgeon or the patient is uncomfortable revisiting the surgical site, referral of the patient to a colleague for support may be warranted. It may also help to preemptively counsel patients about how their underlying conditions can influence outcomes prior to initiating the repair process. This is true of all of the succeeding sections with the addition of some functional implications associated with nasal valve dysfunction and free margin violation.

Preventive Interventions

There are many widely accepted beliefs among surgeons regarding the techniques that can be used to reduce or eliminate wound edge necrosis. Although some data from rigorous evidence exists, the majority of the dogma regarding wound edge necrosis arises from collective experiential wisdom of experts in the field. In general, the best practices and techniques that avoid flap necrosis should apply for the prevention of wound edge necrosis as well, and this section will deal only with evidence related to wound edge necrosis specifically and a literature search focused on wound edge necrosis as a search term.

Proper suturing technique is often mentioned as a means of avoiding wound edge necrosis. Recommendations that can be found without citations in texts and that are taught in many training programs often center around placing sutures in a manner meant to avoid interference with blood flow to the wound edges. Suturing techniques that may impede blood flow to the wound edge include the placement of too many sutures in a wound and placement of sutures too close to one another, both of these being very subjective as to what constitutes too much or too close (5). Sutures placed too tightly can also contribute to wound edge necrosis. Extreme cases of sutures being placed too tightly can be readily identified by tissue bulging between each suture bite. Less readily identifiable cases of overly tight suturing occur when suture technique and suture materials do not allow for the increased

tension caused by post-procedural tissue edema. The suturing pattern can also increase the risk of wound edge necrosis by wound edge ischemia with the use of horizontal mattress, vertical mattress, or running locked sutures (5). One technique that has been shown in studies to reduce wound edge necrosis is proper wound edge or epidermal apposition [4, 5]. A microscopic study of the healing process in sutured wounds in rats, pigs, and humans showed that imperfect apposition of the epidermal edges caused increased dermal necrosis from the overhanging margin as the regenerating epidermis follows the most superficial plane that supports its growth and effectively planes through the overhanging dermis and epidermis. The dermis that is lost is replaced by a scar, and the greater the failure of approximation, the greater the amount and width of scar that is formed (2c) [4].

Handling of tissue is another potential cause of wound edge necrosis. We know from studies of traumatic wounds that tissue that has been subjected to crush injury tends to undergo necrosis [6]. (D) Further, it is widely held that delicate tissue handling, such as with skin hooks or gently with the teeth of tissue forceps, can avoid crush injury to the wound edge and is recommended both during the process of undermining and hemostasis and during suturing or any other scenario where the edges of a wound are to be handled with instruments (5). Further, during the suturing process, multiple attempted passes of a needle through the same region of the wound edge causes tissue trauma that may result in wound edge necrosis (5). Undermining in a superficial plane may possibly predispose to wound edge necrosis due to interruption of blood supply to the skin from deeper perforating vessels that traverse the subdermal fat (5).

A small internally controlled study on piglets compared wound tension forces on sutured wounds closed with and without undermining and/or the use of a skin stretching device for 30 min. The study showed a statistically significant reduction in wound closure tension when the stretching device was used without undermining compared with undermining without the use of the stretching device ($p < 0.001$). This study also showed deep and shallow wound necrosis in 8 out of 15 cases where undermining was employed, while only 1 out of 15 cases that closed with the skin stretching device without undermining showed superficial necrosis. No statistical analysis was done on the significance of this difference, but if significant, this decrease could be due to less vascular interruption by the elimination of undermining or decreased wound tension through use of the skin stretching device (2b) [7].

Another widely held principle of proper wound closure is that wounds under tension will exhibit a greater degree of wound edge necrosis and dehiscence than wounds under little or no tension. This concept is based at least in part on Poiseuille's law, which states that the flow rate through a vessel is proportional to the radius of that vessel to the fourth power. As a vessel is stretched under tension, the lumen shrinks, and according to this concept even small reductions in the radius of a vessel can dramatically reduce the flow of blood to the edges of a wound. One study has demonstrated that there is a measurable inverse relationship between tension and blood flow with necrosis becoming significantly more likely when experimental skin flaps are put under 250 g or more of tension (5) [8].

Electrocautery used injudiciously around wound edges has also been implicated in wound edge necrosis (3b) [5]. This can occur by two key mechanisms: direct injury of the wound edge tissue by contact with the electrosurgical electrode or burning of the wound edge by contact with boiling liquid due to insufficient removal of blood from the operative field during hemostasis.

Other factors that may contribute to wound necrosis were presented in a secondary analysis of data from a multicenter prospective RCT assessing tissue closure techniques, which found that in addition to the factors mentioned previously, extremity location of the wound and wound width resulted in poorer cosmetic appearance of wounds on both univariate and multivariate analysis when applying a validated ordinal scale for wound cosmesis. Interestingly, the development of wound infection and the use of

buried sutures showed statistically insignificant effects on wound cosmesis (2b) [5].

Several topically applied agents have been shown to reduce random-pattern skin flap necrosis, such as topical nifedipine, topical trolamine salicylate, topical nitroglycerin, and others (4) [9]. With respect to flap edge necrosis specifically, topically applied 60% dimethylsulfoxide (DMSO) postoperatively and for the week following breast reconstruction with flap closures showed significantly less flap edge necrosis by weight than untreated flaps (23.48 vs. 126.27 micrograms, $p = 0.03$) with shorter hospital stays postoperatively as well (9.6 vs. 11.8 days, $p = 0.02$). This study on breast reconstruction may, however, not be generalizable to facial reconstruction with random-pattern flaps (2b) [10].

Corrective Interventions

There is no published evidence of treatments for poor or marginal scarring following wound edge necrosis other than what is traditionally done for suboptimal scarring. These interventions include but are not limited to dermabrasion, subcision, pulsed dye laser, fractional resurfacing, and excision of the scar with reclosure.

Flap and Graft Necrosis

Epidemiology

Flap and graft necrosis constitutes an uncommon but potentially devastating outcome following dermatologic surgery. Rates of necrosis have not specifically been assessed in large prospective trials, but rough incidence data in the United States can be extracted from studies looking at complication rates in cutaneous surgery. In a multicenter prospective cohort study of 20,281 Mohs micrographic surgery (MMS) cases, the rate of reported partial and complete necrosis was only 0.14% (1b) [11]. In single-center studies, the necrosis rates have been somewhat higher. A cohort of 1911 MMS patients found flap and graft necrosis rates as 1.7% and 8.6%, respectively (1b) [12]. A prospective single-year study of 578 combined flaps and grafts found some degree of necrosis in 1.9% of cases (1b) [13]. When reviewing 422 cheek reconstructions, investigators found that 1% of the flaps had distal necrosis (2b) [14]. Retrospective analysis of 1334 nasal reconstructions after MMS found that 13 (roughly 1%) experienced partial flap necrosis (2b) [15]. In a study of 171 bilobed transposition flaps, Moy et al. (2b) [16] reported a 7% incidence of partial necrosis.

Any comorbidities, substance use habits, or wound conditions that impair wound healing can increase a patient's risk for necrosis. Diabetes [16–18], older age (4, 5) [17–19], alcohol consumption [20], (5) immunosuppression (5) [21], malnutrition (5) [22], hypercoagulable states [21], (5) and obesity [23, 24] (4) can all retard wound healing (5) [25, 26]. The most important patient factor, however, is tobacco exposure. Cigarette smokers undergoing facelifts had over 12 times the relative risk of superficial necrosis compared with nonsmokers [27] (2b) and experienced greater degrees of tissue ischemia in skin flap surgery (2b, 2b, 5) [28–30]. Goldminz et al. [29] (2b) showed a striking dose-response effect between the packs per day smoked and the development of necrosis in flaps and full-thickness skin grafts (FTSGs). In the study of 1334 nasal reconstructions mentioned earlier, 75% of patients with skin graft death were active smokers (2b) [15].

Wound conditions that increase risk for necrosis include high tension closures, inadequate vascular supply, crush injury, hematoma, seroma, and infection [31, 32].

Severity and Duration

No human studies have examined the severity and duration of flap and graft necrosis. Clinical experience has shown that the seriousness and resolution will greatly depend on the degree of underlying ischemic insult. With epidermal ischemia, patients experience superficial sunburn-like sloughing that resolves within a week or so.

For partial-thickness skin necrosis, the dead tissue may take a couple of weeks to work loose prior to revealing residual intact dermis underneath that then completes healing via re-epithelialization originating from follicular appendages and wound edges. Full-thickness necrosis will take even longer to declare itself and require complete healing by second intent from the wound edges. This may take several weeks depending on the defect size and may result in the greatest severity of cosmetic or functional impairment. Fortunately, severe adverse events appear to be extremely rare. Hospitalization or death as a result of failed dermatologic reconstructions is not reported in the literature as part of the larger case series looking at MMS complications (1b, 1b, 1b, 2b, 2b, 2b) [11–16].

Preventive Evaluation

Specific evidence-based preoperative protocols for evaluating patients in whom a flap or graft is being considered do not exist. A review of medical comorbidities and substance use is important so that patients can be educated on treating their other health conditions that could compromise healing and stopping tobacco and alcohol use in the perioperative period. There is a dose-response effect between packs per day smoked and development of necrosis (2b) [29]. In heavy smokers who are unable or unwilling to limit their tobacco use, avoiding random-pattern flaps and skin grafts may be preferred, if possible.

Scanning laser devices exist for evaluation of adequate cutaneous blood flow (5, 2b) [33, 34] for use in research purposes but are of limited utility in measuring the critical blood flow thresholds that would predict flap survival [35], (5) especially in an outpatient, real-world setting. Intraoperative clues to future random-pattern flap necrosis include pallor, cool temperature, and delayed capillary refill (5) [36]. If in doubt about the distal viability of a flap, the blood can be manually exsanguinated from the tip toward the pedicle base using a cotton dental roll. The tip can then be pricked with a pin; if there is adequate vascularity, the vessels should have been refilled and bright red droplets of blood should be visible (4, 5) [30, 37].

