Skin Cancer Management

A Practical Approach

Deborah F. MacFarlane
Editor

Second Edition

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To my mother, Dorothy M. MacFarlane, who always thinks of the bigger picture and is my inspiration.

Foreword

Useful books are hard to come by. Some books are long and authoritative, suitably imposing, and heavy on the bookshelf, but too bewildering in their complexity to be often consulted. There are brief treatments as well, with these more accessible and practical, less prone to injure the user, yet frequently lacking in substance, devoid of enough detail to be a primary text. Fortunately, there is a sweet spot. A textbook crafted by an expert editor can straddle the middle, presenting a wealth of information distilled to its essence. We all have a few such books in our libraries. We guard them, seldom lend them, and frequently turn to them when we are confused. Like a reliable friend, they are reasonable and wise, providing not just instruction but also nuance. When we read a passage on an unfamiliar topic, we come away feeling like experts, happy to share our newfound knowledge with the next physician or patient we meet.

This is such a book. It has a broad charge: to help us manage skin cancer. And it has already succeeded admirably, as this is a second edition after a well-received first.

There are at least three elements of this book that make it remarkable. First, in terms of physical dimension and thickness, it is neither too long nor too short, but rather just right in size. Second, it has a scope that is sufficient, not excessive or ill-defined. While entire books have been written on the topics covered in each of the chapters, for instance Chap. 3 on chemical peels, or Chap. 4 on photodynamic therapy, such specific texts tend to have narrower audiences. Many of us treat skin cancer, and combining all the relevant techniques and considerations in one volume is extremely helpful. Third, this book is truly multidisciplinary. All too often, textbooks are respectful of the boundaries of a particular medical specialty, and stay within the silo, seeing their subject from a single vantage point. Patients are more complicated, and deserve more. This volume rises to the challenge, spanning the range of skin cancer treatment from topical prophylaxis and superficial procedures, to surgical excision and repair, and all the way to treatment of advanced cancer with radiation and systemic medications. Some of the chapters are rare but precious, and we are delighted that the editor thought to commission them. Specifically, we all want to know when to refer, how to treat cancer in patients with skin of color, and what sort of imaging to order for head and neck tumors. Now we do. There is also copious information about non-surgical treatments for local disease, including not only PDT and chemical peels for skin cancer, but also other topical therapies, intralesional and perilesional treatments, and chemoprevention.

Dr. MacFarlane is a careful and exacting editor who has worked hard so we, the readers, do not have to. We can trust the quality of the chapters and the expertise of the chapter authors. To some extent, this is also the felicitous result of this being a second edition. Minor discrepancies have been corrected and new information has been added. All in all, this is a wonderful contribution to the literature on skin cancer. It is also a useful companion, which I expect to consult again and again.

Chicago, IL, USA Murad Alam

Preface

Ten years ago when this book was first published, it represented a novel approach to textbooks. At the time I had wanted to provide a practical guide to the management of skin cancer by having experts in their fields share their pearls of wisdom, their recipes for anesthesia, their bleomycin doses for instance, in short the sort of advice which is presented quickly or not at all in lectures and is not always found in textbooks. I had purposefully wanted to present as much information as possible in a visual format using figures, case histories, and tables along with the most relevant references. I had wanted to bridge the boundaries between dermatology and other specialties such as imaging and radiation oncology. At that time this text represented the first discussion of the radiologic imaging of skin cancers in the dermatology literature. Some 10 years later, radiologic imaging in dermatology is now a topic of discussion at dermatology meetings.

It has been gratifying to see that more dermatologic texts have adopted this practical approach. I have been pleased to learn that so many dermatology residents have found this text helpful in studying for the boards and that, in addition to my dermatologic surgery colleagues, practitioners from other specialties have found it useful.

Houston, TX, USA — Deborah F. MacFarlane

Acknowledgments

I am indebted to my friends and colleagues who yet again patiently updated their chapters for this edition. I would be remiss not to thank my patients who have taught me some of the most important lessons of my life and to whom I am deeply grateful.

Lastly, my gratitude to Robert and Lara for their loyal support.

Houston, TX, USA Deborah F. MacFarlane

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Chapter 1
Biopsy Techniques and Interpretation

Deborah F. MacFarlane and Ronald P. Rapini

The performance of a skin biopsy is an intrinsic part of the initial management of a patient suspected of having a skin cancer [1, 2]. This chapter will therefore begin with a discussion of the various skin biopsy techniques most commonly used in the diagnosis of skin cancer and their clinical indications. This will be followed by a frank discussion of the interpretation of biopsy results. Discussion of other biopsy techniques such as curettage and sentinel lymph node biopsy will be dealt with elsewhere (Chaps. 6 and 15, respectively).

Biopsy Technique

Pre-op

Before performing a biopsy, it is important to have taken a medical history and performed a physical exam. The presence of potential problems such as coagulopathies and drug allergies including lidocaine allergies, artificial joints, and heart valves should be ascertained (Chap. 8). Most biopsy procedures can be safely performed in patients on blood thinners if sufficient care is taken and hemostatic agents are available. The risks and benefits of the biopsy should be explained and consent obtained.

Site Preparation and Anesthesia

The site should next be cleansed with an antiseptic such as isopropyl alcohol, chlorhexidine, or povidone-iodine, for example. Local anesthesia is best performed with a 30-gauge needle used to slowly infiltrate a buffered lidocaine solution [3]. Most physicians utilize 1% lidocaine with 1:100,000 epinephrine. A buffered lidocaine solution can be less painful, and for larger procedures a 0.5% lidocaine solution reduces the possibility of toxicity that may occur when large amounts of lidocaine are used. One common dilution is nine parts of 0.5% lidocaine with 1:200,000 epinephrine to one part of the standard available sodium bicarbonate solution. With such a dilute concentration of epinephrine, one does not need to worry about potential interactions between epinephrine and beta-blockers, for instance, and patients do not experience the tachycardia that sometimes occurs with a stronger epinephrine solution.

Hemostasis

For biopsy sites that are not sutured, styptic agents are often used. Ferric subsulfate (Monsel's solution) may pigment the tissue, complicating histologic interpretation and 20% aluminum chloride hexahy-

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drate (Drysol) is preferable. The styptic is applied on a cotton-tipped swab with pressure to the biopsy site and held in place for several seconds and reapplied if necessary. Another alternative in a freely bleeding biopsy site is to apply a piece of hemostatic sponge, such as Gelfoam, and to bandage the site [4]. Larger wounds may require electrocoagulation for hemostasis prior to wound closure (Chap. 10). If cautery is used, care should be taken to dispose of any Drysol-impregnated gauze or applicators as this agent is highly flammable [5].

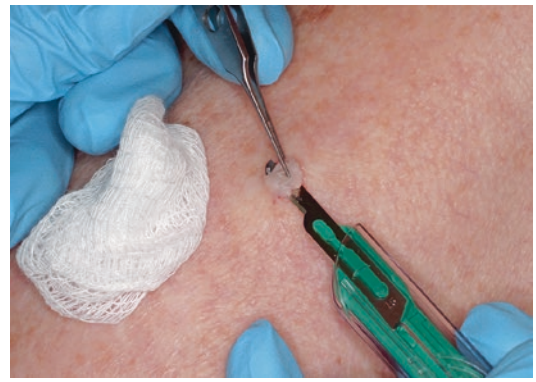

Fig. 1.1 Shave biopsy

Shave Biopsy

As the superficial layer of the skin is sampled this technique is minimally invasive and usually not associated with significant scarring. Shave biopsy can be used in the diagnosis of superficial skin cancers such as actinic keratoses (AK), squamous cell carcinoma in situ (SCCis), and basal and squamous cell carcinomas (BCC and SCC). One disadvantage of this technique is that tumor existing deep to the plane of the shave can be missed (see Table 1.1) [6].

Table 1.1 Biopsy techniques

Biopsy type	Lesion
Shave	AK, BCC, SCC
Saucerization	Pigmented lesions, SCC
Punch	SCCis to check for invasion
Incisional	Melanoma in situ to check for invasion
Wedge	Ulcerated SCC
Excisional	Atypical nevi, melanoma

Equipment

A number 15 blade, toothed forceps, hemostatic agent, cotton-tipped applicator, gauze, and bandage are the equipment used. Please note that a razor blade may also be substituted for a number 15 blade [7].

Technique

After cleansing the area, the local anesthetic is slowly infiltrated to raise a wheal. The skin is stabilized using the first and second fingers of the nondominant hand; then the belly of the blade is held against the skin in a horizontal position and a gentle sawing motion is used to slowly separate the specimen and some surrounding skin from its base (Fig. 1.1). The specimen should include full-thickness epidermis and superficial dermis. Forceps may be used to gently hold the specimen toward the end of the procedure. If the specimen is especially small and/or thin, a drop of India ink can be placed on it before transfer to the container. This will reduce the possibility of it being lost and will in no way interfere with pathologic interpretation [8]. The specimen is then transferred to the specimen container using the wooden end of the cotton-tipped applicator, sparing the forceps from being immersed in formalin. Artifactual changes occur if the specimen is not immediately and continually immersed in the formalin [9].

To assure that the correct specimen is placed in the correct pathology bottle, it is essential that the bottle label be checked. Similarly the specimen should be fully immersed in the formalin solution and the bottle shaken and visually inspected by the physician to confirm the presence of the specimen in the bottle [10].

Hemostasis is achieved; the biopsy site is then dressed with an application of antibiotic ointment or petrolatum and covered with a dressing, which is changed daily for approximately 1 week until the area has healed.

Complications

Hypopigmentation and cutaneous depression may occur if the biopsy is deep.

Saucerization

In a saucerization biopsy, a razor blade is bent into a U shape to obtain a deeper specimen. This is indicated for the biopsy of lesions reaching the upper to mid-dermis such as SCC, atypical nevi, and superficial melanoma.

Equipment

A Gillette super blue razor blade and the same equipment as used with the shave biopsy.

Technique

After cleansing and infiltrating the area as previously described, the razor blade is bent into a U shape and held between the first two fingers of the dominant hand. A sawing motion is used to obtain the biopsy (Fig. 1.2). Hemostasis and aftercare are as previously described.

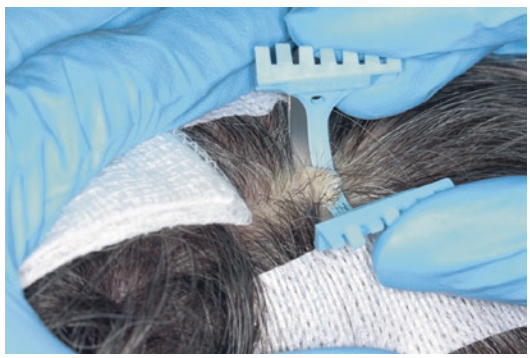

Fig. 1.2 Saucerization biopsy. Note hair is taped down to facilitate biopsy

Punch Biopsy

Punch biopsy is useful for providing information about the depth of tumor invasion as, depending on the size of punch used, it can reach subcutaneous tissue. A 3-mm punch is standard, but 6- and 8-mm punches may be used for removing larger lesions. A 2-mm punch is most often used for cosmetically sensitive areas such as the face, but may be harder to process in the lab and may give an inadequate sample for diagnostic purposes, especially for melanocytic neoplasms.

Equipment

Sterile punch, scissors, toothed forceps, suture.

Technique

Prepare and anesthetize the skin as previously described. Next, stabilize the skin by stretching it taut between the first and second fingers of the nondominant hand and perpendicular to the relaxed skin tension lines, creating an oval defect, which can be more easily sutured. Holding the punch between the first two fingers of the dominant hand, place the punch on the area to be biopsied so that all edges of the punch are in contact with the skin. Rotate the punch between the fingers pressing down at the same time until there is a loss of resistance and the subcutaneous plane is reached (Fig. 1.3). Next remove the punch and gently lift the specimen; divide its base and place it in the bottle of formalin. If forceps are used, be careful not to squeeze the specimen as this will cause "crush" artifact resulting in cellular distortion and complicating histological interpretation [9].

For esthetic and sometimes hemostatic purposes, the biopsy site may be sutured with 6-0 interrupted epidermal sutures on the face and 5-0 interrupted sutures on the body. The suture can be removed at 7–10 days depending on the site.

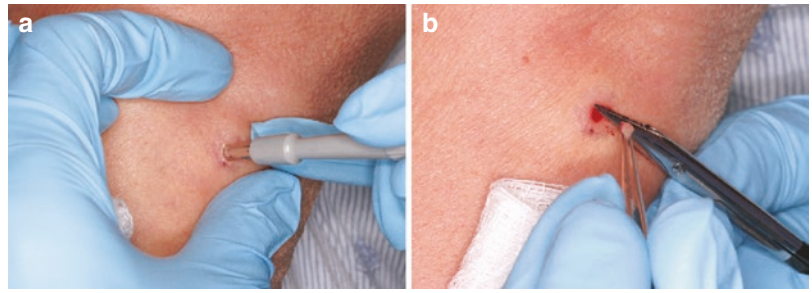

Fig. 1.3 (**a**) Punch biopsy. Note that punch is perpendicular to relaxed skin tension lines. (**b**) Punch biopsy specimen is gently handled with toothed forceps to prevent crush artifact

Biopsy Care

The biopsy site should be cleansed with water daily and covered with an antibiotic ointment and an occlusive dressing. The incidence of contact dermatitis is fairly high with certain antibiotics and this should be taken into consideration. White petrolatum may be used instead. Leaving the wound open to air or allowing it to dry will slow reepithelialization and may not optimize the final appearance [11].

Incisional Biopsy

The incisional biopsy is used when a larger specimen is needed for examination, such as with large pigmented lesions where total excision is not easily achieved [9].

Equipment

Sterilized instruments including a #15 scalpel, toothed forceps, scissors, suture, and gauze.

Technique

Prepare and anesthetize the skin as previously described. Holding the scalpel perpendicular to the skin, make a fusiform incision through the middle of the lesion down to the subcutaneous tissue (Fig. 1.4). Remove the specimen and suture the wound.

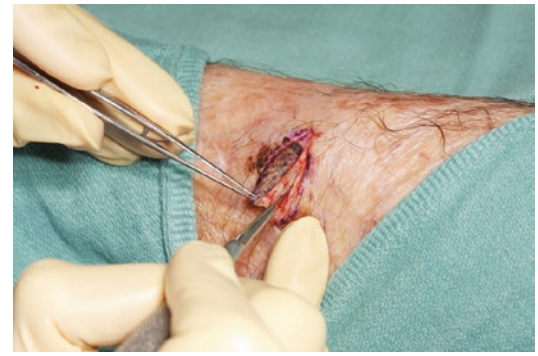

Fig. 1.4 Incisional biopsy of a suspected melanoma

Complications

Wound infection, hematoma, dehiscence, scar, and pigmentation change.

Wedge Biopsy

Wedge biopsies are used mainly to examine ulcer tissue—as with an ulcerated squamous cell cancer—and, as the name implies, are designed to include the normal tissue at the edge with the apex of the triangle pointed into the affected tissue. Thus, normal and affected tissues are sampled together and the resulting specimen is therefore pie-shaped. The defect can then be sutured or left to granulate.

Complications

Bleeding, infection, scar, and pigmentation change.

Excisional Biopsy

Excisional biopsies are defined as extending completely around the clinically apparent lesion, extending to fat, and not necessarily intended to remove the entire lesion. If the intent is to remove the entire lesion, then it is more correctly called an "excision," since the term "biopsy" means that the intent is not to remove the entire lesion. Excisional biopsies are performed for atypical nevi or when melanoma is suspected, for example [12].

Technique

The borders should be marked before the excision (Fig. 1.5). Once the area has been prepped and anesthetized as above, the specimen can be removed in a fusiform manner including subcutaneous tissue [13, 14]. To aid the dermatopathologist, a suture should be placed at the 12 o'clock position to orient the lesion with respect to the patient's body. This is only necessary for larger lesions if the surgeon wants to know more precisely where involved margins are present. For smaller excisions, or those where the entire area would be excised anyway if margins are involved, detailed orientation may not be needed. It is advisable to place this suture before excising the specimen to avoid misorientation.

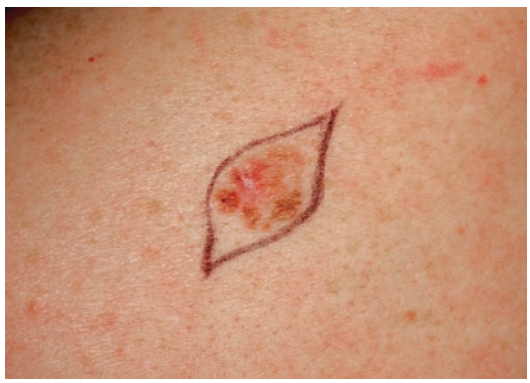

Fig. 1.5 A border is outlined around a suspected melanoma prior to excisional biopsy

Complications

Bleeding, hematoma, infection, scar.

Biopsy Log

It is the physician's responsibility to track the biopsy and a protocol must be established within the practice [10]. The importance of a biopsy log cannot be overemphasized even in these days of electronic medical records. If the biopsy is lost, it is necessary to inform the patient of the situation and to discuss whether or not to re-biopsy the lesion site. There is no credible legal defense if a skin cancer later develops at or near the site of a lesion that had been previously biopsied, the specimen lost, and the patient never informed of the situation [8].

Interpretation of Results

In general, biopsies obtained by skin punch and elliptical excision provide better specimens than those obtained by shave or tangential biopsies, as punches and ellipses are more likely to sample

Table 1.2 Advantages and disadvantages of punch, shave, and excisional biopsies [1]

Punch	Shave	Ellipse
+ Better depth	– Often too superficial	+ Best depth
– Maximum 8 mm width	+ Easier to remove wider lesions	– Difficult closing wide lesions
– More scarring (unless sutured)	– Less scarring (unless deep shave)	– Most scarring
– More equipment	– Least equipment	– Most equipment
– Slower	+ Fastest	– Slowest
– Little skill needed	+ Little skill needed	– More skill needed

Reprinted from Dermatologic Clinics, Vol 12/Issue 1, Rapini RP, Obtaining a Skin Biopsy Specimen and Interpreting the Results, Pages 83–91, © 1994, with permission from Elsevier
+, advantage, –, disadvantage

deeper dermis or subcutaneous tissue. There are general advantages and disadvantages to each biopsy type (See Table 1.2).

The least helpful type is that obtained by curettage. The many fragments are often difficult to process and the pathologist has to reconstruct the lesion mentally. In some instances curettage may be helpful and it is then preferable for the clinician to shave the bulk of the lesion, send this to pathology, and then to curette the base, discarding the curetting.

Elliptical excisions, both incisional and excisional, are preferred for the complete removal of dysplastic nevi and malignant skin cancers.

Tissue Orientation and Margin Evaluation

The first step in examination of a skin biopsy specimen consists of gross cutting and orientation of the specimen referred to as "grossing" [15]. All pathology reports need to contain a description of the gross examination and should specify the orientation of the specimens so that the margins seen on the slides can be appropriately determined. In addition, the report should state whether all the tissue was embedded ("in toto") or if "representative sections" were embedded.

Various decisions may be made at grossing and for this reason the process is performed by a physician or a trained pathology assistant. One decision is to determine if representative sections are to be made, just which tissue will be examined, and which will be discarded. Another grossing question to consider is whether or not to bisect punch biopsy specimens. If punches are bisected, and assuming the clinician placed the most specific changes in the center, then the initial sections are more likely to exhibit the desired histological changes. Sometimes, however, the two bisected pieces may become fragmented, difficult to orientate, or even lost. In addition, important sections may be discarded in the process of "facing" where initial incomplete sections are removed from the paraffin block and discarded until the block becomes smooth, providing complete sections. In contrast, a larger unbisected punch specimen may be easier to handle, but initial sections may be nonspecific, and deeper levels may be needed.

Various tissue orientation errors can occur. Sectioning the surface of a punch specimen will result in a round specimen with epidermis present around most of the edges, and curling of a thin shave biopsy specimen will produce a section with epidermis on opposite sides. Tangential sectioning may give the false impression of hyperkeratosis, hypergranulosis, acanthosis, an apparent increase of melanocytes and basal cells, or perhaps even a pseudomalignancy [16].

Reporting of Surgical Margins

Some pathologists like to state on the report that re-excision is indicated. However, this may place the clinician in a bind, feeling that they have to either follow this suggestion or explain why they do not in the chart. Other clinicians may appreciate this advice.

It is preferable, though not always practical, for pathologists to measure precisely in millimeters how close a tumor is to the margin, rather than to use terms such as tumor "near," "adjacent to," or "approximating the margin."

Fundamental Slide Interpretation

Low Power

Initially, the number of sections can be examined by holding the glass slide up to the light without the microscope. Next, low-power microscopy should be used to scan the slide; indeed, many cases can be diagnosed with low power alone. It is important to examine all sections or at least to look at each type of section that is different grossly.

Develop a Method for Examining Skin Specimens

It is important to develop a method for systematically examining skin sections. Some dermatopathologists will start in the dermis and later examine epidermal changes, while others will start in the stratum corneum and proceed down to the subcutaneous tissue. While observation of the architectural pattern will allow for preliminary diagnosis, it is also important to view cytologic detail such as mitoses and pleomorphism with high power. When looking at a clinical lesion, one should try to imagine what it would look like under the microscope. Similarly, when looking at a pathology specimen, one should imagine what the lesion would look like clinically. A differential diagnosis is then considered by focusing on individual histologic changes together.

Knowing the Clinician

Since many clinicians often have customary treatment habits, it is often possible for the dermatopathologist to guess who performed the biopsy or excision. The best clinicians modify their treatment based on the clinical circumstances. The following are extreme examples presented with the hope that some readers may recognize a pattern and, if applicable, maybe modify their behavior.

Too Small a Sample

Some clinicians send curettage fragments or shave biopsy specimens in more than 95% of the specimens they submit. Pieces of epidermis are submitted when there is clinical suspicion of dermal tumor. It is useful for the dermatopathologist to know if the biopsy procedure was followed by electrodesiccation and curettage, for instance, because then it is not necessary for them to comment on margin involvement. In this way confusion can be avoided if the patient gets another opinion from another physician who is unaware that the lesion has been destroyed.

Too Aggressive a Sample

Other clinicians may be too aggressive in the size of the specimen they submit for diagnosis. One instance of this would be the excision to adipose tissue of seborrheic keratoses. Another example would be the excision of a suspected melanoma with 1–3-cm margins, which is later found to be benign.

Two-Step Management

Some clinicians always perform a biopsy and then have the patient return for a subsequent visit. There are instances where one should biopsy first rather than initiate treatment at the first visit, for instance, in the case of a facial lentigo maligna. However there are other instances, such as a patient with nevoid basal cell nevus syndrome, where it is expedient and cost-effective to initiate treatment in one step when possible.

Too Little or Too Much Information

It is important to include all relevant history or diagnosis on the laboratory requisition slip. Extensive differential diagnoses are not helpful.

Know Your Laboratory

It may be helpful for clinicians to recognize certain characteristics of their dermatopathology laboratory.

One Diagnosis Only

Some pathologists may provide one specific diagnosis and rarely comment on other possible diagnoses. For some of these pathologists, there may be little doubt about the diagnosis of a Spitz nevus. For others, the possibility of a melanoma is considered with less dogmatic certainty.

Too Many Diagnoses

Some pathologists may not give a specific diagnosis, instead providing a descriptive one such as: "perivascular and spongiotic dermatitis." While these pathologists will often not elaborate further, others may at least give a differential diagnosis.

Summary

In conclusion, it behooves the clinician to understand the various biopsy techniques and to be aware of the clinical indications for each type. In the interest of patient care, accurate communication between the clinician and the dermatopathologist is important. It is also helpful for clinicians to recognize certain characteristics of the dermatopathology laboratory they use.

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Chapter 2
Topical Therapies for Nonmelanoma Skin Cancers

Richard R. Winkelmann, Tejas D. Desai, Maheera Farsi, and Abel Torres

As the incidence of nonmelanoma skin cancer (NMSC) continues to rise, topical therapies may be used with increasing frequency. Topical therapies are currently being utilized, both on- and off-label, as primary or adjunctive means of treating NMSC. Surgical therapies, such as Mohs micrographic surgery (MMS), remain the mainstay for tumor removal; however, topical therapy can provide an alternative treatment modality for some skin cancer patients and serve as a useful adjunct to surgery. Topical therapies may also increase overall NMSC treatment efficacy in the management of subclinical lesions and identify asymmetrical growth. In some patients, such as those with multiple NMSCs or those with high surgical risk, topical therapy may be used to avoid surgery or minimize its extent. In instances where biopsy sites are equivocal, topical therapy may also facilitate tumor identification prior to surgical intervention. In some patients who have issues with scarring in general, topical therapies may be preferable to other methods of treatment for NMSC.

The most commonly employed topical therapies include imiquimod, 5-fluorouracil (5-FU), ingenol mebutate (IGM), and diclofenac. Each agent has a different pharmacologic action and may be used in various clinical settings. Photodynamic therapy (PDT), with a variety of compounds and energy sources, has also been used for the treatment of AKs and NMSC, but this topic will be discussed in (Chap. 4). Drawing from their own experience with each topical therapy for NMSCs, the present authors will provide tips to optimize treatment outcome. Particular attention is paid to US Federal Drug Administration (FDA)-approved treatment modalities and select off-label indications. Experimental and/or non-FDA-approved therapies are also briefly mentioned in this chapter for their potential future significance.