Preventive Interventions

An understanding of the pathophysiology of necrosis is important for mitigating the damage as much as possible. Skin flap failure causes can be divided into extrinsic (infection, shear forces, trauma) and intrinsic (inadequate blood flow, tension) (5) [38]. After flap elevation, vascular flow diminishes, especially to the distal end of the flap. The recipient bed site must have an adequate blood supply to revascularize the flap or graft (5) [33, 39]. Neural increases in sympathetic flow can result in vasoconstriction (5) [30, 40]. Animal skin studies suggest that random-pattern flaps get roughly 50% of their blood supply from their pedicle and the other half, especially distally, by behaving like a graft and sustaining themselves from their recipient bed (5) [41]. Irreversible ischemia, when it happens, occurs approximately 12–15 h following a procedure (5) [42–44].

Exacting surgical technique is paramount in preventing necrosis (C). Techniques that may improve outcomes include designing flaps so that the pedicle can support the distal-most tissue, removing standing cones in a way that does not jeopardize the pedicle, placing tacking sutures parallel rather than perpendicular to underlying feeding blood vessels to avoid a tourniquet effect [45], (5) avoiding excessive cautery [11] (1b) and undermining sufficiently to maximally reduce wound closure tension (5) [45, 46]. Expanding hematomas should be evacuated acutely and hemostasis achieved (5) [42].

For full-thickness skin grafts, defatting the graft and achieving hemostasis of the recipient bed can improve outcomes (5) [47]. Adipose tissue is poorly vascularized and not a good medium for new vessel growth between the graft and wound bed (3a) [48]. Exposed bone, cartilage, and tendon without their associated connective tissue sheaths cannot be relied upon to support the metabolic needs of grafts (D) (5) [32, 33]. Most studies and surgeons support the use of some version of a bolstering apparatus in order to

encourage apposition between the graft and recipient bed (C) (all 5) [20, 32, 49–52]. A few surgeons have successfully used basting sutures instead (5, 2b, 5) [47, 53, 54].

There is evidence to suggest that cessation of smoking improves wound healing and decreases necrosis (level B). Measurements of forearm circulation in smokers versus nonsmokers showed that smoking is associated with cutaneous microvascular dysfunction and that the severity of impairment is related to the duration and intensity of exposure to smoking (2b) [55]. The outcome following flap necrosis was three times worse in former smokers when compared to nonsmokers (2b) [29]. Facelift patients who had stopped smoking for at least 1 year before surgery had a complication rate similar to that of never-smokers (2b) [56].

A systematic review of nicotine replacement therapy (NRT), while acknowledging the need for large randomized trials, found no increased risk in complication rates in patients using NRT and suggested that this can be considered in heavy smokers who may not otherwise be able to tolerate perioperative smoking cessation (C) [57]. In very high-risk patients, surgical delay of the flap may be advisable (level B) (2b, 5, 5) [15, 30, 43]. A prospective trial of immediate versus delayed FTSGs of the nasal tip and ala overlying denuded cartilage showed improved graft survival in the cohort where grafting was delayed by 12–14 days and allowed for the formation of granulation tissue [58]. (2b) Others have replicated these results (5, 5, 2b) [47, 59, 60]. Although specific data regarding alcohol's impact on necrosis is not available, it increases hemorrhage and infection susceptibility (5, 2b) [61, 62]. Many dermatologic surgeons recommend alcohol cessation for a short period following reconstruction [30, 63] (5) and a Cochrane review [64] (1a) supports this general recommendation (C).

A variety of studies, primarily in rat and pig animal models, have attempted to explore the impact of vasodilatory medications on flap survival (5) [9, 65, 66]. Most of these have not been replicated in humans. An exception is topical nitroglycerin, which has been examined in humans with mixed results (1b, 4, 1b, 4) [67–69]. In neonates it was found to decrease skin necrosis after neurosurgical procedures [70] (4), and in women undergoing radical breast cancer resection, it was thought to prevent flap necrosis after a single application (1b) [69]. However, after being applied to 88 skin flaps and grafts as a single immediate postoperative application in dermatology skin cancer patients, topical nitroglycerin 2% ointment failed to show any survival benefit when compared with controls (1b) [67]. Daily application as slow-release pads in a different study also did not offer greater flap survival than in controls [68]. At this stage, more information is needed to understand the potential role of nitroglycerin and other topical agents in ischemic reconstructions and a firm recommendation cannot be made.

Hyperbaric oxygen therapy (HBOT) has also been used for tenuous flaps and grafts. A Cochrane review noted that HBOT might improve outcomes of skin grafting in burn patients but evidence is limited and does not robustly support its use, especially with respect to generalizability to skin grafts and flaps in other patient populations (2a) [71]. Negative pressure wound therapy (NPWT) may also be of benefit in minimizing skin graft necrosis. A Cochrane review included data from three trials involving skin grafts and concluded that NPWT may decrease graft loss, but given that all trials had a high or unclear risk of bias, more data is needed before NPWT can be routinely recommended (1a) [72].

Leeches can be used to improve tissue circulation after reconstruction and help save skin grafts, although they were not useful in flap-tip necrosis when applied after tissue death was clinically evident (5, 3a, 4) [73–75]. Early recognition of venous congestion and application of leeches within 3 h enhanced flap survival (4) [75]. The most dangerous complication of medical leech therapy is infection with *Aeromonas hydrophila*, a bacterium found in the leech gut that can be transmitted to the patient and cause sepsis; this complication is preventable with antibiotic prophylaxis. Hematocrit also needs to be monitored. Arterial insufficiency is a contraindication to use [75].

For composite grafts, there is sparse evidence to support the use of cooling postoperatively to

enhance graft take (5, 3a, 4) [76–78]. As a method to decrease tissue metabolic demand and thereby enhance survival, cooling was investigated in a case-control report of 14 patients with trauma reconstructions (4) [78]. Ice-water and aluminum foil compresses were applied for 3 days postoperatively to composite grafts. The survival rate of these grafts was 87.5% compared to 23.5% in 21 control cases with routine postoperative care. A similar technique using ice applied for 2 weeks in 12 nasal composite grafts in irradiated or scarred skin showed complete take in 10 of the 12 grafts (4) [79].

Corrective Interventions

Early detection of impending necrosis is paramount in limiting damage (5) [43]. A successful flap is usually light pink in color, although healthy grafts may often be red, dark blue, or purple in the early postoperative phase, and this is not a cause for concern; the color will return to flesh tone within a week or so. A black flap or graft signifies tissue death. If a flap becomes pale during reconstruction, the surgeon should analyze whether this is due to excessive tension, vasoconstrictive epinephrine, or a poorly designed or positioned flap. If the cause is not readily correctible at that time, then the prudent course of action is to return the flap to its original bed. The flap can then be delayed for 2–3 weeks and then used to repair the defect, at which point in time it is usually able to be self-sustaining (5) [59, 80].

Once necrosis has occurred, it is usually managed conservatively in the acute period with moist dressings using petrolatum ointment and minimal debriding, unless infected (5) [45, 81]. Infarcted grafts and flaps are left in place to act as biologic dressings under which healing will progress and then slough off naturally. Wounds then finish healing by secondary intent. The end result is often superior to that initially expected, and if patients are supported through the process, most do well. Only if essential tissue building blocks need to be salvaged for future repair should these be recovered as soon as possible by being returned to their donor bed. Once the area heals, a second revision procedure can be planned if needed.

A review of scar treatments is beyond the scope of this chapter, but for minor adjustments, dermabrasion [58], (1b) PDL, and ablative lasers can be used to improve cosmetic appearance. In those cases where an unacceptable cosmetic outcome results, revision surgery can be methodically planned and scheduled. Corrections for the initial cause of necrosis should be made when planning the second surgery so that history does not repeat itself.

Fortunately, necrosis in dermatologic surgery is not common and there has not been a strong impetus for large, comparative trials as the patient population for such a study does not exist.

Appropriate Schedule for Monitoring

Maintaining close and frequent follow-up reassures the patient that the surgeon is committed to helping them realize the best possible outcome (5) [81]. The specific follow-up schedule will depend on the practice setting and what is practical for the patient. More patient reassurance is typically required initially, and then visits can be spaced out as the wound progresses through the acute phase and remodeling begins. Evaluations for revisions are typically performed at least 6 months or longer after the initial surgery in order to allow for wound maturation, edema resolution, and better tissue handling once deficiencies are identified [82].

Pincushioning (Trapdoor Deformity)

Epidemiology

Pincushioning, or the trapdoor effect, is the upward movement of tissue within the confines of surrounding depressed scar. Mustarde described this unwanted surgical complication in 1966 [83]. Despite being a frequent topic in surgical texts and a relatively well-known complication of

transposition flaps, there is a paucity of rigorous data regarding the prevention and correction of this complication. While it is often referenced in regard to correcting defects on the nose, pincushioning can result after the repair of any semicircular wound in a U, C, or V shape [83]. This deformity appears commonly around 3 weeks after surgery but can appear up to 6 months post-procedure.

As Mohs micrographic surgery numbers increase annually, it can be extrapolated that the number of repairs by transposition flaps is also increasing and so is the risk of pincushion defects. At the Gainesville Veterans Administration Hospital, a retrospective analysis was performed on 13 patients who underwent nasolabial flaps after surgical extirpation of tumors by Mohs micrographic surgery. The mean age of these men was 63 years and follow-up mean was 8 months. Out of the 13 patients reported in the study, 6 required subsequent revision of their flap for trapdoor deformity (4) [84]. Although one small retrospective case series of adult men is certainly not indicative of the general population, one can postulate that pincushioning is a common adverse event after transposition flaps.

Preoperative Evaluation

In the preoperative period, the surgeon can start to consider which closure option will be best for the patient. After tumor extirpation, the surgeon will discuss closure options with their patient. Generally, the surgeon should discuss pincushioning as a possible risk during scar formation with any reconstruction having a U, C or V shape, particularly, when a transposition flap is used for wound closure.

Preventive Interventions

Several factors have been suggested in the past for the cause of trapdoor deformity including lymphatic and venous obstruction, bevel-shaped flap, excess fatty tissue under flap, scar hypertrophy, and wound contracture (5) [85]. However, currently the prevailing view among many surgeons in various disciplines seems to be that the most effective way to decrease the risk of trapdoor deformity is by minimizing recipient site wound contraction. There are several factors the surgeon needs to consider when planning a flap. Many texts state that geometric linear flap design is less prone to developing trapdoor deformities due to the theoretical dispersion of contractile forces away from the center of the flap, but to our knowledge this hasn't been confirmed with a controlled trial (5). Another consideration is the concept of contact inhibition, which has been explored in animal models. It has been demonstrated that coverage with full-thickness skin grafts and split-thickness skin grafts decreases myofibroblast concentration and function and ultimately wound contraction in rats (5) [86]. It has also been demonstrated that placement of a flap that occupies the full three-dimensional space of the defect induces apoptosis of granulation tissue fibroblasts and decreases wound contraction (5) [87]. If the base of the flap does not come into contact with the wound bed, then the inhibition of wound contracture that happens with appropriately sized flaps does not take place. The most discussed method of prevention of trapdoor deformities is wide local tissue undermining of the recipient site (5) [88–90]. Kaufman and colleagues demonstrated that wide undermining decreased the risk of pincushion effect in wounds on guinea pigs (5) [91]. In the absence of wide recipient site undermining, all of the wound contractile forces are directed inward, toward the center of the recipient site, and as the recipient site decreases in size due to wound contraction, the body of the flap is forced in an outward direction. With wide recipient site undermining, there are opposing contractile forces into the surrounding tissue as the sheetlike scar develops and the effect of centripetal wound contraction decreases (5) [92].

Corrective Interventions

Corrective interventions for the trapdoor effect include intralesional steroid injections, Z-plasties along the surgical wound, massage, and debulking.

One approach, if the wound is well approximated and the edges blend well with the surrounding skin, is injection of intralesional kenalog (ILK) into the subcutaneous tissue beneath the flap where the contracted scarring has occurred (5) [90]. By combining Z-plasties along the scar line as well as wide undermining, longitudinal and horizontal forces of contracture are corrected. The goal of correction is to re-direct the contractile forces tangentially away from the wound instead of into it.

Koranda and Webster treated 22 patients with trapdoor deformity with either intralesional Kenalog (ILK), Z-plasties along the scar line, or Z-plasties with wide undermining. Fifteen of the patients were treated with ILK 20 mg/mL once, and then if not improved, 40 mg/mL on repeat treatment 3–4 weeks later. Out of those patients, three improved to a satisfactory scar. Eight patients were treated with multiple Z-plasties along the scar line; each of the arms of the incisions was 8–10 mm in length and angles were between 45° and 60°. Of the eight patients treated with Z-plasty alone, five had complete resolution of the trapdoor defect. Six patients were treated with both Z-plasties and wide undermining, and all six patients had complete resolution of the trapdoor defect (4) [83].

Nasal Valve Dysfunction

Nasal valve dysfunction is a potential complication of dermatologic surgery involving the nasal ala. The term "nasal valve" was first described by Mink in 1903 and was defined as the angle between the cartilaginous septum and the caudal end of the upper lateral cartilages. It has been proposed that the valve maintains an evolutionary protective function, that of preventing large volumes of unhumidified and unheated air into the lower respiratory tract (5) [93]. That definition has evolved to separate the nasal valve into internal and external components. Much of the literature involving nasal valve dysfunction has been published by otolaryngologists who are interested in preventing internal nasal valve dysfunction which is most often associated with rhinoplasty or nasal trauma [94]. In contrast to the internal nasal valve, the external nasal valve is often disrupted after Mohs micrographic surgery, although the inner nasal valve can also be narrowed after surgery due to post-surgery scarring.

The external (outer) nasal valve is formed by the columella, nasal floor, and caudal border of the lower lateral cartilage. The lateral crus supports the anterior half of the ala, while the shape of the posterior half of the ala is supported by thick dermis and fibrous tissue [95]. The nasal valve structure is the point of maximal nasal flow resistance during inspiration. The external nasal valve allows the ala to remain patent during inspiration but is a collapsible flow-limiting segment should the nasal airflow reach critical transmural pressure. If the nasal valve structure is not intact, the negative pressure created during inspiration will result in collapse of the ala. The loss of patency of the ala is explained by Bernoulli's principle which states that as the velocity of flow increases, the pressure decreases. Nasal resistance is inversely proportional to the fourth power of the radius of the nasal passage according to Poiseuille's law and therefore small changes in the size of the nasal valve can have large effects on resistance [95].

Epidemiology

Mohs micrographic surgery that involves the nasal ala and defects that come within 1 mm of the alar groove are at risk of nasal valve dysfunction after surgery. It is important to recognize this risk because appropriate initial repair to avoid dysfunction is preferred over needing to correct valve dysfunction after surgery. Robinson and Burget report that 27% of patients at risk of nasal valve dysfunction due to proximity of the defects to the nasal ala developed symptomatic nasal valve dysfunction (4) [96]. Reynoulds and Gourdin also validated this finding in their own retrospective study in which 21% of their patients who had at-risk surgery developed nasal stuffiness on the operated side (4) [97]. Other risk factors for external nasal valve collapse include compression from a bulky flap or hematoma and nasal-tip ptosis [98, 99].

Severity and Duration

The primary symptom of nasal valve dysfunction post-surgery is a sense of nasal congestion although prolonged dysfunction can result in difficulty breathing while supine (4) [94]. Subjective assessment my include the nasal obstruction symptom evaluation (NOSE) which was validated by Stewart (2b) [100]. This questionnaire is frequently used to evaluate the degree to which nasal obstruction is affecting quality of life. It evaluates nasal congestion, nasal blockage, trouble breathing through the nose, trouble sleeping, and inability to get enough air through the nose during exercise. Another tool that has been used is the sino-nasal outcome test (SNOT 22) (5) [101], although it has not been as well validated. Objectively, the Cottle and the modified Cottle maneuver can further evaluate degree of obstruction. In the Cottle maneuver, one nare is closed and the patient inspires. Lateral pressure is applied to the open nare side, and the patient is asked if there is improvement. The modified Cottle maneuver is similar; the difference being lateral pressure is applied to the open nare with a swab rather than the lateral pressure on the cheek. As the symptoms of nasal obstruction are bothersome to the patient, so too is the cosmetic outcome of the constant collapse of the ala.

Preoperative Evaluation

It would be reasonable for the surgeon to evaluate a patient for external and internal valve dysfunction prior to starting surgery on the nasal ala. Although evaluation would not change the final outcome, the repair could aim to correct previous dysfunction while also avoiding further difficulty. This can be done objectively by use of the Cottle or modified Cottle maneuvers; indeed, Fung et al. demonstrated that this method is effective at predicting those with collapse prior to surgery (4) [98].

Effect of Nasal Valving on Patients

Nasal valve dysfunction can contribute to both cosmetic and respiratory concerns for patients. As discussed earlier, suboptimal scarring can have a negative impact on the patient's psychosocial functioning [3]. There is the additional concern of inspiratory deficits that can make respiration suboptimal [100].

Preventative Interventions

Prevention of external nasal valve dysfunction is preferable to addressing it as a postoperative complication. Burget and Menick have published descriptions of various techniques for cartilage grafting to correct the alar rim [102]. Ratner and Skouge published a simplified technique in 1997 describing the use of free cartilage grafts to restore the alar rim during repair of a Mohs defect. They state that the length of the cartilage graft should be the length of the defect plus 4–5 mm. The defect is undermined medially and laterally to create pockets in which the graft is placed. Lastly, the cartilage is sutured in place. At the time of their publication, they had completed the free cartilage graft on 20 patients with reportedly good outcomes (5) [103].

A retrospective analysis of 13 patients in 2009 showed that free cartilage grafts followed by secondary intention healing can provide another method for closure when the defect is between 10 and 20 mm. All of the patients treated with free cartilage graft and secondary intention healing with defects less than 20 mm and average follow-up of 17 months assessed their results as either good or satisfactory. Two patients did develop hypertrophic scarring, and one patient developed alar notching (4) [104].

Cartilage grafting is common to prevent nasal valve collapse but several other methods have also been published with good results. Wang and colleagues describe a lateral suspension suture technique that is a modification of the suspension technique frequently published in the otolaryngology literature. A suture enters the nasal tissue at the point of greatest depression and then is tied to the periosteum of the maxilla 2 cm laterally. They state that in over 100 patients they treated with this technique, none of them experienced collapse or infection (4) [105].

Another study looked at the use of titanium mesh rather than a cartilage graft to correct the alar rim. The authors retrospectively reviewed 11 patients who were repaired with titanium mesh with a mean follow-up time of 59.63 years, and none of the patients had infection, extrusion, or nasal valve collapse (4) [106]. Another report from Great Britain involving five patients who were repaired with titanium mesh also showed that patients had good outcomes with no complications (4) [107]. Mucosal defects that lead to scarring can also result in nasal valve incompetence and should be repaired.

External pressure from flaps can also result in closure of the nasal valve. Reynolds and Gourdin report two patients that received thicker paramedian forehead flaps who subsequently required thinning of the flaps because of valve collapse (4) [97].

Corrective Interventions

Repair of nasal valve dysfunction is more difficult than prevention. In a systematic review written in 2009, Spielmann and colleagues discuss seven studies which addressed external nasal valve collapse [108]. On further review of these articles, it should be noted that patients frequently do not undergo one single procedure during correction. Instead, multiple techniques including spreader grafts, alar batten grafts, auricular cartilage grafts, and columellar struts are employed. In the first study, 20 patients were treated with rhinolift procedure, and the outcome measured was subjective nasal patency. Out of the 20 patients treated, 10 were treated with rhinolift alone, while the others also had modifications in their upper lateral cartilage. All but one of the patients stated that they had subjective improvement in nasal patency (4) [109].

A Lateral crural spanning graft was used to treat 11 patients diagnosed with external valve dysfunction by positive Cottle test and all patients noted improvement of nasal symptoms. This technique is particularly helpful when the ala has been repaired but still remains too medial in position (4) [110].

Alar batten grafting can be placed through an external or endonasal approach. A small pocket is created in the ala and the auricular cartilage is inserted into this pocket. When the patient is also undergoing septoplasty, septal cartilage can be utilized as published by Millman and colleagues. This procedure was performed on 21 patients, and all patients were pleased with the aesthetic result as well as improvement in airway patency (4) [111].