Imiquimod

Mechanism of Action

Imiquimod is a type of imidazoquinolone, a class of immuno-enhancing drugs that mobilize several cytokines having antiviral and tumoricidal properties [1]. This cytokine recruitment occurs due to a highly intricate process involving the innate and adaptive immune response through cell surface receptors named toll-like receptors (TLR), located on macrophages, Langerhans cells (LC), and dendritic cells. Imiquimod agonizes TLR-7 and TLR-8, thus activating NF-kB and the formation of cytokines that stimulate both innate and acquired immune response pathways modulating subsequent antitumor activity [2–6].

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Side Effect Profile

Side effects of imiquimod may be local and/or systemic in nature. Common local reactions include erythema, erosion, pain, and ulceration in severe cases [7] (Fig. 2.1). Dyschromia, namely, hyperpigmentation and hypopigmentation, due to postinflammatory changes is not uncommon, although usually mild. Vitiligo-like hypopigmentation has been reported on several occasions [7–11]. Rare reactions have been reported including drug-induced pemphigus of the vulva and aphthous ulcers, presumably mediated by various proinflammatory cytokines such as IFN-α and TNF-α [12–15]. Acute urinary retention and eruptive epidermoid cysts are nonimmunologic effects of imiquimod therapy [16, 17]. Since imiquimod is an immunostimulant of TH_1 cell-mediated immunity, exacerbation of preexisting conditions that are mediated by this part of the immune system may potentially occur. Multiple studies reporting a worsening of psoriasis following imiquimod application have been noted [18–20]. Moreover, exacerbations of atopic dermatitis and HLAB-27 spondyloarthropathy have also been observed after imiquimod therapy [21, 22]. Systemic symptoms have also been reported with the use of imiquimod. These likely occur when proinflammatory cytokines enter the systemic circulation, but it could also be the result of an individual hypersensitivity response to these cytokines. Albeit uncommon, systemic signs and/or symptoms are often likened to a "flu-like" illness, including malaise, fatigue, anorexia, weight loss, diarrhea, postural hypotension, and elevated erythrocyte sedimentation rate [23]. These systemic symptoms typically resolve quickly upon discontinuation of imiquimod therapy. Imiquimod is pregnancy category C, and its use during pregnancy should be avoided [24].

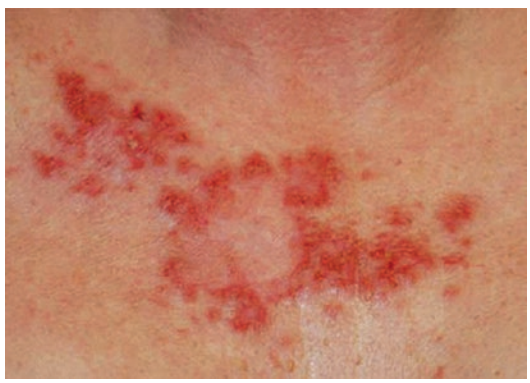

Fig. 2.1 An acceptable reaction after imiquimod use. Note the subclinical areas represented by the satellite erythematous regions

5-Fluorouracil

Mechanism of Action

5-FU is a structural analog of thymine that competes for enzymes with normal metabolites such as uracil [6]. It is eventually incorporated into ribonucleic acid (RNA) and inhibits deoxyribonucleic acid (DNA) formation by covalent bonding that blocks thymidylate synthetase [6]. This ultimately results in cell death since protein synthesis is halted. No immunomodulatory mechanisms have been identified. Nevertheless, it has been postulated that the intense inflammation caused by 5-FU contributes to tumor regression or that the release of antigens, by destroyed tumor cells, may contribute to an immunologic response [6].

Side Effect Profile

Like imiquimod, 5-FU may cause intense erythema, erosions, and ulceration depending on the dose and schedule (0.5–5%). However, the 5-FU reaction most likely depends on the destruction of proliferating cells in NMSCs and sun damage and not on the body's innate ability to mount an immune response. True allergic contact dermatitis to 5-FU, like imiquimod, is infrequent and more commonly triggered by a preservative or vehicle compounded within the cream [25, 26].

Systemic responses to topical 5-FU are rare but have been known to occur in patients with variable deficiency of dihydropyrimidine dehydrogenase, an enzyme critical for metabolism [27]. One should carefully consider applications of 5-FU to large body surface areas, since damaged skin could theoretically result in increased absorption with possible systemic effects. 5-FU is pregnancy category X and absolutely contraindicated during pregnancy [24].

Diclofenac

Mechanism of Action

Topical diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) primarily used to treat actinic keratoses. The main effects of NSAIDs occur through the inhibition of cyclo-oxegnase-2 (COX-2), which is overexpressed in several epithelial tumors and catalyzes the synthesis of prostaglandins [28]. In addition to having anti-inflammatory activities, diclofenac may inhibit neoplastic cell proliferation by inducing apoptosis [28]. Apoptotic pathways via bcl-2 and caspase-8 are similar to the ones seen in imiquimod-induced apoptosis [28].

Side Effect Profile

Several reports of allergic contact dermatitis to topical diclofenac have been observed [29, 30]. These eczematous eruptions are likely a result of the diclofenac molecule itself and less the vehicle or preservative. Photoallergy from topical use has also been reported [31]. The importance of clinical surveillance for an allergic reaction is imperative since an eczematous dermatitis may mimic local reactions induced by topical diclofenac. Diclofenac is the only FDA-approved topical chemotherapeutic agent that is pregnancy category B [24].

Ingenol Mebutate

Mechanism of Action

Ingenol mebutate (IGM) is a hydrophobic, macrocyclic diterpene ester extracted from the weed *Euphorbia peplus* with a dual mechanism of action [32, 33]. Several hours following application, IGM causes rapid cellular death followed, within days, by an inflammatory phase capable of clearing residual cells [34]. Cell necrosis is caused by mitochondrial swelling, chemical destruction, and plasma membrane disruption. The inflammatory phase is mediated by protein kinase C catalyzing neutrophil-mediated, antibody-dependent cellular toxicity [32, 35, 36].

Side Effect Profile

Reported side effects from IGM during initial studies include transient erythema, flaking/scaling, crusting, blistering, pustulation, and erosions. Most importantly, scarring was not reported during these comprehensive trials [32, 34]. The most common side effects resolve within 2 weeks for the face and scalp and 4 weeks for the trunk and extremities. IGM has also demonstrated little potential for skin sensitization, photo-irritation, or photoallergy [37]. There are no known drug interactions for IGM, and its metabolites have no effect on cytochrome P450 enzymes [38]. Although systemic absorption has not been demonstrated, IGM is pregnancy category C and not recommended during pregnancy [24].

Topical Therapy for Actinic Keratoses: The Authors' Experience

Monotherapy for Actinic Keratoses

Actinic keratoses are induced by ultraviolet light radiation (UVR) and, in some cases, develop directly into full-blown squamous cell carcinomas (SCCs) [39]. Topical therapies including imiquimod, 5-FU, IGM, and diclofenac may offer some advantages over traditional treatment modalities. Several major trials demonstrating the clinical efficacy of each topical treatment as monotherapy for AKs have been well studied [40–62]. Table 2.1 summarizes the authors' approach for each topical therapy. Figure 2.2 illustrates the concept of field therapy.

Table 2.1 Topical agents for actinic keratoses

5% imiquimod	5-Fluorouracil	Diclofenac	Ingenol mebutate
Apply over a cosmetic unit, such as one cheek or forehead (approx. 25 cm^2) until the skin retains a shiny appearance	Apply 0.5–5% formulation in the same manner as for imiquimod (Fig. 2.2)	Apply 3% gel (similar to imiquimod and 5-FU) twice daily to any part of the body for 90 days	Apply 0.015% gel to face/scalp once daily for 3 days Apply 0.05% gel to trunk/extremities daily for 2 days
Start application 3×/weekly for 4 weeks	Apply twice daily on face/scalp for 3 weeks and up to 4 weeks for trunk/extremities	The side effect profile is more favorable than other topicals, but its efficacy is inferior	Most common local skin reactions are erythema, flaking/scaling, and crusting
If no response after 2 weeks, increase dose to once daily until an acceptable reaction occurs and treat for 4 weeks (Fig. 2.1)	If the reaction becomes brisk, titrate to once daily or every other day	May be used for patients with contraindications to other topical therapies, patient preference, or if unable to follow-up as recommended	Can apply as field therapy but small amounts dispensed make it more practical for individual lesion treatment
After a 4-week treatment, monitor for residual lesions	Keratolytics may be added to penetrate depth of a thick lesion	Contact or irritant dermatitis may be more common and should be monitored	<25 cm^2 recommended treatment area
Repeat treatment if lesions are still persistent after a 4-week rest period posttreatment	Large body surface area application is discouraged due to potential risk of absorption on damaged skin		Short treatment schedule encourages patient compliance
If no response even after daily dosing, treatment should continue through 16 weeks (per package insert)	Topical steroids may be used to calm the treated area since the mechanism does not solely depend on the inflammatory response		No local reaction to medication could mean inactivated product due to poor storage and handling
For hypertrophic lesions, keratolytics or retinoids may be added to aid penetration	Topical anesthetics are not regularly implemented since pain can help to titrate therapy and avoid contact sensitization		Persistent reaction to non-lesional skin could indicate infection
A thorough history and physical is important to screen for cell-mediated preimmunologic conditions to prevent exacerbation	Infection may be assessed in the same manner for imiquimod		
Topical steroids are not used to reduce inflammation since they may inhibit imiquimod's mechanism of action			
The regular use of topical antibiotics is not encouraged unless infection is diagnosed			
Infection may be present if the area feels worse than it appears or if purulence or signs of cellulitis are present			

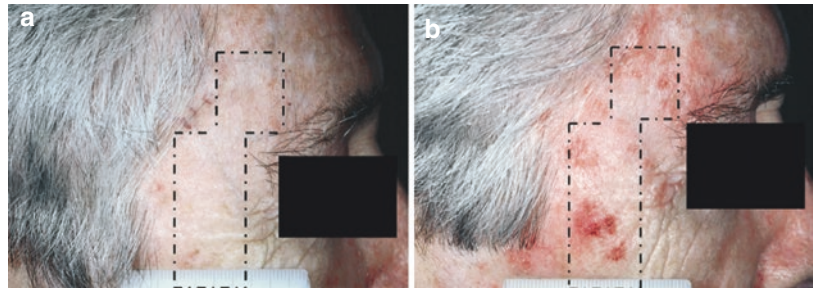

Fig. 2.2 Field therapy depicting the presence of hidden AKs. (**a**) Baseline AK lesion count of 5, (**b**) but after imiquimod therapy commenced, 10 visible lesions appeared in the area treated

Imiquimod Versus 5-Fluorouracil for AKs

One study compared the efficacy of imiquimod (three times per week for 4 weeks), 5% 5-FU (twice daily for 4 weeks), and cryosurgery (20–40 s per lesion) for treating actinic keratosis [63]. Twenty-five patients were randomized to treatment with imiquimod, 5-FU, or cryosurgery and displayed 68%, 96%, and 85% initial clearance, respectively [63]. However, after a 12-month follow-up, a higher rate of recurrence and new lesions were seen in the 5-FU and cryosurgery arms [63]. Furthermore, imiquimod-treated lesions showed greater histologic clearance [63]. In addition, the imiquimod-treated group was judged to have the best cosmetic outcomes [63]. The study concluded that although imiquimod did not clear AK lesions as well as 5-FU or cryosurgery initially, sustained clearance over time was greater.

Another article compared the clinical efficacy between imiquimod (twice weekly for 16 weeks) and topical 5-FU (twice daily for 2–4 weeks) applied as field therapy [64]. Five percent 5-FU was more effective than imiquimod in exposing what were presumed to be subclinical AK lesions, reducing the final count (total AK count declined during the 24-week study by 94% vs. 66%, $p < 0.05$), achieving complete clearance (incidence of 84% vs. 24% by week 24, $p < 0.01$), and attaining clearance rapidly [64]. Tolerability was similar except for erythema, initially significantly higher with 5-FU than imiquimod, then resolved rapidly and was significantly lower than imiquimod by week 16 [64].

A meta-analysis examined ten different studies comparing topical 5-FU and imiquimod with various treatment doses and schedules [65]. Results suggested that imiquimod may have higher efficacy than 5-FU for AK lesions located on the face and scalp (70% for imiquimod vs. 52% for 5-FU) [65]. Interestingly, a study of community observational data found 5-FU reduced the short-term risk of subsequent AKs in a 2-year follow-up period compared to imiquimod, although there was no statistically significant comparative reduction of AK risk during the 5-year follow-up period [66]. Our experience is similar to studies that suggest imiquimod maintains clearance longer than its counterparts for AKs [47, 66].

To date, there are no randomized controlled trials evaluating the risk of subsequent NMSC in patients treated with 5-FU or imiquimod for AKs. Therefore, the authors practice a case-based approach for each patient with AK lesions. In obvious situations, any patient who cannot tolerate one topical medication, for various reasons, may benefit from the other. It is important to obtain a pertinent medical history with respect to cellular immunity. As described before, imiquimod has induced exacerbation of preexisting dermatoses (i.e., psoriasis) and even systemic conditions (i.e., spondyloarthropathy) [18–20]. In these cases, topical 5-FU may be a better option. On the other hand, it has been demonstrated that 5-FU may increase gene mutations, with an unclear implication of the risk of carcinogenesis [47]. Although additional studies are required, the use of imiquimod is encouraged when it is a viable option.