There was one prospective randomized trial comparing cartilage lateral crural strut grafting vs. cephalic crural turn-in flap for correction of external nasal valve dysfunction. Clinical endpoints included VAS, NOSE, and SNOT22 as subjective data and also included objective data including minimum cross-sectional area (MCA), nasal peak inspiratory flow (NPIF), and nasal airway resistance (NAR). Both procedures worked well, and there was significant improvement relative to baseline reports with regard to the VAS, NOSE, and SNOT22 scores, despite the only objective improvement being the NPIF. There was a difference between the two groups favoring the lateral crural strut group in the NAR and total MCA; however, all subjective outcomes were statistically insignificant (1b) [112].

Apart from cartilage grafting, suspension sutures can also be used to prevent or treat nasal valve collapse. As discussed in preventative interventions, during Mohs surgery, the deeper tissues are exposed; therefore, the procedure is different from a corrective procedure. Twelve men treated with nasal suspension sutures all noted immediate improvement in nasal symptoms after surgery but there is question if the improvement will continue over time (4) [113].

Nasal valve dysfunction represents a very real complication that can adversely affect patients' lives. The literature regarding the prevention and treatment of this adverse outcome is not robust and for the most part represents retrospective case series. However, there are some validated tools that can be used to evaluate the severity of the dysfunction and determine if treatments have been effective. The most important point is that nasal valve dysfunction can be averted if the surgeon is cognizant of risk factors including size of defect and proximity to alar rim. Cartilage grafting has a reasonably good track record of bolstering the structural

integrity of the nasal valve. Prevention of this adverse outcome is important and should be utilized in at-risk patients, often in conjunction with other reconstructive options.

Free Margin Violation

Epidemiology

Free margin violation has many consequences that must to be considered. Even small deviations of these structures can be aesthetically catastrophic. While this violation can include any of the free margins of the face including the eyelids, nasal ala, and lips, herein we will focus primarily on the eyelids and lips. Both the lips and eyes play a critical role in facial expression and both verbal and nonverbal communication. Perhaps the most important consideration is that violation of these free margins can have significant functional implications and can lead to other symptoms. With regard to ectropion, it can lead to a variety of subsequent ophthalmologic concerns including xerophthalmia, epiphora, exposure keratopathy, and ultimately blindness [114]. Significant free margin deviation of the lips can lead to deficits in phonation and feeding/drinking; however, the degree of deviation required to cause a functional deficit is much higher in the lips than the eyelid [115]. Despite being known as a possible consequence of surgery of the central face, the incidence of ectropion and eclabium following Mohs micrographic surgery has not been specifically published to our knowledge. There were no reported cases of ectropion in a large prospective cohort study examining complications following Mohs surgery (1b) [11]. The prevalence of ectropion was examined in an Australian cross-sectional study evaluating patients aged 49–97. Ectropion was seen in 3.9% of respondents and when correlated to a history of tumor removal revealed an odds ratio of 1.8 (4) [116]. We are not aware of any specific literature regarding the incidence or etiologies of eclabium; however, in our experience, eclabium is typically caused by trauma or a surgical procedures (5).

Severity and Duration

Ectropion or eclabium, when present, is typically persistent and requires surgical intervention for resolution. Severity is variable as there is inherent variability of the degree of free margin distortion. Severe cases, while disfiguring, can also cause functional issues such as corneal ulceration in the case of ectropion and with significant distortion of the lip difficulty with speaking, eating, and drinking.

Preoperative Evaluation

As with all patients with cutaneous malignancies, tumor extirpation with concomitant conservation of surrounding tissue is vital. It is, perhaps, more important when performing procedures adjacent to free margins because even small changes in surgical defect size can sway which reconstructive options are available. There are some additional considerations when performing periorbital procedures. Older patients with increased lid laxity are at higher risk for developing ectropion (4) [116], including ectropion that may not be associated with surgical procedures. There are some additional assessment tools for evaluating lid laxity which include examination for scleral show, evaluation of lid resilience, and evaluation of lid position with maximal tension. Typically, the corneoscleral junction is inferior to the superior margin of the lower eyelid. If white sclera is visible above the lower eyelid, there is concern for excess lower lid laxity. The “snap-back” test is performed by pinching the lower eyelid between the thumb and index finger and retracting the lower lid from the globe. The test is positive if there is a delay in return to the surface of the globe or if the lid only returns after blinking (5) [117]. Laxity can be determined with maximal tension on the lower lid by having the patient look upward with simultaneously opening the mouth. It is prudent to evaluate and document any pre-existing ectropion or eclabium so as to help maintain appropriate patient expectations.

Additionally, there may be potential to incorporate a corrective component into the reconstructive option that is chosen.

Effect of Free Margin movement on Patients

What is most troublesome to patients is contingent on the severity of the free margin distortion and includes both function and form. The primary goal for the eyelid is to maintain its critical functions which include maintaining vision, protection of the globe, and maintenance of the lacrimal system. A secondary goal of reconstruction is restoring form and allowing for a maximally normal aesthetic appearance. Ectropion can lead to disruption of that function and can range from increase in dry-eye symptoms [118] and suboptimal cosmesis in mild cases to exposure keratopathy and vision loss in severe cases [119].

Preventive Interventions

Most the literature regarding iatrogenic ectropion involves blepharoplasty procedures rather than tumor removal. Of the data regarding ectropion and tumor extirpation, there is primarily a combination of retrospective cohorts, anecdotal/expert opinions, and cases involving reconstructive challenges. The underlying theme, which is applicable to any free margin including the lips, is to prevent any centrifugal tension vectors. This includes overt tension due to the closure and subsequent pull due to wound contraction. In small defects that are amenable to linear repair, the orientation should be with the long axis perpendicular to the lid margin or otherwise ensuring that the tension vectors course lateral to the lateral canthus (5) [90]. This prevents vertical tension vectors from pulling on the lid during wound closure by placing tension as horizontally as possible. There is potential for a less optimal cosmetic result, as this typically forces the closures against the relaxed skin tension lines, but helps satisfy the primary goal which is maintenance of function (5) [120]. This can be overcome by utilizing an S-plasty or O-Z repair. For smaller reconstructions involving the eyelid margin, an inverted pentagonal wedge closure is relatively simple and achieves both good aesthetic and functional results (5) [121].

Full-thickness skin grafts are an option available. A retrospective study following tumor excision and repair of the lower eyelid [122] reported a rate of ectropion of 14.2%. Interestingly 14.7% of all cases demonstrated positive margins after excision, which speaks to the importance of histologic margin control. Of the cases that developed ectropion, 25% (4 out of 12) were cases where the tumor had been incompletely excised (4). Another retrospective study with 100 patients showed only 4% of patients undergoing full-thickness skin grafts for periorbital defects developed ectropion (4) [123]. Neither of these studies discussed the nuisances of their grafting procedures, including if the grafts were oversized for the defect. Some advocate that grafts and flaps near or on the eyelids be oversized to compensate for wound contraction and to push upward on the lower lid (5) [121]. For large defects near free margins with involvement of cosmetically similiar adjacent tissue, Burrow's grafts offer a solution (5) [124]. This technique is not ideal for deep defects or those that require structural reconstruction [120].

Local flaps are frequently used for reconstruction of moderate-to-large defects of the lower lid and cheek. One such option is the cheek rotation or cervicofacial rotation flap (Mustarde). As patients age, increased laxity of the eyelid and reduced muscle tone combined with the vertical tension that a heavy flap can impose on the lower lid can lead to lid distraction and frank ectropion. A useful technique to help prevent this is the use of periosteal tacking sutures medially on the nasal bone and orbit or laterally on the orbital rim, which can prevent pull on the lower lid by suspending the weight of a flap in the infraorbital region to rigid support (4) [125, 126]. Inferiorly based cheek rotation flaps have been shown to be an effective method for closure with good aesthetic results and no incidence of ectropion in a case series of 20 patients (4) [127]. A retrospective study of 23 V-Y flaps

compared with 11 cervicofacial flaps found no difference in ectropion rate between the groups (3b) [128]. The authors emphasized the importance of careful preoperative assessment of lower lid laxity. If lower lid laxity is found, adding a lateral canthopexy or canthoplasty to the reconstruction is recommended.

Comparable to avoiding ectropion, avoidance of eclabium requires repairs to be oriented with the long axis perpendicular to the lip margin in the case of primary closures (5). This prevents vertical tension vectors from pulling on the lip during wound closure. Flaps on the lips are typically executed in a manner to replace surface area of the lip that is lost during tumor extirpation as this makes distortion of the lip less likely (5). Cosmetic subunits should be defined with gentian violet prior to infiltration of anesthesia, which can distort anatomic structures and prevent accurate realignment of important landmarks like the white roll upon reconstruction. For defects of the mucosa or vermillion that do not extend deeper than the superficial orbicularis oris, granulation should be strongly considered. Even relatively large defects, up to 2.5 cm, can be left to heal via second intent with excellent aesthetic and functional results (4) [115]. Although eclabium tends to be a focus for discussion of perioral free margin violation, it is important to recognize that inward projection of the lip can also be an issue. While it is less likely than eclabium to cause functional impairment, it can be cosmetically distracting and distressing to patients. Even simple primary closures can cause inward push of the lip (5) [129].

Grafts used for deep defects on the philtrum may have a higher risk of eclabium than flaps [130]. Island pedicle flaps are an option for defects of the philtrum between 50% and 150% the width and less than 50% the height of the philtrum. This allows advancement of an adequate amount of tissue to limit upward pull on the lip. This flap rebuilds the philtrum and vermilion border, minimizes distortion, and preserves cosmesis and function of the central upper lip. In a small case series of four patients with tumors of the philtrum cleared by Mohs surgery, reconstruction with island pedicle flaps achieved excellent cosmetic results with minimal deformation (4) [130].

Corrective Interventions

As discussed earlier, FTSG offers an option for treating ectropion. In a retrospective study, 76% of patients who underwent FTSG for ectropion had complete resolution. Of those, 83% underwent a concomitant procedure, with a lateral tarsal strip being the most common (4) [131]. There are several case series discussing various methods of correcting iatrogenic cicatricial ectropion. In a series of 19 patients treated with lateral tarsal strip and vertical vector cheek lift, 84% had resolution while 16% required a second procedure (4) [132]. A case series of 17 patients with cicatricial ectropion from periorbital burns reported full resolution of ectropion, patient satisfaction with final scar, and no major complications, with a vertical V-Y advancement technique (4) [133]. V-Y advancement flaps have also been reported in texts. However, given that the V-Y advancement flap is dependent on mobility derived from the subcutis and that the orbicularis oris inserts into the dermis, it should be used judiciously on the lip. In mild cases in which a revision surgery is not possible, digital massage for cicatricial ectropion following lid surgery may help loosen the scar (5) [134]. Revision by Z-plasty can be used to treat ectropion or eclabium. The traditional Z-plasty and modified "sliding Z-plasty" can improve vertical lip reconstruction and avoid or correct various lip deformities that arise during or from lip reconstruction (4) [135, 136].