Imiquimod and 5-FU Combination Therapy

Combination therapy involving the use of topical 5-FU and imiquimod has been used successfully

to optimize therapy. Each topical treatment has a different mechanism of action, thereby affecting AK lesions uniquely. Thus, imiquimod and 5-FU may be utilized to complement each other. This is analogous to the use of different chemotherapeutic agents for the treatment of cancer in order to maximize outcomes. In one study, patients applied 5-FU in the morning and imiquimod each night to their lesions daily for 1 week each month over the course of 3 months [67]. The study concluded that this combination was a relatively more rapid and convenient form of therapy compared to each medication alone [67]. Probably the biggest hurdle to this approach is insurance reimbursement since most insurance requires a failed response to one regimen before allowing for a different topical regimen. The authors' approach to combination therapy is described in Table 2.2.

Table 2.2 Combination therapy for actinic keratoses

Combination therapy with imiquimod, 5-FU, and IGM is intended for patients that fail monotherapy or have numerous lesions
Two suggested regimens
1. Separate: Start with a course of imiquimod daily for 1 month immediately followed by a course of 5-FU twice daily for 1 month or IGM once daily for 2 or 3 days
2. Concurrent: Start alternating daily treatment with imiquimod and 5-FU until a sustained inflammatory response for 1 month is observed

5-FU and Calcipotriol Combination Therapy

Calcipotriol, FDA approved for the treatment of psoriasis, has shown to impact the induction of thymic stromal lymphopoietin (TSLP) [68–70]. TSLP, an epithelium-derived cytokine, has been discovered to have potent antitumor effects in skin with barrier dysfunction; this allows for consideration when discussing treatment of skin cancers [70, 71]. In one investigator-blind study, calcipotriol 0.005% ointment was applied as monotherapy to one side of the scalp and face and Ultrabase cream as placebo on the other for 12 weeks [72]. The calcipotriol side showed a statistical improvement in AKs, from baseline, as compared to the placebo side [72]. This antitumor mechanism of calcipotriol was studied in combination with 5-FU, which revealed a synergistic response against AKs via induction of CD4+ T cells [70]. This proposed novel immunotherapeutic regimen was tested in a randomized, double-blinded clinical trial in which 64 patients applied 0.005% calcipotriol ointment plus 5% 5-FU and 67 patients applied Vaseline plus 5% 5-FU twice a day for 4 days [70]. The combination group, 5-FU plus calcipotriol, lead to an 87.8% reduction in AKs as compared to 26.3% in the 5-FU plus Vaseline group ($p < 0.0001$) [70].

Combination Therapy with Cryotherapy

AK lesions may not completely clear with topical treatments alone. Topical therapy may be used in conjunction with cryosurgery and serve to clear residual AK lesions. The opposite technique may be performed as well, by starting with topical therapy first, then destroying remaining lesions with liquid nitrogen. One randomized trial has demonstrated the use of 0.5% 5-FU subsequent to cryotherapy to be more statistically significant than using liquid nitrogen therapy alone for the head and neck [73]. Another open-label study depicted the advantages of applying 0.5% 5-FU prior rather than after cryotherapy, with significant decreases from the baseline number of AK lesions [74]. On a comparable level, the sequential application of topical 3% diclofenac gel for 90 days after cryotherapy has been shown to be more effective in treating AKs than monotherapy with cryotherapy [75]. Similar findings have been reported with IGM in a limited number of patients [76].

Cryotherapy in combination with immunotherapy has also been studied for the treatment of superficial BCC and SCC in situ [77]. After 24 months, recurrence rates of 2% and 0% were observed for superficial BCC ($n = 50$) and SCC in situ ($n = 31$) patients, respectively [77]. The combination of liquid nitrogen followed by imiquimod was more effective than either treatment alone [77]. The authors' approach to combination therapy with cryosurgery is described in Table 2.3.

Table 2.3 Combining topical therapy with cryosurgery for actinic keratoses

Even when failing to clear lesions, topical therapies may highlight lesions to a more confined distribution, facilitating cryosurgery
Two possible regimens: Treat hypertrophic lesions with liquid nitrogen followed 1–2 weeks later with monotherapy with either imiquimod or 5-FU for 1 month, IGM for 2–3 days, or diclofenac for 90 days Treat with initial monotherapy with imiquimod, 5-FU, IGM, or diclofenac followed by liquid nitrogen to residual lesions. (Caveat: If lesions are clinically suspicious or persist after both monotherapy and liquid nitrogen, consider a biopsy to rule out invasive SCC.)

Ingenol Mebutate

At the time of this writing, there are presently no trials comparing the efficacy of IGM to other topical chemotherapeutic modalities. A large multicenter, randomized, and double-blinded study demonstrated 42.2% and 34.1% complete clearance of AKs for face/scalp lesions and trunk/extremity lesions, respectively, utilizing different concentrations if IGM [32]. An additional study demonstrated sustained lesion reduction rates of 87.2% for face/scalp lesions and 86.8% for trunk/extremity lesions after 12 months [32]. IGM is limited in that each package provides enough medicine to treat an area of 25 cm^2 and may provide substantial cost to the patient for multiple treatments or treatment areas. There are no randomized trials evaluating the use of IGM in combination with cryotherapy for the treatment of AKs.

Cost and Treatment Choice for Actinic Keratoses

While the authors focus on the clinically ideal treatment, they realize that cost will always be a limiting factor when treating AKs, and this impacts direct patient care and compliance. A recent review reports that 5-FU and IGM are the most cost-effective topical chemotherapeutic agents for AKs [78]. Yet, the cost of failed therapy must also be evaluated. Since many authors have observed sustained clearance with imiquimod, it may be more economical than 5-FU and/or IGM if repeated treatments are required. Similarly, pharmaceutical companies often provide discount coupons/cards that can help minimize the cost differential, and this should be considered when making cost a central factor in decision-making. Ultimately, the clinical picture, not cost, should guide the decision-making process.

Experimental Topical Therapies

Emerging topical therapies for actinic keratoses include topical retinoids, resiquimod, piroxicam, dobesilate, and betulinic acid [71]. These are either not FDA approved for the treatment of AKs, not widely available, or experimental with only animal subject studies to support them. Perhaps with additional studies, these treatment modalities may impact the treatment of AKs in the future.

Topical Therapy and Nonmelanoma Skin Cancer: The Authors' Experience

Basal Cell Cancer Monotherapy

Imiquimod

Currently, imiquimod 5% is approved by the FDA for the treatment of biopsy-confirmed, primary superficial basal cell carcinomas (BCCs) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet) [79]. The average clearance rate for superficial BCC using imiquimod, in an aggregate number of lesions (n = 1416), is 79% [80]. Furthermore, when reviewing many studies with imiquimod regimens varying in terms of application frequency and/or duration, cure rates for superficial and nodular BCCs range from 43–94% to 50–65%, respectively [81–94].

Imiquimod, in other treatment settings, may be considered as an off-label application and is not FDA approved. Yet, several studies have shown that lesions larger than 2 cm, above the neck lesions, and nodular BCCs can be effectively treated with imiquimod [82–86, 95–98]. Moreover, multiple trials have established imiquimod's clinical efficacy for superficial and nodular BCCs, and to a lesser degree more aggressive BCC varieties, but for the latter, caution is recommended since there are no randomized control trials in this regard (Figs. 2.3 and 2.4) [82–86, 95–98]. Aggregate data suggest a clearance rate of 65% using imiquimod off-label for the treatment of nodular BCCs ($n = 421$) [80]. As with AK lesions, the authors do not advocate one schedule over another and simply present the data and our experience to help the provider prescribe imiquimod for their patients in the most effective manner.

The package insert states that imiquimod cream should be applied to the lesion including a 1-cm margin five times per week for 6 weeks prior to normal sleeping hours (h) and left on the skin for at least 8 h [79]. In a double-blind, placebo-controlled study looking at 5% imiquimod cream as an adjunct modality to Mohs micrographic surgery for the treatment of basal cell carcinoma, results were similar for patients using imiquimod five times weekly for 4 and 6 weeks [98]. Thus, the package label recommendation is emphasized, and the authors instruct patients to apply imiquimod five times per week for at least 4 weeks, aiming for 6 weeks if patients are able to tolerate the medication and don't have to stop it for any period of time [98]. The package label recommendation is emphasized. See Table 2.4 for the authors' approach to BCC monotherapy.

A question frequently raised by clinicians is how do we assure that tumor has been completely removed after using topical imiquimod or any other topical therapies? In reality, this is no different than knowing if tumor has been removed after any treatment. There is a probability that tumor can recur even after excision, and the prudent and

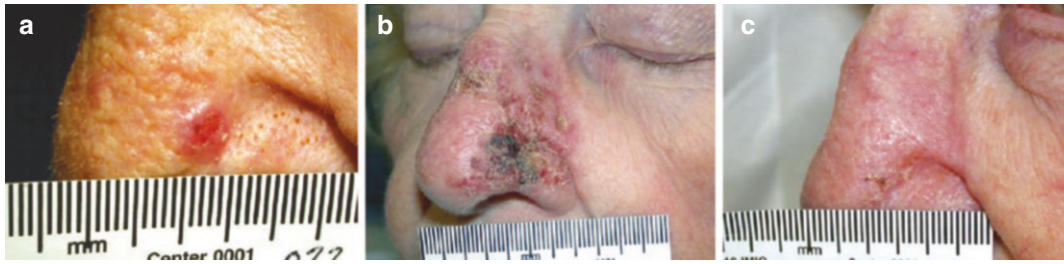

Fig. 2.3 (**a**) A nodular BCC (**b**) treated with imiquimod (**c**) showing complete clinical and histologic devolution. However, we do not treat nodular BCC with imiquimod as monotherapy. We pretreat nodular types with imiquimod prior to surgery, but sometimes clearance may be achieved. We view this as a serendipitous event

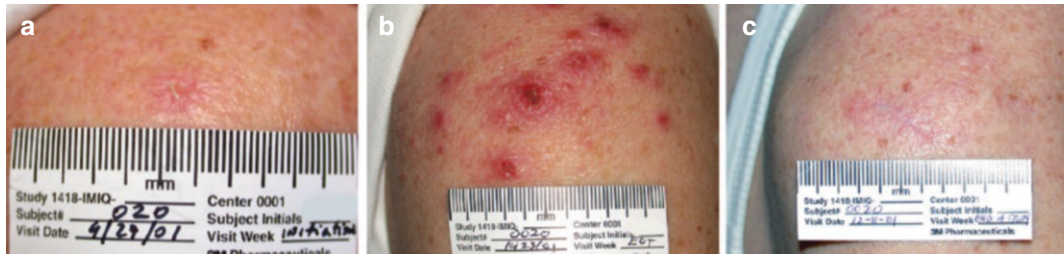

Fig. 2.4 (**a**) Imiquimod treatment for superficial BCC on the left upper arm. (**b**) Note the intense reactionary radius that extends up to the left upper shoulder. Clinically, this is not observed prior to treatment. (**c**) Note that although a biopsy may have appeared to remove the entire superficial BCC on clinical examination, imiquimod may nonetheless incite a robust reaction, which we hypothesize is because of remaining cellular atypia that cannot be detected with the naked eye

Table 2.4 Topical therapies for nonmelanoma skin cancers

	BCC	SCC
5% imiquimod	Apply 5×/weekly on consecutive days for at least 4 weeks, aiming for 6 weeks if tolerable If no response after 2 weeks, daily dosing may be implemented Sometimes twice daily dosing is required to incite a reaction if no reaction with daily dosing at 2 weeks, but caution should be taken, decreasing to daily or 5×/weekly once signs of an initial response ensue If clinical response has occurred but residual tumor is clinically evident, consider further treatment. A 4-week wait period can be allowed to pass before a clinical evaluation for residual tumor since the immunologic response may persist If tumor is still present, we encourage a biopsy or procedural therapy If the clinical assessment is ambiguous, the option is given to the patient to re-biopsy or follow-up after 4 weeks for re-evaluation For BCCs other than superficial types, we do not routinely recommend monotherapy unless a patient is bedridden, terminal, or unable to tolerate a procedure (Fig. 2.3) Warn patients with extensive, adjacent photodamage to expect severe reactions from epidermal field carcinogenesis (Fig. 2.4) For patients concerned about cosmesis, curettage with imiquimod can be recommended for non-high-risk tumors	For SCCs other than superficial in situ types, we do not routinely recommend topical monotherapy unless a patient is bedridden, terminal, unable to tolerate, or refuses a procedure Surgery is the mainstay for treatment for all SCC types, including Bowen's disease, KAs, and superficial or invasive SCCs The main goal of topical therapy is to shrink the tumor prior to surgery or remove confounding adjacent AKs Apply daily dosing from 4 up to 16 weeks planning for a need to extend therapy to 16 weeks since SCCs may take longer to respond The patient should follow up intermittently during the 16 weeks to monitor for clinical improvement or worsening Regular topical use for treating KAs is not encouraged due to conflicting clinical and histopathologic diagnosis
5% 5-fluorouracil	It is FDA approved for superficial BCC regardless of site Evidence-based studies evaluating efficacy and long-term recurrence are lacking Used by authors if there are apparent contraindications to imiquimod and clinically indicated The recommended dose is twice daily for 3–6 weeks up to 10–12 weeks or until erosion occurs, in the amount sufficient to cover the lesion as per package insert	For SCCs other than superficial types, we do not routinely recommend monotherapy unless a patient is bedridden, terminal, or unable to tolerate a procedure The authors typically reserve its use as an adjunct to surgery for all SCC types, including Bowen's disease, KAs, and superficial or invasive SCCs Bowen's disease is the prototypical SCC type. 5-FU may be considered for monotherapy when surgery is not the best option for a patient For Bowen's disease, twice daily dosing for up to 10–12 weeks is recommended Regular topical use to treat KAs is not encouraged due to conflicting clinical and histopathologic diagnosis

traditional course is always to clinically follow the patient for evidence of recurrence. The negative predictive value for imiquimod treatment, defined as the probability of a negative clinical assessment confirmed as being histologically free of tumor, has been reported to be 88.9–93% in various trials [83, 90, 97]. This suggests that most clinicians would be able to determine if a treated superficial BCC has responded appropriately to imiquimod. Longer follow-up periods may be warranted to decrease the amount of false-positive evaluations while observing for evidence of

recurrence. It has been our experience that no perfect follow-up time period exists, and the key is to assure that follow-up occurs based on the histology of the tumor, location, and risk factors for a particular patient.

5-Fluorouracil

If a physician is going to use 5-FU for the treatment of superficial BCCs, then the recommended dose and strength according to the FDA labeling is 5% applied twice daily in an amount sufficient to cover the lesions [99, 100]. Treatment usually is continued for at least 3–10 weeks or until superficial erosion occurs. Therapy may be required for as long as 10–12 weeks before the lesions respond [99]. Refer to Table 2.4 for the authors' approach to the treatment of BCC with 5-FU. An aggregate clearance rate of 92% (n = 144 lesions) has been reported for the treatment of superficial BCC using 5% 5-FU cream twice daily [80]. However, it has been commonly debated as to the actual recurrence rates after this type of therapy.

It is important to note that there can be a wide variability in cure rates due to application methods including utilization of occlusion, once daily or twice daily frequency, or duration of treatment [81]. Although a consideration in superficial BCC, the primary monotherapy use of 5-FU is not commonly recommended for nodular or infiltrative BCCs [101].

Ingenol Mebutate

Although not FDA approved for the treatment of BCCs, IGM has been shown to provide improvement in superficial BCC in a few reports [81]. Histologic clearance was observed in five out of eight (63%) patients after two-day application of IGM gel 0.05% for superficial BCC [102]. The proposed treatment regimen to consider for superficial BCCs is 2–7 consecutive days [81].

Diclofenac

The off-label use of diclofenac to treat superficial BCCs has been reported in some cases [81]. The efficacy of topical application, twice daily for 8 weeks, of diclofenac sodium 3% gel, calcitriol 3 μg/g ointment, and a combination was studied for both superficial and nodular BCCs [103]. Histologic clearance of superficial BCC was observed in 64.3% and 43.8% of patients in the diclofenac monotherapy group vs. the combination therapy, respectively; no statistical improvement was observed for nodular BCCs [103]. The downside of this therapy is suboptimal patient compliance due to several weeks of twice daily application [81].

Squamous Cell Cancer Monotherapy

There is growing evidence that topical agents may serve as noninvasive treatment options for SCC, including Bowen's disease, but neither imiquimod nor 5-FU have an FDA indication for this use. The concern has been that the superficial component may respond, but the deeper invasive components may persist and, yet, not be clinically obvious. Topical treatments may benefit patients with large, superficial bowenoid lesions that may be ill-defined or extend beyond the clinical margin. Likewise, inoperable, invasive SCC may sometimes respond to topical therapy to minimize morbidity or as palliative treatment. A few clinical trials and a host of case reports have demonstrated efficacy for SCC treatment with the use of imiquimod and topical 5-FU. Nevertheless, surgery should be considered the mainstay of treatment for SCC, especially in light of the increased risk of metastasis and perineural invasion with SCC and lack of data to establish removal of deeper invasive components of cutaneous SCC.

Imiquimod

The authors' approach to the treatment of SCC with imiquimod is described in Table 2.4. Our treatment goal is a minimum of 4 weeks and maximum up to 16 weeks, although 20-week regimens have been utilized [100]. The cure rate for SCCis with topical use of imiquimod ranges from 57% to

80% [81, 88, 89, 101]. In this study, complete clinical and histologic clearance was assessed in 80% of patients with SCCis and 71.4% with invasive SCC after daily application of imiquimod 5 days per week for 8–12 weeks [89].

The authors err on the side of caution when treating SCCs with imiquimod, and neither treatment of SCCis or invasive SCC is commonly recommended as primary monotherapy [101]. We reserve imiquimod and other topical treatments for those patients that cannot tolerate, or refuse, surgery or other prescriptions and for adjunctive preparation prior to surgery. Since Bowen's disease may exemplify subclinical extension beyond clinical margins, these lesions tend to be ill-defined. Imiquimod, as well as other topical treatments, may help define the true clinical margins under most circumstances and help reduce the subclinical component, sometimes clearing tumor completely. The authors consider complete clearance as a fortuitous incident, with the main goal of adjunctive therapy being to shrink the tumor before surgery, and thus the extent of surgery. Part of our reasoning for this approach is that we have seen residual SCC with perineural invasion in some patients who appeared to have significant clinical clearance following imiquimod use. New evidence theorizes this may be due to an imiquimod-induced switch from a T_H2 to T_H1 immune response and subsequent reduction in immunosurveillance and tumor editing processes [104]. There is the risk that residual tumor can be left behind, but in our experience with surgery post-imiquimod use, we have not experienced higher recurrence rates nor cases of postsurgical adverse events.

5-Fluorouracil

Topical 5-FU is not FDA indicated for the treatment of SCC but has been used with varying success [105]. This is surprising to many people as they assume that since 5-FU is approved as a therapy for AKs, that by extension, it would be indicated for treatment for SCC. The authors prefer to use topical 5-FU for the treatment of SCC in combination with a surgical modality, as an adjunctive therapy. When surgery is not the best option for the patient, 5-FU has documented high efficacy in an off-label manner against cutaneous SCC in situ, albeit lower cure rates are reported when compared to treatment of superficial BCC as discussed earlier [81, 106].The suggested treatment regimen for SCC in situ is 5% cream applied twice daily for 3–6 weeks, and that can be continued for ≤10–12 weeks if necessary [107]. We find that invasive SCC responds to 5-FU poorly, but 5-FU can still be effective in clearing up confounding collision AK lesions and the SCC in situ component often surrounding invasive SCCs, thus making the subsequent surgery much less burdensome for the patient. Both in morbidity and cost, we are cognizant of the risk that a deeper invasive component can be missed, and thus, it can be utilized to decrease the margin of excision while still taking a conservative excision margin when the anatomy allows. To date, our recurrence rate and lack of significant adverse events support this approach but would welcome randomized controlled trials to assess this approach.

Diclofenac

Diclofenac, although off-label, has been reported to show clearance of SCCis in several cases [81]. In this case series, two patients with Bowen's disease, or SCCis, were successfully treated with twice daily application of 3% diclofenac gel for 80–90 days, and no recurrence was noted for up to 10–12 months both clinically and histologically [108]. In an additional study, five patients with SCCis had histologic clearance at 1 month follow-up after daily application of diclofenac 3% gel for 8 weeks [109]. Although diclofenac can be considered for topical therapy of SCCis, it has not been usually recommended for invasive SCC [81, 109].

Combination Topical Therapy

Topical combination therapy with 5-FU and imiquimod has been used for Bowen's disease in patients who have failed monotherapy with

either treatment [110]. The logic being the same as for systemic chemotherapy regimens where agents can have a synergistic effect because of different mechanisms of action. It may be that the effects of 5-FU are enhanced in the presence of several cytokines induced by imiquimod, producing a synergistic reaction whose mechanisms are not fully understood [110]. It has been our experience that lesions on the extremities and digits have the propensity to be thicker, where topical treatments may find it more difficult to penetrate, and thus may not be as effective.

Topical Therapy as a Surgical Adjunct to NMSC

Preoperative Topical Therapy

The authors prefer to use imiquimod or 5-FU preoperatively to help reduce the size of the surgical defect and thus subsequent repair (Table 2.5). Although MMS may approach cure rates up to 99%, incomplete removal can occur (see Chap. 11 for further details). Imiquimod has also been used as adjuvant treatment following incomplete MMS for large, mixed type BCCs to help clear any residual tumor [111].

The authors investigated the mean reduction in tumor size after using imiquimod prior to MMS [98]. Subjects applied imiquimod five times weekly for 2, 4, or 6 weeks in this double-blind, randomized, placebo-controlled study [98]. The 4- and 6-week treatment groups demonstrated statistically significant reductions in pretreatment versus posttreatment tumor target areas and surgical wound sizes. Yet, they also found cure rates were equal for both the 4- and 6-week treatment groups at approximately 66%. Thus, presurgical adjunctive therapy with imiquimod resulted in elimination of surgery in two-thirds of the patients or a reduction in the extent of surgery in the remaining poor responders (Fig. 2.5).

If there is a contraindication to imiquimod, topical 5-FU may be considered to reduce tumor

Table 2.5 Preoperative topical therapies as surgical adjuncts for NMSCs

5% Imiquimod	5% 5-Fluorouracil
Goal is to facilitate excision by reducing tumor load/size and complete clearance is a fortuitous incident	Goal is to facilitate excision by reducing tumor load/size, and the patient should be aware of this
May be used to clean up actinic and in situ changes adjacent to invasive SCC or BCC, helping to better delineate the neoplasm	Used if there is a contraindication to imiquimod for debulking of tumor
Dosing schedule is similar to treating superficial BCC as monotherapy	May be used to clean up actinic and in situ changes adjacent to invasive SCC or BCC, helping to better delineate the neoplasm
A wait of 2–4 weeks is encouraged before MMS or excision so inflammation may subside, and the excised tissue can be better evaluated histologically	When treating invasive SCC, it is important to confirm the location prior to surgery since the skin lesions may at times appear to have clinically resolved, and post-excision tissue should include some clinically normal skin

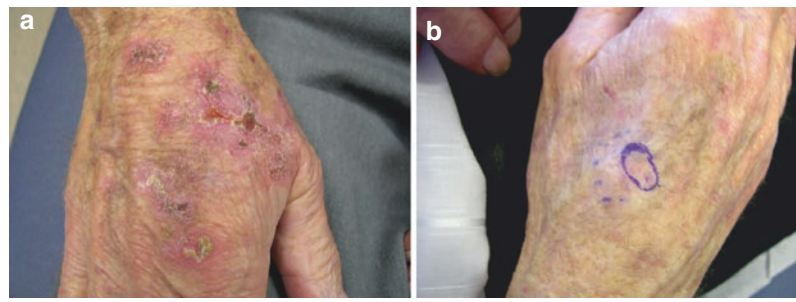

Fig. 2.5 (**a**) A biopsy proven SCC with surrounding actinic damage. After pretreatment with 5-FU, the area was considerably debulked for MMS. (**b**) The circle represents the SCC site

size [112]. Anecdotally, before imiquimod was available, the authors used 5-FU for the preoperative treatment of SCC. The logic behind this is that SCC often occurs in sun-damaged skin with a background and collision of actinic keratoses. The margins of SCC in situ and superficial forms of SCC can be difficult to differentiate from AK in the above described scenario. The authors found that often the entire SCC cleared with 5-FU use, but even when the SCC did not clear, a substantial part of the AK and/or SCC in situ component resolved making the final surgery smaller and easier. It is important to confirm the location of the SCC, when using this approach, so that surgery can be performed in the appropriate area and where more invasive SCC is suspected. The authors emphasize to patients that this is adjunctive therapy, and surgery is recommended to ensure the tumor has been removed appropriately even if the lesion appears clinically removed.

Intraoperative Topical Therapy

It has been reported that 30–47% of NMSCs located on the head and neck that are treated with electrodesiccation and curettage (ED&C) are associated with residual tumor [113–115].