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Wound edge necrosis	
Smoking cessation 4–6 weeks prior to a planned procedure (A)	A
Avoiding suturing techniques that may predispose to wound edge necrosis such as sutures placed too tightly, too close to one another, horizontal mattress, or running locked sutures	D
Reducing trauma to the wound edge by crush injury, multiple needle passes through the same area of tissue, or any other cause	D
Preventing electrocautery or electrocoagulation-induced thermal damage to the wound edges either from direct contact or from contact with boiling blood	C
Minimizing wound tension can all reduce the chance of wound edge necrosis	C
Topical agents may have an effect on lessening flap necrosis and wound edge necrosis, but further study is required to make evidence-based recommendations on these	N/A
Flap and graft necrosis	
Good intraoperative planning and technique is paramount to preventing necrosis	C
Watchful waiting is the main management strategy with flap and graft necrosis	C
Smoking cessation is the most helpful patient factor in limiting risk of necrosis	B
Delayed flap and graft reconstructions may be useful in those patients clinically at high risk for necrosis	B
Trapdoor deformity	
As with all flap designs it should be appropriately designed and meticulously executed	C
Wide recipient site undermining should be performed	C
Ensure that flap base makes contact with wound bed	D
Intralesional steroids can be used to correct modest trapdoor deformities	C
Z-plasties can be utilized in correcting this deformity	C
Incision and thinning of flap is an available option to correct moderate-to-severe trapdoor deformities	C
Nasal valve dysfunction	
Defects in close approximation to the alar rim with significant disruption of the integrity of the ala can result in nasal valve dysfunction	C
Nasal cartilage grafting used appropriately can help prevent nasal valve dysfunction in surgical defects of the ala	B
Lateral crural spanning grafts and ala batten grafting can all be used to correct nasal valve dysfunction	C
Free margin violation	
Free margin violations can be avoided with careful reconstructive planning and meticulous surgical technique	B
Free margin violations can lead to severe functional impairment	A
Creating smaller defects within cosmetic subunits can decrease the likelihood of free margin distortion	D
A variety of techniques are reconstructive options that will minimize the risk of free margin violation including primary closures without centrifugal tension, grafting, and local flaps with judicious use of suspension sutures	B
Scar lengthening and tension re-directing techniques including Z-plasty and V-Y advancement flaps are alternatives for correcting free margin violations	B

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Self-Assessment Questions

1. A 57-year-old female presents to clinic in follow-up following Mohs surgery 6 months ago for a 1.3 cm basal cell carcinoma (BCC) of the cheek repaired with a primary linear-layered closure. She is concerned about how indented and noticeable the linear scar is. Her social history is significant for smoking one pack per day for 20 years and drinking 8–12 drinks per week. She works in a local meat-packing plant. During Mohs surgery and her repair, the tissue was handled with skin hooks alone, and use of electrocoagulation was focal and minimal. Which of the following likely played the most significant role in producing the scarring of concern to the patient?
   (a) High wound closure tension
   (b) Alcohol intake
   (c) Preoperative trauma
   (d) Smoking
   (e) Thermal damage
   (f) Crush injury

2. An 80-year-old diabetic female undergoes Mohs excision of a large basal cell carcinoma on her nasal tip. A two-stage reconstruction is undertaken with a paramedian forehead flap. After 3 days, a 3rmm area at the tip becomes black, and a clear line of demarcation develops between necrotic and viable tissue. Which of the following would be the best management options for the patient?
   (a) Aggressive debridement of obviously necrotic tissue followed by moist wound care with Vaseline and daily bandage changes
   (b) Return as soon as possible to take down the flap and let the entire wound heal with granulation
   (c) Postpone the pedicle division and inset for 6 weeks to give the necrosis time to declare itself and allow the rest of the flap to survive
   (d) Apply leeches to the necrotic area until it improves

3. A 54-year-old female underwent Mohs surgery for a basal cell carcinoma on the left nasal supratip/nasal sidewall with a final defect size of 1.1 cm. After a clear discussion of risks, benefits, and alternatives of a variety of reconstructive options, the patient and surgeon elect to perform a bilobed transposition flap. Which of the following is an effective way to minimize development of a trapdoor deformity?
   (a) Wide undermining of the recipient site
   (b) Extensively thinning the flap to help ensure it will not push up with wound remodeling
   (c) Ensuring the flap is inset without undermining with recipient site
   (d) Use of a rhombic flap

4. A 67-year-old male underwent Mohs for a squamous cell carcinoma of the left alar groove and alar rim. A tumor-free plane was achieved after two layers, leaving a final surgical defect of 1.2 cm that has encroached on the alar rim. What steps can be used to help prevent postoperative nasal valve dysfunction?
   (a) Second intention healing
   (b) Closing the defect with a bilobed flap and addressing any nasal valve dysfunction after it occurs
   (c) Use of a full-thickness skin graft to close the surgical defect
   (d) Use of a cartilage strut to maintain structural integrity of the nasal valve

5. A 32-year-old female, with a diagnosis of a rather large BCC of the left malar cheek (2.5 × 1.7 cm), is treated with Mohs. After three layers a tumor-free plane is achieved and a cheek rotation flap (Mustarde) is chosen for closure. Which of the following will help prevent postoperative cicatricial ectropion?
   (a) Wide recipient undermining
   (b) Ensuring adequate removal of the inferior tricone
   (c) Utilizing a backcut to help maximize flap mobility
   (d) Use of a periosteal suspension suture at the lateral canthus

Correct Answers

1. d: Smoking. Of the options listed, only the patient's history of smoking is a concern for causing wound edge necrosis. High closure tension, trauma, thermal damage by electrocautery, or superheated blood and crush injury are all potential causes of wound edge necrosis, but these factors are less likely given the information presented in the clinical vignette.
2. c: Postpone the pedicle division and inset for 6 weeks to give the necrosis time to declare itself and allow the rest of the flap to survive. Much of the flap may still be viable underneath the visible necrosis. Allowing the tissue time to heal and declare itself gives the body the chance to make the most of the repair that has already been done. If the tissue becomes infected, it must be debrided but there is no urgency to revising the surgery. Intervening too soon may result in unnecessary procedures and ineffectual attempts to mimic what the body's normal physiology would have done better.
3. a: Wide undermining of the recipient site. Wide undermining is thought to be the most effective way to help prevent trapdoor deformity by cancelling out the inward contractile forces with outward contractile forces. Thinning the flap not only threatens flap viability by sacrificing vascular supply, but it also prevents the contact inhibition that happens with appropriate flap/wound bed contact. Choice c is wrong as discussed earlier. Choice d is wrong because you have already chosen a bilobed flap.
4. d: Use of a cartilage strut to maintain structural integrity of the nasal valve. Choice a is incorrect in an unbelievable number of ways. It is almost universally preferable to prevent complications than treat them, excluding choice b. Choice c is virtually guaranteed not to provide the structural integrity to maintain function of the nasal valve. The correct answer is choice d.
5. d: Use of a periosteal suspension suture at the lateral canthus. Choice a and b should be done in most adjacent-tissue transfer closures unless there are mitigating circumstances. Choice c will help improve mobility but will not prevent downward pull on the lower eyelid.

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Prevention and Management of Patient Dissatisfaction After Primary Cosmetic Procedures

Wayne Joseph Overman and Abigail Waldman

Abstract

Noninvasive cosmetic dermatologic procedures are generally safe and well tolerated when used by well-trained physicians; however, undesirable outcomes and adverse reactions are possible. This chapter focuses on both common and rare adverse outcomes of dermatologic cosmetic procedures with a focus on the most common procedures performed: Botulinum toxin injections, filler injections, and laser treatments. We will review the available evidence, the epidemiology of these adverse events, patient selection, prevention methods, and management.

Keywords

Cosmetics · Adverse reactions · Complications · Botulinum toxin · Filler · Laser

Millions of noninvasive cosmetic dermatologic procedures are performed each year. Although shown to be generally safe and well tolerated when used by well-trained physicians, undesirable outcomes and adverse reactions are possible and a reality of practice. This chapter focuses on both common and rare adverse outcomes of dermatologic cosmetic procedures with a focus on the most common procedures performed: Botulinum toxin injections, filler injections, and laser treatments. We will review the available evidence, the epidemiology of these adverse events, patient selection, prevention methods, and management to ensure good outcomes and patient satisfaction in your practice.

Common Adverse Outcomes

All Cosmetic Procedures

Some of the most common side effects are shared by filler injection, laser treatment, and to a lesser extent botulinum toxin injections. These include *pain* (incidence 5.2–90% filler) [1–3] (1b, 1b, 1b), *swelling* (12–91% filler) [1, 4] (2b) (68–82% non-ablative fractionated laser) [5, 6] (2b, 2c), *bruising* (10–62% filler) [7] (2a) [1] (0.01% fractionated non-ablative laser) [8] (2b), *redness* (12–90% filler) [2] (1–12.5% non-ablative laser, 100% ablative lasers) [8], and *itching* (23.9–38.5% filler) [2, 3] (36.6% laser) [6]. There are few known risk factors for many of these outcomes. Bruising may be more common in patients on blood thinners and elderly patients [9] (2a). Redness is seen more in patients with a history of "sensitive skin" or rosacea [10] (2a) or

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when laser resurfacing is non-fractionated or laser pulses are stacked or multiple passes performed.

Filler

Nodules/lumps (5–80% filler) are a common side effect of fillers, particularly in highly mobile areas such as the perioral area. Nodules are most common with polylactic acid fillers (PLLA) and are thought to occur in 5–40% of those cases. Nodules may be more apparent in patients with darker skin or elderly patients with thin skin [2].