It is the authors' experience that using imiquimod with curettage without electrodesiccation for nodular and/or superficial BCC patients may induce at least equivalent cure rates to curettage and electrodesiccation with better cosmetic results [116]. In this study, 57 nodular and superficial BCCs were curetted without electrodesiccation. Imiquimod 5% cream was then initiated once daily five times per week for 6 weeks. There were three investigators, one of whom started the cream at the time of surgery, one that started 1 week after surgery, and one that waited for reepithelialization before therapy. The patients were evenly divided among all three approaches. At 1-year follow-up, 0 of the 57 BCCs treated had clinical recurrences. Cosmetic results were deemed to be very good to excellent and depicted superior cosmetic outcomes when compared to curettage and electrodesiccation [116]. See Table 2.6 for the authors' approach. Figure 2.6 compares the cosmetic results of curettage with electrodesiccation and curettage with imiquimod cream. Patient satisfaction was much higher postoperatively when adding imiquimod rather than using electrodesiccation alone. The cost of combination therapy is a consideration when choosing the appropriate treatment modality. The

Table 2.6 Intraoperative topical therapies as surgical adjuncts for NMSCs

Curettage followed by imiquimod may facilitate tumor clearance and improve overall cosmesis and cure rate
Curettage without electrodesiccation may serve to improve imiquimod penetration
Curettage without electrodesiccation is performed; then the patient waits for 1 week after curettage and is followed by imiquimod 5×/week y on consecutive days for 4–6 weeks
The patient may return for a clinical evaluation 4 weeks after completing imiquimod to see if more topical therapy is needed
The same rules apply as if it were being used as monotherapy, performing a re-biopsy if the BCC appears to be present, or clinical observation if tumor presence or absence is ambiguous to interpret
This procedure is not recommended for SCCs, since they may portend more aggressive behavior unless the patient is deemed a better candidate for electrodesiccation and curettage

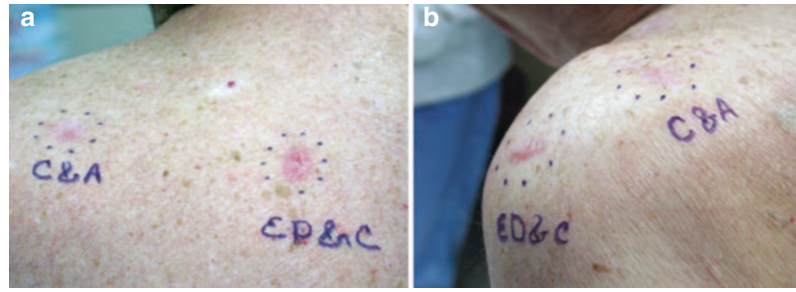

Fig. 2.6 (**a**) Curettage with imiquimod consistently appears to induce pink, flat scars that tend to fade quickly. (**b**) Electrodesiccation and curettage may cause atrophic or hypertrophic cicatrices, depending on a patient's skin type

average cost of curettage and imiquimod cream together may be greater than treatment with excision if patients use each imiquimod packet only once [117]. In practice, most patients apply multiple applications from each individual packet, which substantially decreases the cost of this treatment and, in many cases, can make it less expensive than excision since unused packets can be used to treat multiple lesion [117]. Another consideration is the cost for the procedure and mediation with insurance for coverage. One author's approach is to either bill for the curettage alone or bill for an office visit and not the procedure; since the curettage does not require electrodessication, it does not need to be repeated three times, making it relatively easy to do.

Postoperative Topical Therapy

There is scant data to prove if postoperative use of imiquimod or 5-FU prevents recurrence; however, in theory it would seem logical that use of these topicals may serve to benefit patients with tumors that have a high chance of recurrence. In addition, imiquimod or 5-FU treatment may address discontinuous growth patterns susceptible to recurrence after surgery. It is our opinion that imiquimod may facilitate the clearance of remaining tumor in high-risk lesions successfully due to its unique immunomodulatory mechanism, and we use it in situations where the nature of the tumor is suggestive of a greater risk of recurrence, either because of the host status or presenting nature of the tumor.

Unusual Situations/ Complications/Variations

Problematic Areas

Lips

Diclofenac is an FDA-approved treatment for AK lesions of the lip [57]. Cure rates with 90 days of diclofenac have been shown to be similar when applied to skin after a 30-day follow-up [118]. Furthermore, the tolerability profile of diclofenac would appear to lend itself well, especially when treatment decisions involve cosmetic appearance during and subsequent to therapy [118]. An isolated study also illustrated that topical diclofenac after 6 weeks of therapy may improve this condition with minimal adverse events [119]. Nevertheless, the author's experience is that diclofenac can still result in an occasional robust reaction or allergic contact dermatitis when used on the lips. It is also a slow process, which can affect patient compliance.

Topical 5-FU has been used to treat isolated lip AKs as well as diffuse actinic damage of the lower lip [120]. Although it produced considerable temporary discomfort, final results in one study proved excellent, with recurrences in only 2 of 12 patients [120]. The mean length of therapy was 12 days of topical 5-FU application every other day up to once daily, and patients were clear up to an average of 22 months. Actinic cheilitis has also been treated with imiquimod three times weekly for 4–6 weeks [121]. All 15 patients showed clinical clearing of their actinic damage at 4 weeks after discontinuation of imiquimod. Sixty percent of patients experienced a moderate to marked increased local reaction consisting of increased erythema, induration, erosions, or ulcerations, which in some cases continued through the period of therapy [121]. A recent 6-month follow-up study compared the efficacy of diclofenac, imiquimod, and IGM in 30 patients with actinic cheilitis [122]. Greater clearance of lesions was achieved with imiquimod than IGM or diclofenac (50% vs 40% vs 20%, respectively).

The authors contend that topical therapies have an important role in the treatment of lip AKs and actinic cheilitis. Although topicals may result in uncomfortable side effects during treatment, they may help avoid more aggressive forms of therapy such as carbon dioxide laser ablation. In addition, topical therapies may "biologically image" and discern malignant lesions from more benign varieties, especially in this area at high risk for metastasis. These medications may obviate the need for biop-

Table 2.7 Pearls for topical treatment of lip AKs/actinic cheilitis

5% imiquimod	5-Fluorouracil	Diclofenac
Initially, twice weekly application is employed	5% formulation is used every other day and then increased gradually to daily after a week and, finally, twice daily after 2 weeks as tolerated	Applied every other day and gradually increased to daily as tolerated and stopped when reaction occurs
Careful and slow titration to daily treatment may be required if no evident reaction occurs after 1–2 weeks	Once the patient develops a reaction, it is recommended the patient stay on that regimen or steps down to the prior dosing scheme to prevent a severe dermatitis and possibly subsequent discontinuation	Observation to differentiate response from contact dermatitis is important
If any type of response is experienced, then the patient is highly encouraged to continue with that schedule or the previous schedule	An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV	An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV
An antiviral agent may be prescribed to prevent a herpes labialis flare, if there is a history of HSV	Strong clinical suspicion for a more invasive process is imperative, especially if persistent after several treatment cycles	If no response with diclofenac or other topical medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS
If lesion is persistent after several treatment cycles, suspect a more invasive process	If after 4 weeks of therapy there is no reaction, the topical agent can be switched to imiquimod or diclofenac	
If after 4 weeks of therapy there is no reaction, the topical agent can be switched to 5-FU or diclofenac	If no response with either medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS	
If no response with either medication, treatment is discontinued, and procedural therapy is recommended such as surgical excision or MMS	Pretreatment lymph node examination is recommended as nodes can enlarge posttreatment secondary to inflammation	

sies if clinical success ensues after their use. Nevertheless, patients have to be advised that effects such as swelling can persist for unpredictable periods even after discontinuing use of the topical agent, and the reactions to therapy can be robust with any topical treatment. The authors' suggested approach in this regard is described in Table 2.7.

Eyelids

Eyelid BCCs have been treated with success with imiquimod on numerous occasions according to smaller published studies [123–125]. We have treated two patients with eyelid margin lesions that have shown no recurrence at 5 years. However, this is an off-label use and the safety profile would have to be further investigated before we could advocate the regular use of imiquimod for eyelid lesions. Nevertheless, for the patient that refuses surgery or radiotherapy, after a biopsy reveals a clinically removed nodular or superficial BCC, this can be a consideration.

Avoiding the use of 5-FU near the eye, especially the conjunctiva, may be wise since multiple cases of ectropion have been reported [126–128].

Other ocular side effects include a transient keratitis, erythema, and irritation [129]. As a result, we do not promote the use of 5-FU on or near the conjunctival margin, medial, or lateral canthi. The degree of irritation may be exaggerated in these areas, and cicatricial ectropion has been reported [126].

Penis

No randomized trials exist to determine the true value of imiquimod for Bowen's disease of the penis. However, multiple cases treated with imiquimod have been reported with various dose regimens [130–132]. Bowenoid papulosis has been successfully treated with imiquimod, probably a testament to the medication's antiviral properties [133]. In some instances, a penectomy may have been prevented with the use of topical imiquimod for an invasive SCC [134]. Our experience has been that topical imiquimod has been moderately efficacious for SCC in situ lesions of the penis, including erythroplasia of Queyrat and bowenoid papulosis. We find that topical imiquimod, prior or subsequent to surgery, can be considered as an adjunct, although not FDA approved, for SCC in situ of the penis to minimize more invasive procedures that would not allow maximal sparing of tissue. However, patients need to be prepared for possible significant associated discomfort, swelling, and irritation in the area. The authors do not advocate the use of imiquimod for invasive SCC of the penis because of the unknown risk of locoregional spread. Although Schroeder et al. depicted complete resolution of SCC in situ of the penis, a case-by-case assessment should be made before any patient receives imiquimod as the sole treatment for SCC in situ of the penis [135].

Basal Cell Nevus Syndrome

Imiquimod has been used to treat patients with Gorlin's syndrome and/or multiple acquired BCCs with varying degrees of success. The BCCs described in these studies were usually not only superficial but also included nodular and morpheaform types [136–139]. The authors have had success with several patients with a similar presentation, and often some lesions will respond while others do not, so patients need to be advised of this and monitored closely. Nevertheless, our experience is that imiquimod has been useful in decreasing the extent of surgery necessary for these patients, especially if used early when lesions are first clinically noticed to be developing. Patients with this disorder become very adept at identifying these early lesions (Fig. 2.7).

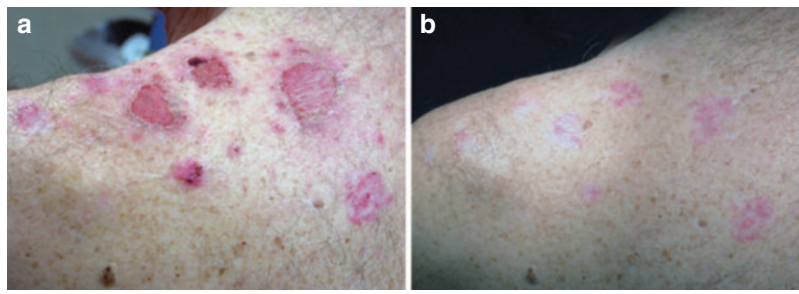

Fig. 2.7 (**a**) Multiple acquired superficial BCCs of the left posterior shoulder. These BCCs resolved after imiquimod 5×/weekly application for 6 weeks. (**b**) The residual pink, flat scar may erroneously cause false-positive readings. We recommend close follow-up and observe for recurrence. These pink areas usually fade with time

Transplant Patients

NMSCs are one of the major causes of morbidity after organ transplantation [140]. This immunosuppressed population chiefly includes organ transplantation recipients but may include any patient that may be undergoing chemotherapy for various reasons (i.e., lymphoma). Of all NMSCs, SCC is the predominant type with a 65- to 100-fold increased incidence in transplant recipients compared to the general population [141]. Therefore, although the exact progression rate of a single actinic keratosis in this patient population is unknown, thorough treatment of these lesions is warranted [142].

A 2018 systematic review of eight randomized controlled trials evaluating 242 organ transplant recipients demonstrated complete clearance rates of actinic keratoses in patients treated with imiquimod (27.5–62.1%), diclofenac (41%), and 5-FU (11%) [143]. Combination therapy of imiquimod and topical 5-FU has also shown clinical efficacy in an open-label study [144]. However, consulting with the transplant physician, when contemplating imiquimod therapy in transplant patients, is advisable since there is controversy regarding immune-enhancing therapies in the setting of therapeutic immunosuppression.

Delayed Mohs Micrographic Surgery

For surgical candidates with BCCs whose MMS procedure is delayed (i.e., scheduling conflicts, travel, insurance issues), the authors employ imiquimod or 5-FU during the waiting period (Table 2.8). The authors treat SCCs in a similar manner with some reservation, depending on the characteristic of the tumor. Although NMSCs are slowly evolving tumors, we feel that the benefits of treating with imiquimod outweigh the alternative of doing nothing during the treatment delay, especially when the length of delay is unclear. The behavior of untreated NMSCs may be unpredictable and pose potential risk of increasing in size or worse. When the patient is ready for MMS, the authors observe for residual disease and often find the tumor has considerably decreased in size or even cleared. Of course, it is important to take either good photographs or measurements using skin landmarks to accurately assess the tumor location posttreatment.