Laser

For ablative and non-ablative fractionated and non-fractionated laser resurfacing, common side effects include *crusting* (80% incidence with fractionated ablative resurfacing) [11] (4), *acne and milia* (14–80% ablative resurfacing, 2–19% non-ablative) [5, 6, 8, 12–14] (2a, 4, 4), and *contact dermatitis* (10–65% ablative resurfacing) [6, 15, 16] (4, 2b). Using ablative resurfacing is strongly associated with increased risk of acne and milia. Patients with history of acne [12] are predisposed to develop this outcome.

Pigment change may be noted in various laser types, and the incidence ranges from rare (1%) to common (32%) depending on the treatment type and patient risk factors [8, 17–21] (2b, 4, 2a, 4). The highest-risk patients for pigment change are those of darker skin types (Fitzpatrick IV–VI), those with preexisting pigmentary disorders, those on photosensitizing medications, or patients with a recent tan or photodamage. Using high-energy laser settings predisposes to this risk factor.

Botulinum toxin

Common events in the injection of botulinum toxin include *headache* (1–20%) [22, 23] (2a, 4).

Patients should be dutifully informed of these common effects prior to the procedure so that expectations are managed and so that the patient can appropriately plan their schedule. While bruising and swelling may not be severe and may be expected outcomes of the procedure, they can be embarrassing for patients (especially those who are trying to hide their treatment), and they may want to avoid treatment prior to a social event.

Rare Adverse Events

All Cosmetic Procedures

Infection is a rare complication of both lasers and filler injection. HSV and mycobacterial infections are thought to occur at an incidence of 0.04–0.2% of filler injections [24] (2b). The incidence is higher with laser treatments and can mostly be attributed to reactivation of HSV (0.2–8% HSV reaction) 0.1–4.5% bacterial infection [16, 25, 26] (1b, 2b). In the treatment with filler, risk factors include use of CaHA and prior local trauma or dental procedures. A prior history of HSV predisposes patients for reactivation during either laser or filler treatment.

Filler

Rare but serious side effects of filler injection include *granulomas and other delayed-type hypersensitivity reactions* (0.01–1%) [27–29], (2a, 2a, 4), *immediate-type hypersensitivity reactions* (0.02–0.8%) [30] (2b), *necrosis* (0.0001–0.05%) [31] (2a), and *blindness* (98 reported cases) [32] (2a).

Laser

Scarring is rarely seen with laser treatment (0.01% of cases) [33] (4) and is seen most commonly after treatment of thin skin such as the eyelid or neck area. *Lidocaine toxicity* due to topical numbing agents prior to procedure has only been reported in a few case reports (0.002% incidence) [34] (4).

Botulinum toxin

Rare events associated with Botulinum toxin injection include *eyebrow ptosis* (3–5.4%) [35–37] (2A, 2A, 1B); *eyelid ptosis* (0.12% incidence) [38] (2A); *diplopia*, *smile asymmetry*, *or other perioral complications*; and *dysphagia* (incidence not available). Eyebrow ptosis is a potential complication for patients who use the

frontalis muscle to lift excess upper eyelid skin. Perioral asymmetry and weakness is not more common in musicians or singers, but this complication may be more life affecting, and caution should be used when injecting Botulinum toxin periorally in this population.

Table 67.1 provides a list of both common and rare adverse events associated with com-

Table 67.1 Incidence of adverse outcomes and patient demographics

Undesirable outcome	Incidence	Quality of evidence	Patient risk factors	Quality of evidence	Resolution	Quality of evidence
			Filler			
Pain	5.2%–90%	B	na		97.7% resolved within 2 weeks	B
Swelling	12%–91%	B	na		91.6% resolved within 2 weeks	B
Bruising	10–62%	B	Blood thinners, elderly patients	B	85% resolved within 2 weeks	B
Redness	12–90%	B	History of rosacea	B	96% resolved within 2 weeks	B
Lumps/nodules	5–80%	B	PLLA> CaHA, highly mobile areas (e.g., lips), poor mixing, may be more apparent in patients of color, elderly patients, thin skin	B	66% resolved within 2 weeks	B
Granulomas/ delayed-type hypersensitivity reaction	0.02–1%	B	HA filler	B	n/a	n/a
Immediate-type hypersensitivity reactions	0.02–0.8%	B	n/a		Hours to days with appropriate care	C
Itching	23.9–38.5%	B	n/a		100% resolved within 2 weeks	B
Infection	0.04–0.2%	B	CaHA, local trauma, and dental procedures	B	n/a	B
Necrosis (severe), other vascular compromises, cerebral embolism	0.0001–0.05%	B	Patients with prior trauma	C	<1 month in most cases with 7–30% resulting in permanent scarring	B
Blindness	98 cases reported in literature	B	Location – 38% glabella, 25.5% nasal region, 13.3% NLF, and 12.2% forehead	B	Permanent in 50% of cases	B
			Laser			
Pain	na				Hours to weeks	B
Swelling	68–82% (non-ablative fractioned)	B			3 days	B
Bruising	0.01% 1550 nm erbium-doped fractionated laser	B	Anticoagulants	B	7–14 days	B

(continued)

Table 67.1 (continued)

Undesirable outcome	Incidence	Quality of evidence	Patient risk factors	Quality of evidence	Resolution	Quality of evidence
Redness	1–12.5% (52), 100% with ablative CO_2	B	History of rosacea, non-fractionated laser resurfacing, stacking of pulses, multiple passes	B	Up to 4.5 months	B
Crusting	80% CO_2 ablative fractional resurfacing	C	Ablative CO_2	B	2–7 days	B
Pigment change	1–32%	B	Fitzpatrick IV-VI, preexisting pigmentary disorders, photosensitizing medications, tan/photodamage, high-energy laser settings	B	Months to years	B
Acne and milia	14–80% (ablative), 2–19% (non-ablative resurfacing)	B	Ablative resurfacing, patients with history of acne, occlusive dressings or moisturizers	B	5–7 days	B
Itching	36.60%	B			2 weeks	B
Infection	0.2–8% (HSV reactivation), 49, 58 0.1–4.5% bacterial infection	B	Non-fractionated laser treatments, prior history of HSV	B		
Scarring	0.01%	C	Treatment of neck area	C		
Lidocaine toxicity	0.00%	C				
Post-ablative contact dermatitis	10–65%	D				
Botulinum toxin					*All Botulinum toxin adverse events will resolve by 3 months	
Headache	1–20%	C	n/a		n/a	
Eyebrow ptosis	3–5.4%	B	Patients who use the frontalis muscle to lift excess upper eyelid skin	B		
Eyelid ptosis	0.12%	B			2–4+ weeks with apraclonidine eyedrops	B
Diplopia	na		n/a		7–10 weeks with ophthalmology management	B
Cheek paralysis and lip droop	na		n/a		*	
Perioral complications	na		Musicians, singers should be treated with caution	B	*	
Dysphagia/voice change	na		n/a		*	

na, *n/a* Not available

mon dermatologic cosmetic procedures, patient risk factors for developing these outcomes, and the expected resolution.

Severity and Duration

All Cosmetic Procedures

Dermatologic cosmetic procedures are typically very safe. Even when undesired outcomes occur, they tend to be mild and remitting. Events that typically appear immediately or soon after the procedure include bruising, swelling, itching, pain, and redness. These side effects are typically mild and easily tolerated. Bruising is thought to spontaneously completely resolve within 2 weeks and typically resolves prior to 7 days [39, 40] (2A, 1B). Swelling, itching, pain, and redness dissipate within hours to weeks; however, permanent telangiectasias can form at the injection site [31], and redness can be persistent up to 5 months with ablative resurfacing.

Fillers

Serious adverse outcomes from fillers are very rare (thought to occur 0.001–0.0001% of cases) [31] but can lead to serious consequences. These adverse events include immediate- and delayed-type hypersensitivity, infection, necrosis, and other cerebrovascular occlusions that can lead to blindness or stroke. These rare events culminate in death in only one case reported in the literature, which was associated with autologous fat injections into the glabella [41] (4). Delayed-type hypersensitivity reactions typically appear on average 14.6 ± 5.27 months after injection, and of these, granulomatous-type reactions are most common (34.2%) [42] (2b). Immediate-type hypersensitivity resolves quickly after receiving appropriate care. Infections can present as recurrent herpetic lesions [43] (2a). Bacterial or atypical mycobacterial infections have also been reported and resolve with appropriate antimicrobials. Necrosis heals with no sequela within 1 month in the majority of cases (65–86%) [44, 45] (2a, 4). Permanent scarring occurs in 7–30% of cases, and often those were moderate scarring requiring resurfacing [44, 45]. When occlusion of the optic artery occurs, vision impairment is severe and results in permanent blindness in 50% of cases [31]. In 17% of cases, the patients had complete recovery of vision [31]. Stroke is rarely reported, and only one case of death is available in the literature. Table 67.1 lists resolution time for each adverse event associated with filler (Table 67.1).

Lasers

Crusting after laser treatment typically resolves within 2–7 days [6]; acne and milia resolve in 5–7 days. Pigmentary changes due to laser treatment may persist for months to years or may be permanent.

Botulinum toxin

Poor outcomes from Botulinum toxin are typically temporary since Botulinum toxin will lose effect after 3 months. Eyelid ptosis can be improved, or the course can be shortened to 2–4 weeks by using apraclonidine eyedrops 2–3 times daily until resolved [46] (1b). Diplopia can be improved over the course of 7–10 weeks with ophthalmic management, including eye patches [47] (2a).

Preoperative Evaluation

At this time, there are no labs, imaging, or anatomic tests available to aid in determining the likely incidence or severity of an undesirable outcome after a cosmetic procedure. The physical exam and history may be most useful in preventing adverse event and patient dissatisfaction [9, 22, 48] (2a). The best cosmetic outcomes will be achieved with a clear understanding of the patient's cosmetic goals. These goals and expectations must be consistent with realistic treatment options. Expectations can and should be managed by discussing the available treatments, the cost, anesthesia if applicable, potential risks and complications, and recuperation time. Depending on the offered treatment, a comprehensive history should be performed including

increased risk of bleeding, allergies, past cosmetic procedures/surgeries, recent sun exposure, pigmentary conditions, history of acne, medications (including topical regimes such as retinoids, glycolic acid, etc.), profession (e.g., musician/singer), and a history of herpes labialis or recent history of other infections [8–10, 17–20, 24, 31, 49] (4, 4, 2a, 4, 2b). Active cold sores or infection may be a reason to delay treatment [48]. Antiviral prophylaxis such as valacyclovir 500 mg before treatment and again 12 h after treatment may be considered in patients with recurrent cold sores [16, 25] (2b). Past medical history should include current pregnancies, active autoimmune disease, and history of neurologic condition such as multiple sclerosis [48, 50] (2a). Patients should be encouraged to avoid salicylate and anti-inflammatory drugs and herbs, including gingko biloba, garlic, ginseng, St. John's Wort, fish oil, and vitamin E for 7–10 days before treatment [9, 51] (2a). Some authors argue that prior trauma or surgery can increase the chance for necrosis since the normal anatomy has been altered [52]. Trauma or dental work may also increase the chance of infection, but this is based on anecdotal evidence. Pregnancy and breastfeeding are contraindications to treatment with elective cosmetic procedures because safety has not been established. Routine touch-ups may be performed to decrease the chance of asymmetry or lumps and to be alert to any early signs of infection, necrosis, or other adverse events [9]. Relative contraindications for Botulinum toxin include preexisting neuromuscular conditions of the neuromuscular junction, peripheral motor neuropathies, and skin conditions at the site of injection (e.g., contact dermatitis) and in patients with prior history of lower eyelid surgery which may predispose to ectropion when injected periocular [50]. Medications that are contraindicated in Botulinum toxin injections include aminoglycosides, cholinesterase inhibitors, succinylcholine, curare-like depolarizing blockers, magnesium sulfate, quinidine, calcium channel blockers, lincosamides, and polymyxin [50].

Troublesome to Patients

While physicians may have particular concerns (e.g., necrosis), patients may have other concerns. In particular, privacy and discretion may be critical to patients. Many patients do not want relatives to be aware that they are undergoing cosmetic procedures; therefore, contact with patients must be discrete. Consensus panels recommended that patients be asked for permission to contact them after their initial visit [9]. Common and self-remitting side effects such as bruising may be more bothersome to patients than to the physician for the same reason. Patients may not wish to have questions regarding the procedure and may have social events. A well-informed patient prior to the procedure will help to set expectations of the recovery and allow him or her to plan accordingly. Even if an outcome is expected or will self-resolve, it may be reasonable to offer treatment to help shorten the course and improve patient satisfaction (e.g., using PDL to treat post-procedure bruising). Other patient concerns are not well categorized, and our knowledge of patient-reported outcomes after filler may improve with the expansion of patient-centered research.

Prevention

All Cosmetic Procedures

There are several methods that may be used to help prevent or alleviate *pain* associated with cosmetic procedures. These methods include mixing lidocaine with hyaluronic acid or other fillers [53] (1b), nerve blocks or local lidocaine [35] topical numbing [54, 55] (1b, 2a), topical cooling [56] (1b), and using thinner fillers and appropriate needles [57] (2a). Using the smallest possible needles has been shown to decrease injection pain with Botulinum toxin [58] (1b). *Bruising and swelling* can be prevented by applying cold compresses [56, 58, 59] discontinuing nonessential blood thinning medications prior to procedure [39] using long pulse-dura-

tion PDL, arnica taken 3 times a day for 4 days immediately postoperatively, and vitamin K [40, 60–63] (1b, 2a, 2b). HSV *infection* can be prevented by giving prophylactic antivirals (e.g., 400 mg BID acyclovir) prior to filler or laser procedures in patients with a past history of cold sores [8, 16]. In patients with a past history of bacterial infection, it may be reasonable to give prophylactic topical or systemic antibiotics prior to full thickness resurfacing [16].

Filler

Nodules can be avoided by decreasing the speed and volume of injection [9] and to take extra precaution in areas that move around the mouth for PLLA and caHA, or cheeks and hands for PLLA [64] (2a). (For poly-l-lactic acid, increasing product dilution, mixing vigorously prior to injection, and using a large bore needle can help to prevent nodule formation) [64]. *Granulomas* can be prevented by avoiding infraorbital injection of PLA [65] (4) as well as avoiding large injection volumes or repeated injections [27]. Silicone and PLA are associated with increased risk of nodules and delayed-type hypersensitivity, and extra precaution should be used [42].

With the use of small needles, cannulas [66–68] (2b, 4, 2b), microdroplet technique, or small increment injections [69–74] (2b, 2a, 2a, 2a, 2a, 2b), proper knowledge of the facial anatomy and injection plane [48, 52, 75, 76] (2a, 2b) can help prevent *necrosis and other vascular complications*. It is controversial whether aspirating prior to injection is beneficial in helping to prevent necrosis, since the viscosity of the fillers may prevent an accurate flash [70, 72]. There is theoretical support for mixing filler with epinephrine to cause vasoconstriction and thus decrease the size of any arterial targets; however, the data is insufficient to recommend this at this time [70] (2a). Necrosis is most common on the nose (33% of cases) and the nasolabial fold (31.2%), so special precaution should be taken in these areas [31]. *Blindness* or other ocular changes are associated with injection into the glabella in 38.8–50% of cases [31, 32]. Ocular changes are most commonly associated with autologous fat injections in 47.9% of cases, and autologous fat injections resulted in the most severe adverse events [32].

Laser

Crusting experienced after laser treatment can be minimized by discontinuing retinoids prior to procedure [10]. Patients should avoid sun exposure for 2 weeks prior to laser treatment to avoid *hyperpigmentation* [8, 49]. For darker-skinned patients, the use of higher fluencies and lower-density settings with longer treatment intervals can reduce the chance of dyspigmentation [49, 77] (1b). Patients with a prior history of *milia/acneiform eruption* after laser should be treated with prophylactic low-dose doxycycline [8]. To avoid *scarring* with lasers, it is important to avoid treatment on those with prior surgery that may have moved neck skin onto the face and to decrease energy or density on thin skin (e.g., eyelids, neck) [33] (4).

Botulinum toxin

Headache after Botulinum toxin injections is thought to be due to tapping against periosteum, and so avoiding this may help to prevent this adverse effect [22]. "The Spock" can be prevented by injecting the medial frontalis with balanced injection of the lateral frontalis [12] (2a). *Eyelid ptosis* can be prevented by avoiding massaging Botulinum toxin in corrugators [12] reconstituting Botulinum toxin with smaller amounts of diluents to decrease local toxin diffusion [50] as well as injecting 1 cm above the orbital rim and medial to midpupillary line [37]. *Eyebrow ptosis* can be prevented by first assessing frontalis compensation by pressing finger above brow and ask patient to open eyelid, which will demonstrate any subtle lid ptosis [78] (2a). *Diplopia* can be avoided by injecting outside the bony orbital margin to prevent diffusion to extraocular muscles [79–81] (2a, 2a, 2a). *Asymmetric smile and unwanted perioral changes* can be avoided by staying 1 cm above the zygomatic notch when treating crow's feet [81] and per-

forming conservative treatment of the orbicularis oris [12]. *Dysphagia and voice changes* can be prevented by avoiding deep injection in the neck and using less than 10 units of ONA per platysmal band, 50 units per session [28, 82] (2a).

Table 67.2 lists all methods for preventing complications and undesired effects of fillers, as well as the expected effect of the intervention (Table 67.2).

Correction Procedures

All Cosmetic Procedures

For *pain* after fillers, laser, and Botulinum toxin, ice compresses are a tried and true remedy [83] (2c). Icing after the fillers has also been shown to reduce the incidence of *bruising* by 88% [59]. For severe cases of pain and *swelling* after fillers or laser, pulse prednisone may be utilized [6] (2c). For redness and bruising after cosmetic procedures, PDL or IPL 2–5 days after the procedure can be used to minimize these adverse events [12, 84] (1b). Treatment with arnica [40, 85] (3a) and vitamin K [61, 62] has shown to help minimize bruising. *Itching* after procedures can be corrected with antihistamines or mild topical steroids [86] (2a).

Fillers

Lumps and nodules after filler can be treated in several ways. For hyaluronic acid fillers, injecting hyaluronidase can be effective [45, 54]; however, extrusion with a 26-g needle or 11

Table 67.2 Methods for preventing complications and undesired effects of fillers

Filler	Methods to prevent complications	Quality of evidence for methods to prevent complications
Pain	Lidocaine in HA	B
	Nerve blocks	B
	Topical numbing	B
	Topical cooling/ice	B
	Small needles (Botulinum toxin)	B
Swelling		
Redness		
Bruising	Cold compresses (reduces bruising 88%)	B
	PDL with long pulse duration	B
Itching		
Lumps	Decrease speed of injection	B
	Increase product dilution	B
	Large bore needle	B
Rare		
Granulomas	Avoid infraorbital injection of PLA	D
	Avoid large or repeated injections	B
Necrosis/vascular compromise	Use of cannula	C
	Proper knowledge of facial anatomy	D
	Microdroplet technique/small increment injections	B
	Inject in correct plane	B
	Mixing filler with epi to vasoconstrict	B
	Aspirate	B
	Use extreme caution injecting patient who has had local surgery that could alter the anatomy	B
Blindness		
Infection	ppx antivirals (e.g., acyclovir 400 mg BID) for patients with past history	B
	ppx oral or topical antibiotics for patients with past history of infection or full thickness resurfacing	B

Table 67.2 (continued)