Table 2.8 Pearls for using topical therapies when MMS is delayed

Patients with scheduling conflicts, travel, or insurance issues may use either topical agent in the same manner as recommended for preoperative use until they can return for surgery
When the patient is ready for surgery, careful inspection for residual disease is performed using the prior confirmation of the pretreatment lesion site by photograph and/or measurements
Even when the tumor appears to be cleared, a frozen biopsy may be helpful on the day of MMS to confirm tumor removal. MMS or surgery is advisable for invasive SCC depending on location and tumor characteristics

The Skip Area Controversy

An issue often raised by physicians is whether skip areas will occur after presurgical treatment with imiquimod or 5-FU. In other words, can the topical therapy destroy only parts of the tumor so as to make it appear clinically resolved, when in fact, it is now broken up into subclinical islands of tumor? To answer this question, the authors treated 72 BCCs, in a randomized, double-blind controlled fashion, with imiquimod, then performed MMS, followed by posttreatment biopsies. Note that this was obtained from unpublished data because the evaluation of the tissue, from skip areas, was not deemed to have been part of the initial intent to treat analysis; see reference [145]. The biopsies and MMS were performed regardless of whether tumor appeared clinically resolved posttreatment. Accuracy, of the biopsies and MMS, was established through the use of pretreatment plastic templates localizing the anatomic sites and tattooing of the treatment site. In this double-blind, randomized,

placebo-controlled trial, there was no statistically significant increase in skip areas in the treatment versus placebo arm. Five skip areas were identified in the placebo group, and one skip area was noted in the imiquimod arm. Thus, there does not seem to be any greater risk of leaving behind untreated BCC by topical pretreatment prior to surgery. The authors have not performed a similar study with 5-FU in the pretreatment of SCC. However, an unpublished QI review of more than 40 patients, treated by the authors in this manner, did not reveal any higher incidence of recurrence or complications with SCC tumor pretreatment with 5-FU prior to surgery.

Summary

Topical therapies, including immunomodulators, provide a useful addition to the list of agents used to treat skin cancers, and it behooves the physician to be conversant with their modes of action. Their value lies not just as monotherapy or combination therapy but also as adjuncts either before, during, or post-surgery. As the incidence of NMSC continues to rise, further advances can be expected in the use of topical therapies for the treatment of NMSC.

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Chapter 3
Chemical Peels for Precancerous Skin Lesions

Gary D. Monheit and Chad L. Prather

Chemoexfoliation with various agents such as fermented milk, salt, sulfur, and plant resins dates back to ancient Egypt [1], but the modern era began in the early twentieth century with phenol used as a peeling agent for post-acne scarring [2]. In the early 1960s, Baker and Gordon pioneered the safe use of a phenol formula still utilized today (Table 3.1) [3].

Table 3.1 The Baker-Gordon phenol formula

88% liquid phenol, USP	3 ml
Tap water	2 ml
Septisol liquid soap	8 drops
Croton oil	3 drops

During this period, exfoliating agents that caused milder peeling, such as sulfur, resorcinol paste, salicylic acid, and solid carbon dioxide were also popularized and at times combined to cause a deeper dermal injury than could be achieved with any single agent alone. One example, Jessner's solution, is a combination of resorcinol, lactic acid, and salicylic acid in ethanol (Table 3.2).

Table 3.2 Jessner's solution

Resorcinol	14 g
Salicylic acid	14 g
85% lactic acid	14 g
95% ethanol (q.s.a.d.)	100 ml

Trichloroacetic acid (TCA) became a popular agent for superficial, medium, and deep chemical peeling. Low concentrations of TCA were found to cause light peeling, and more highly concentrated solutions were used to achieve greater peel depths, but with a higher incidence of scarring and pigmentary complications. Such adverse effects directed a search for peeling agents and protocols that approached the efficacy of phenol and highly concentrated TCA, but demonstrated a higher level of patient safety with fewer complications. Brody first combined solid CO_2 ice with 35% TCA, which produced a deeper resurfacing procedure than low concentrations of TCA alone and demonstrated fewer side effects than highly concentrated TCA [4]. This was soon followed by the Monheit combination of Jessner's solution and 35% TCA and the Coleman combination of glycolic acid and 35% TCA (Table 3.3) [5, 6].

The past few decades have seen myriad new peels, most of which employ some proprietary combination or reformulation of known peeling agents. Salicylic acid, glycolic acid, Jessner's solution, lactic acid, resorcinol, TCA, phenol, and many other formulations are regularly employed for improving acne; for reversing actinic damage in the form of precancerous lesions, fine rhytides, and hyperpigmentation; and for rejuvenating the texture and appearance of aged or damaged skin. As the global skincare market soars, chemical peeling remains one of the most common procedures performed today by dermatologists and

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Table 3.3 Agents used for medium-depth chemical peeling

Agent	Comment
40–50% TCA	Not recommended due to higher risk of complications
Combination 35% TCA + solid CO_2 (Brody peel)	The most potent combination
Combination 35% TCA + Jessner's (Monheit peel)	The most popular combination
Combination 35% TCA + 70% glycolic acid (Coleman peel)	An effective combination
88% Phenol	Rarely used without modification

indeed has enjoyed a resurgence in popularity over the past several years, with the International Peeling Society being formed in 2012 to promote the highest possible standards in clinical practice [7, 8]. Even with newer modalities that may also lead to tissue tightening, such as ablative and nonablative laser resurfacing, radiofrequency, ultrasound, and microneedling, chemical peeling remains a mainstay of the dermatologist's armamentarium.

Classification

Like all resurfacing modalities, chemical peeling entails the iatrogenic creation of a cutaneous wound. When properly performed, the partial wound of controlled depth will remove the damaged or precancerous epidermal and dermal layers and allow collagen remodeling and reepithelialization from adjacent follicles, generating healthier skin. Diverse acidic and basic chemical agents produce varying effects through their ability to destroy the cellular and noncellular components of the epidermis and dermis. Their level of penetration, capacity for destruction, and degree of inflammation determine the depth, efficacy, and final result of the chemical peel.

Conceptually, chemical peels are best classified into very light, light, medium-depth, and deep categories (Table 3.4). Very light superficial peels remove the stratum corneum portion of the epidermis only and do not cause tissue necrosis. Destruction of the viable epidermis at any level below the stratum corneum defines a light chemical peel, but the basal layer of the epidermis is not reliably and consistently reached. For this reason, light peels are not the peels of choice for treating precancerous lesions. Full-thickness destruction of the epidermis and partial or full-thickness destruction of the papillary dermis constitutes a medium-depth peel [9]. For the treatment of actinic damage and precancerous lesions, the medium-depth chemical peel is considered the practitioner's peel of choice, as it demonstrates the greatest measure of efficacy without compromising an adequate degree of safety. Finally, a deep chemical peel is defined by destruction through the papillary dermis and into the midreticular dermis. Importantly, destruction at this depth begins to approach the level where the stem cells of the hair bulge, which serve as the res-

Table 3.4 Classification of chemical peeling methods

Superficial—very light	Low potency formulations of glycolic acid or other alpha-hydroxy acid
	10–20% TCA (weight-to-volume formulation)
	Jessner's solution (light application)
	<20% salicylic acid
	70% glycolic acid (must be neutralized)
	Jessner's solution (vigorous application)
Superficial—light	25–30% TCA
	20–30% Salicylic acid
	Solid CO_2 slush
	35–40% TCA
Medium depth	88% Phenol
	Jessner's + 35% TCA
	70% Glycolic acid + 35% TCA
	Solid CO_2 + 35% TCA
Deep	Unoccluded or occluded Baker–Gordon phenol peel
	TCA in concentrations >50%

This classification represents an oversimplification. The depth of injury actually varies along a continuum according to method of application. However, it is helpful when discussing the various options with patients

ervoir for reepithelialization, reside. Destruction by any means—chemical, mechanical, thermal, or other—deeper than the level of the hair bulge leaves no local source of epithelium and may result in both prolonged healing and scarring. Thus only the well-qualified and experienced physician should use deep modalities of destruction and resurfacing.

The above classification of chemical peeling by depth has been validated by experience and has proven useful for selecting the appropriate approach for a particular degree of photoaging based on the desired level of cutaneous penetration. Mild, moderate, or severe actinic damage may thus be treated with agents that act very superficially, superficially, at a medium-depth, or deeply.

Indications

While very light and light peels may improve conditions such as acne, photodamage [10], and skin texture, and deep peels may help improve moderate rhytides and acne scarring, the chief indication for medium-depth chemical peels is the reversal of actinic changes such as photodamage, mild rhytides, precancerous actinic lesions (actinic keratoses), and pigmentary dyschromias (Figs. 3.1, 3.2, 3.3, 3.4; Table 3.5) [11]. When performed properly, medium-depth peels have a favorable benefit/risk profile for the reversal of actinic damage, particularly field treatment of precancerous actinic keratoses. Medium-depth chemical peeling compares favorably with other field treatment modalities, such as topical chemotherapy creams and photodynamic therapy, demonstrating a higher clearance rate than photodynamic therapy and a shorter treatment timeline as compared to topical chemotherapy regimens. The medium peel is usually a single treatment with recovery within 7–10 days. Patients typically experience a clearance of existing lesions and a delay in new lesion formation for several months to several years. The procedure is particularly well suited for the male with actinic keratoses that have required repeated removal with either cryosurgery or 5-fluorouracil chemoexfoliation. The entire face can be treated as a unit; or a subfacial cosmetic unit such as the forehead, temples, cheeks, or chin can be treated independently. Both active lesions and as-yet-

Table 3.5 Major indications for medium-depth chemical peels

Destruction of premalignant epidermal lesions—actinic keratoses
Resurfacing moderate to advanced photoaged skin (Glogau levels II, III)
Improving pigmentary dyschromias
Improving mild acne scars
Blending laser, dermabrasion, or deep chemical peeling in photoaged skin (transition from treated to non-treated area)

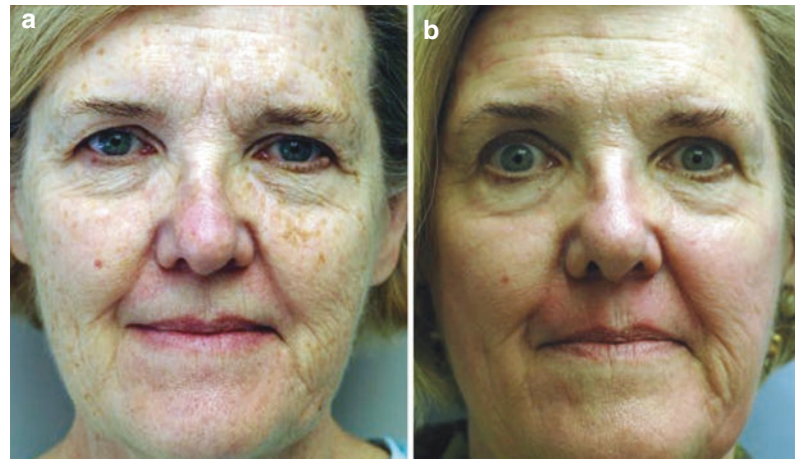

Fig. 3.1 (**a**) A 65-year-old female with rhytides and pigmentary dyschromia prior to medium-depth chemical peel. (**b**) Four weeks after Jessner's/35% TCA combination peel, with improvement in fine rhytides and dyschromia

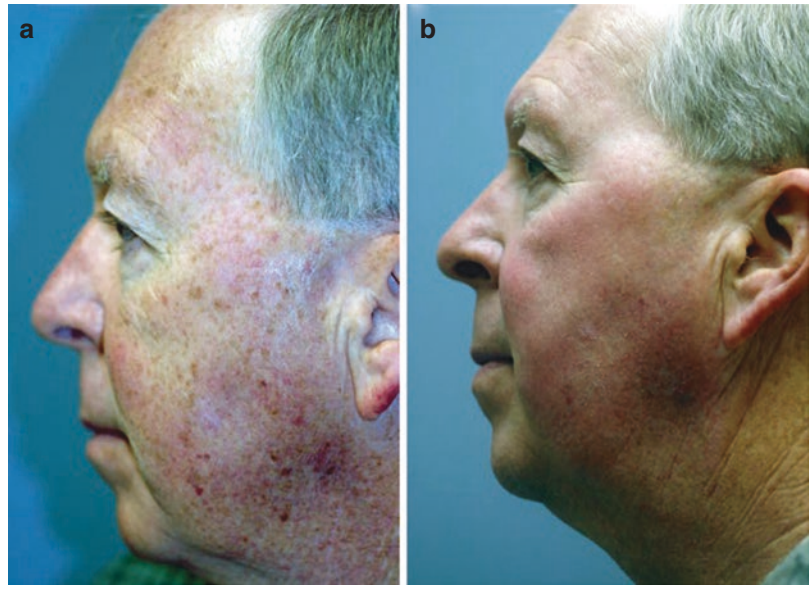

Fig. 3.2 (**a**) A 63-year-old male with facial actinic damage and multiple actinic keratoses prior to medium-depth chemical peel. (**b**) Four weeks after Jessner's/35% TCA combination peel, with improvement in actinic damage and resolution of actinic keratosis

undetected growths will be removed as the epidermis is sloughed. The medium-depth peel is a reliable treatment for full epidermal destruction and can be combined with cryosurgery and/or dermasanding for thicker and more resistant, solitary lesions.