Filler	Methods to prevent complications	Quality of evidence for methods to prevent complications
Immediate-type hypersensitivity reactions		
Lasers		
Crusting	Pretreatment cessation of topical retinoids	B
Hyperpigmentation	Avoid sun exposure for 2 weeks prior to laser treatment	B
	Darker skin-- > use higher fluencies and lower-density settings, longer treatment intervals	B
Hypopigmentation		
Milia	Doxycycline low dose for patients with prior eruptions	B
Scarring	Take history about neck lifts (which can pull neck skin onto the face)	C
	Decrease energy or density on thin skin (eyelids, upper neck, lower neck)	C
Botulinum toxin		
Headache	Avoid going deep and tapping the periosteum	B
Spock	Injection into medial frontalis without balance of lateral frontalis	B
Eyelid ptosis	Avoid massaging Botulinum toxin in corrugators	B
	Injections should be 1 cm above orbital rim and medial to mid-pupillary line	B
	Reconstituting Botulinum toxin with smaller amounts of diluents to decrease local toxin diffusion	B
Eyebrow ptosis		
	Assess frontalis compensation by pressing finger above brow and ask patient to open eyelid. Will demonstrate any subtle lid ptosis	B
Diplopia	Injections should be outside the bony orbital margin to prevent diffusion to extraocular muscles	B
Asymmetric smile, cheek flattening, perioral changes	Stay 1 cm above zygomaticus notch when treating crow's feet	B
	Conservative treatment of orbicularis oris	B
Dysphagia, voice change	Avoid deep injection in the neck	B
	Use less than 10 units of ONA per platysmal and/or 50 units per session, thin necks-- > no more than 3 bands per session	B

blade may be required for persistent lesions, and this method has been shown to be superior by patient-reported outcomes [87, 88] (2c, 2a). Granulomas should be worked up for infectious causes, and empiric antibiotics may be considered [89] (2a). If there is no improvement, granulomatous reactions should be biopsied with tissue culture [89] and can be treated with hyaluronidase 20–60 units/ml of filler for granulomas [45, 90] (2a). Corticosteroid injections (Kenalog 2.5–5 mg/cc every 3–4 weeks per granuloma) with or without 5-FU can be effective [53, 89, 91] (4) as well as prednisone or other systemic steroids [92, 93] (2a, 4). Oral antibiotics and COX2 inhibitors minimize granuloma swelling. For immediate hypersensitivity reactions, prednisone or other systemic steroids should be administered [93, 94] (4). Bacterial and other infections should be cultured and treated with appropriate antimicrobial. For caseating granulomas, it is important to consider atypical mycobacteria such as *M. marinum* or *M. fortuitum* that may be identified with polymerase chain reaction [42, 95] (2a).

Immediate-type hypersensitivity reactions should be treated immediately with prednisone or

other systemic steroids in addition to antihistamines [93, 94].

For necrosis due to hyaluronic acid fillers, injection with hyaluronidase as soon as possible is recommended [45, 90]. Topical nitroglycerine has been advocated, but its efficacy is controversial [96, 97] (2a, 2a). Low-dose aspirin and hyperbaric oxygen have also been proposed [97, 98] (1b). For ulceration secondary to necrosis, topical EGF or stem cells [99] (4) and PRP [100] (4) have shown some promise. Blindness or vision changes can be permanent if intervention does not occur within 90 min. Prompt consultation with ophthalmology should occur for any eye pain or vision changes, and the patient should be brought directly to the ophthalmologist [70, 101] (4). Based on ophthalmology recommendations, imaging may be considered, or reduction of intraocular pressure can be considered using ocular massage, intravenous mannitol, or Diamox based on the urgency of the situation [70]. Hypothetically, retrobulbar injection of 300–600 units of hyaluronic acid can be issued for HA fillers, but this has not been tried in practice and is not recommended at this time [102] (5). Unfortunately, despite intervention, patients rarely regain vision, and it's a modest improvement if any [70, 103] (2b).

Laser

Crusting due to laser may be managed with cool soaks and emollients [10]. Milia may be extracted [8]. Hyperpigmentation secondary to lasers can be treated with glycolic acid peels, hydroquinone, azelaic acid, or ascorbic, glycolic, or retinoic acid [8, 16]. Hypopigmentation can be at least partially corrected with fractionated 1550 nm erbium-doped laser, 308 nm excimer laser, topical bimatoprost and tretinoin, or pimecrolimus [104–106] (4, 4, 2b). Scarring due to laser treatments can be partially corrected using topical steroids, intralesional and antiproliferative drugs, vascular and non-ablative laser [33].

Botulinum toxin

Severe headache secondary to Botulinum toxin injection can be treated with analgesics or short course of steroids [23]. "The Spock" can be corrected by having the patient return in 2 weeks for 1–2 units of ONA or INA or 2.5–5 units of ABO in lateral frontalis [107] (2a). For asymmetric smile after Botulinum toxin, one can treat the contralateral depressor labii inferioris.

For eyelid ptosis, apraclonidine 0.5% drops should be administered 2–3 times/day until resolution occurs [46]. An injection of 0.5–1unit of Botulinum toxin can be placed in the medial and lateral tarsus [79] (2a). For diplopia, the patient should be referred for ophthalmologic consultation, and correction can be accelerated with an eye patch or prismatic lenses [47]. If dysphagia or voice change should occur after Botulinum toxin injection of the neck, the patient should be monitored for airway compromise [28, 38].

Observations and Recommendations

Lists of the observations and recommendations we can support using the available evidence are available in Tables 67.1 and 67.2. The highest level of evidence supporting each recommendation is provided.

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Self-Assessment Questions

1. All of the following are effective methods for preventing necrosis or vascular compromise during filler injection except
   (a) Use a large bore needle for injection.
   (b) Proper knowledge of facial anatomy and injecting in the correct plane.
   (c) Aspirate prior to injection.
   (d) Microdroplet technique (small incremental injections).
   (e) Use of cannula.
   (f) Mix filler with epinephrine for vasoconstrictive effects.

2. Treatment of bruising with a pulsed dye laser is most effective in what time period after the bruising occurs?
   (a) Immediately
   (b) 14–21 days after
   (c) 5–7 days
   (d) 2–5 days
   (e) 1–2 days after

3. All the following are methods to avoid eyelid ptosis during Botulinum toxin injection except:
   (a) Avoid massaging Botulinum toxin in corrugators.
   (b) Injections should be 1 cm above the orbital rim.
   (c) Injections should be medial of the mid-pupillary line.
   (d) Dilute reconstitution of product.
   (e) Concentrated reconstitution of product.

4. Which of the following can decrease the risk of post-procedure bruising?
   (a) Vitamin K
   (b) NSAIDs and aspirin
   (c) Vitamin E
   (d) Arnica
   (e) Both arnica and vitamin K

5. What is the most appropriate management if blindness or other ocular complications are suspected after filler injection?
   (a) Careful monitoring
   (b) Prompt consultation with ophthalmology for any vision change or eye pain
   (c) Injection of 300–1500 IU of hyaluronidase into the filler injection site
   (d) Warm compresses and vigorous massage to the affected eye
   (e) Corticosteroids

Correct Answers

1. a: Using a large bore needle may increase the likelihood of injecting into a blood vessel. Small bore needles or cannulas with slow and incremental injections may decrease the likelihood of vascular compromise. Injecting in the correct plane, aspirating prior to injection, and mixing with epinephrine may help to prevent necrosis.
2. d: Although it may not always be ideal, the most effective time to treat post-procedure bruising with PDL is 2–5 days after the bruising has occurred.
3. d: Dilute reconstitution of botulinum toxin A is not recommended when injecting into the corrugators as dilute product is more likely to diffuse and risks weakening the levator palpebrae superioris and resulting eyelid ptosis. Methods used to avoid injecting near the levator palpebrae superioris muscle (including avoiding massage, injecting 1 cm above orbital rim and medial to the midpupillary line, and concentrated product) may help prevent eyelid ptosis.
4. e: Both arnica and vitamin K have been shown to decrease the risk of post-procedure bruising. The other options are blood thinners and may increase the risk of posttreatment bruising. If not medically indicated, these can be discontinued prior to treatment in order to reduce risk.
5. b: Blindness or other ocular complications are a rare but serious complication of filler injection. If pain or vision loss is noted, immediate consultation should be placed to ophthalmology since these changes can be permanent within 90 min. Other reasonable treatments after consultation may include imaging and methods to reduce intraocular pressure. Careful monitoring is not suggested since the vision changes can become permanent if not addressed immediately. Although retrobulbar injection of hyaluronidase may theoretically prove effective, there is no indication for filler site injection of hyaluronidase. Warm compresses and massage may be used when impending necrosis is suspected but is not useful for ocular complications.

Correction to: Rosacea

Shlomit Halachmi

Correction to: Chapter 58 in: M. Alam (ed.), Evidence-Based Procedural Dermatology, https://doi.org/10.1007/978-3-030-02023-1_58

In Chapter 58, the affiliation of the chapter author was incorrect.
The affiliation is now corrected and updated.

The updated online version of this chapter can be found at: https://doi.org/10.1007/978-3-030-02023-1_58

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Correction to: Repairs of the Nose

Mark E. Burnett and John A. Zitelli

Correction to:
Chapter 32 in: M. Alam (ed.), *Evidence-Based Procedural Dermatology*,
https://doi.org/10.1007/978-3-030-02023-1_32

The book was inadvertently published with an incorrect figure 32.13 which is now replaced with the below correct figure.

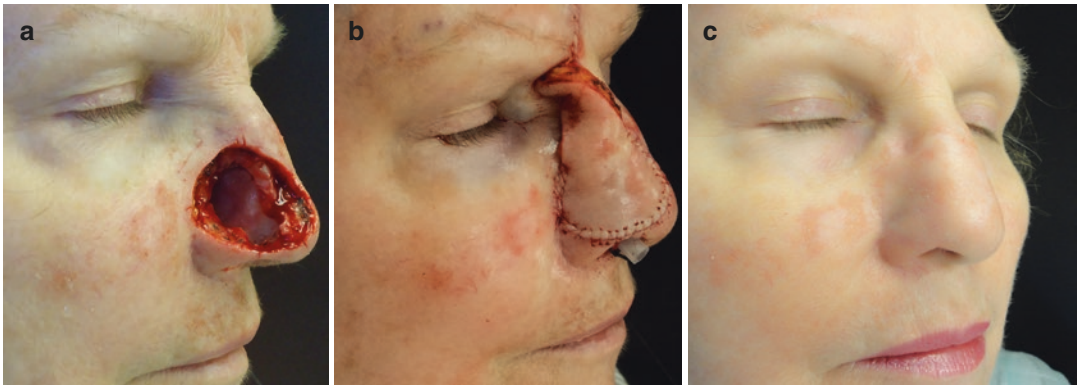

Fig. 32.13 (**a**) Full-thickness loss of the ala, ipsilateral vestibular lining, and lateral half of nasal tip. (**b**) Repair with a fold-under paramidline forehead flap and cartilage strut. (**c**) Result after second-stage inset of flap

The updated online version of this chapter can be found at
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