Jessner's and 35% TCA are also effective on sun-damaged arms, although the risk for scarring is slightly higher. Jessner's solution followed by 25% TCA may also be used on the neck and chest to achieve improvement and reduce the risk of scarring that may occur with a 35% TCA solution in these areas with less regenerative reserve.

Contraindications

Several contraindications should be borne in mind when selecting a medium-depth chemical peel over alternative field treatment modalities (photodynamic therapy, dermabrasion, or topically applied medications such as 5-fluorouracil, imiquimod, and ingenol mebutate) (Table 3.6). A medium-depth peel should not occur in the setting of a poor physician–patient relationship, as patient compliance during the recovery period is essential to avoiding permanent negative sequelae. A frank discussion of what the peel can and cannot accomplish is necessary to avoid unrealistic expectations on the part of the patient. Furthermore, poor general health and nutritional status will compromise wound healing and should also dissuade a consideration of a medium-depth chemical peel. While superficial chemical peels are generally safe for patients taking isotretinoin, medium-depth and deeper

Table 3.6 Contraindications to medium-depth chemical peeling

Absolute
Poor physician–patient relationship
Unrealistic expectations
Poor general health and nutritional status
Active isotretinoin therapy or isotretinoin within the last 6 months
Complete absence of intact pilosebaceous units on the face
Active infection or open wounds (such as herpes, excoriations, or open acne cysts)
Relative
Medium-depth or deep resurfacing procedure within the last 3–12 months
Recent facial surgery involving extensive undermining, such as a rhytidectomy
History of abnormal scar formation or delayed wound healing
History of therapeutic radiation exposure
History of certain skin diseases (such as rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis, and vitiligo) or active retinoid dermatitis

peels are contraindicated for patients on active isotretinoin therapy and should be delayed until 6 months following isotretinoin discontinuation [12]. Isotretinoin therapy within the previous 6 months has been associated with increased risk of scarring [13]. Topical tretinoin, while not associated with an increased risk of scarring, will cause a greater depth of penetration. It is our practice to discontinue topical retinoids 2 weeks prior to a medium-depth chemical peel. Additionally, a medium-depth peel should be postposed in the setting of active infections or open wounds such as herpes simplex vesicles, excoriations, or open acne cysts. All patients with a history of herpes simplex virus I of the facial area should be premedicated with an antiviral agent such as acyclovir or valacyclovir and remain on prophylactic therapy for 10 days (Valtrex 500 mg BID × 10 days) until complete reepithelialization.

While not absolute contraindications, patients with hyperreactive or koebnerizing skin disorders such as atopic dermatitis, seborrheic dermatitis, psoriasis, or contact dermatitis may find their underlying disease exacerbated by a chemical peel. Particularly, patients with rosacea may develop an exaggerated inflammatory response to the peeling agents, which serve as a trigger for rosacea sequelae. A history of keloid formation should be screened for prior to chemical peeling. Likewise, patients with a recent history of extensive or major facial surgery or those who have recently had a medium-depth peel in the preceding months should be evaluated closely with regard to risks and benefits. The collagen-remodeling phase of wound healing due to prior treatments is still underway in such patients, and an altered wound healing response may occur with repeat injury. Another important relative contraindication is a history of radiation therapy to the proposed treatment area. An absence of pilosebaceous units compromises the reserve capacity of follicular epidermal cells to reepithelialize.

A higher Fitzpatrick skin type IV–VI is a relative contraindication for medium-depth chemical peeling (Table 3.7). While Fitzpatrick skin types I and II are at low risk for post-resurfacing pigment alteration, types III through VI are at greater risk for these complications [14, 15]. The authors will readily peel Fitzpatrick skin types I–III, cautiously peel types IV and V, and rarely or never peel type VI due to the high risk of permanent hypopigmentation. A test spot in an inconspicuous area under the chin or behind the ear should be performed to assess long-term cutaneous response in those patients for whom pigment alteration is a concern. A pre-peel hydroquinone regimen may also help lessen risk of post-peel dyschromia [16].

Table 3.7 Fitzpatrick's classification of skin types

Skin type	Color	Reaction to Sun
I	Very white or freckled	Always burns
II	White	Usually burns
III	White to olive	Sometimes burns
IV	Brown	Rarely burns
V	Dark brown	Very rarely burns
VI	Black	Never burns

Though purely epidermal precancerous growths such as actinic keratoses respond well to medium-depth chemical peels, cancerous growths that extend into the dermis do not respond fully. Basal cell carcinomas, squamous cell carcinomas, and malignant melanoma will not be sufficiently destroyed with peeling and will recur. Additionally, squamous cell carcinoma in situ and malignant melanoma in situ may extend down the pilosebaceous apparatus into the dermis beyond the reach of a medium chemical peel. All invasive and in situ carcinomas should therefore be treated surgically.

Advantages

Compared to other modalities used to treat precancerous lesions, chemical peeling is typically low in cost, requires only a single application, may be performed in a standard treatment room without specialized equipment, and has reliable efficacy. The cost of most chemicals used for medium-depth peeling is far less than any laser device or platform, photodynamic therapy, or topical medication used to treat actinic keratoses. Furthermore, only a single treatment session with a healing time of 7–10 days is required, rather than the several days to a few months required with topical medications such as 5-fluorouracil, imiquimod, or ingenol mebutate. Additionally, chemical peeling may be performed

in any office setting with routine dermatological supplies such as 2 × 2- or 4 × 4-inch gauze pads and cotton-tipped applicators and does not require special equipment like that necessary with laser treatment or photodynamic therapy. And chemical peels are reliably efficacious. When performed properly on the correctly chosen patient, a medium-depth peel will usually produce sustained clearing of most precancerous lesions for a period of several months to several years. Of course, chemical peeling also gives the added cosmetic benefit of improving the appearance of photoaging skin.

Current Products Available

TCA in strengths of 40% or higher more fraught with complications such as scarring and have fallen out of favor as a single agent for chemical peel [17]. The agents currently used most often for medium-depth chemical peeling include products combined with 35% TCA into three different regimens: (1) Jessner's solution with 35% trichloroacetic acid, (2) 70% glycolic acid with 35% TCA, and (3) solid carbon dioxide with 35% TCA. All three combinations have proven more effective and safer than the use of 50% trichloroacetic acid alone.

The main advantage of preceding 35% TCA with a lighter peeling chemical is that the TCA application and frosting are better controlled, so that the "hot spots" (representing areas of deeper chemical penetration) seen with higher concentrations of TCA, which can produce dyschromias and scarring, are not a significant problem. The authors' preference of Jessner's solution followed by 35% TCA is that it is a relatively simple and safe combination. It is most effective for mild-to-moderate photoaging including pigmentary changes, lentigines, and epidermal growths such as actinic keratoses, seborrheic keratoses, sebaceous hyperplasia, dyschromias, and fine rhytides. The authors' preferred medium-depth peel is dependent on three components for therapeutic effect: (1) degreasing (removal of surface sebum), (2) Jessner's solution, and (3) 35% TCA. The amount of each agent applied determines the effectiveness of this peel. The variables can be adjusted according to the patient's skin type and the areas of the face being treated. As such, the Jessner's/35% TCA combination can be individualized for most patients we see.

Patient Selection

Skin type and degree of photoaging are the most important factors to consider prior to performing a medium-depth chemical peel for precancerous lesions. It is of utmost importance that the physician understands the patient's skin and its ability to withstand treatment, as patients with extensive photodamage require stronger peeling agents and often repeated applications of medium-depth peeling solutions to obtain therapeutic results. In general, Fitzpatrick skin types I and II, which often have the greatest degree of actinic damage and precancerous changes, also have the least risk for hypopigmentation or reactive hyperpigmentation after a medium-depth peel. Patients with type III through VI skin, however, have a greater risk for post-peel pigmentary hyperpigmentation and hypopigmentation and may need pre- and post-treatment with both sunscreen and bleaching agents to prevent these complications [18].

Both the Glogau and Monheit systems of assessing photodamage are useful in matching the appropriate peel depth for a particular patient [18]. The Glogau system (Table 3.8) categorizes the severity of photodamage into groups I through IV, representing mild, moderate, advanced, and severe photodamaged skin. These categories are devised to assist in guiding therapeutic intervention. Glogau categories II and III benefit most from medium-depth chemical peeling. Monheit and Fulton (Table 3.9) have also devised a system of quantifying photodamage using numerical scores that correspond with indicated rejuvenation programs [19]. A score of 10–14 in this system, as typically seen with precancerous lesions or a history of skin cancer, calls for medium-depth chemical peeling. The patient may be shown his or her degree of photodamage during the consultation and the necessity for an individual peeling program.

Table 3.8 Glogau photoaging classification

Group I—mild (typically age 28–35)	Little wrinkling or scarring No keratoses Requires little or no makeup
Group II—moderate (age 35–50)	Early wrinkling, mild scarring Sallow color with early actinic keratoses Little makeup
Group III—advanced (age 50–65)	Persistent wrinkling or moderate acne scarring Discoloration with telangiectases and actinic keratoses Wears makeup always
Group IV—severe (age 60–75)	Wrinkling: photoaging, gravitational, and dynamic Actinic keratoses with or without skin cancer or severe acne scars Wears makeup with poor coverage

Informed Consent

A thorough pre-treatment consultation allows an opportunity to discuss the risks and benefits, as well as to educate the patient on the expected time frame and course of recovery. Consultation also allows the surgeon to assess the patient's goals and expectations to ensure that the procedure is performed only on appropriate candidates. Those who are not willing to tolerate a recovery period involving 7–10 days of desquamation and 3–4 weeks of erythema are better served by other treatments. The patient must fully understand the potential benefits, risks, and limitations of the procedure, and an informed consent should be signed. Pre-treatment photographs are also highly recommended to allow for posttreatment comparison following recovery.

Setup

All reagents for a Jessner's + 35% TCA medium-depth peel may be obtained in bulk for multi-application use from leading dermatologic suppliers.

The standard setup includes a facial cleanser (such as Septisol), acetone, Jessner's solution, TCA, cotton-tipped applicators, 2 × 2- and 4 × 4-inch gauze pads, and cool-water soaks for patient comfort (Fig. 3.5).

When ordering TCA, one must ensure that the strength of the acid is as intended by the physician. While both weight-to-weight and volume-to-volume methods of calculating acid concentration may be used, the authors prefer the even more common method of weight-to-volume calculations. When changing vendors or ordering new products, the distributor's method of calculation should be confirmed, to avoid application of a more highly concentrated or less highly concentrated than intended product.

Patient Preparation

For medium-depth peeling of the face, all patients, regardless of a positive or negative history of oral or facial herpes simplex virus infection, should be pre-treated with anti-herpetic agents such as acyclovir or valacyclovir to prevent herpetic activation during the post-peel period.

Antiviral agents must be continued after a medium-depth peel for at least 10 days until full reepithelialization is achieved.

Table 3.9 Monheit index of photoaging

Texture changes	Points				Score
Wrinkles (% of potential lines)	1	2	3	4	
	<25%	<50%	<75%	<100%	
Cross-hatched line (% of potential lines)	1	2	3	4	
	<10%	<20%	<40%	<60%	
Sallow color	1	2	3	4	
	Dull	Yellow	Brown	Black	
Leathery appearance	1	2	3	4	
Crinkly (thin and parchment)	1	2	3	4	
Pebbly (deep whitish nodules)	2	4	6	8	
(% of face)	<25%	<50%	<75%	<100%	
Lesions	**Points**				**Score**
Freckle-mottled skin (# present)	1	2	3	4	
	<10	<25	<50	>100	
Lentigines and seborrheic keratoses (size)	2	4	6	8	
	<5 mm	<10 mm	<15 mm	>20 mm	
Telangiectasia-erythema flush (# present)	1	2	3	4	
	<5	<10	<15	>15	
Actinic keratoses and seborrheic keratoses (# present)	2	4	6	8	
	<5	<10	<15	>15	
Skin cancers (# present now or by history)	2	4	6	8	
	1 ca	2 ca	3 ca	>4 ca	
Senile comedones (in cheek bone area)	1	2	3	4	
	<5	<10	<20	>20	
				Total score	

Corresponding rejuvenation program	
Score	**Needs**
1–4	Skin care program with tretinoin, glycolic acid peels
5–9	Same plus Jessner's peels, pigmented lesion laser and/or vascular laser
10–14	Same plus medium peels—Jessner's/TCA peel—skin fillers and/or Botox
15 or more	Above plus laser resurfacing

Analgesia and Sedation

Medium-depth peels may be performed without anesthesia, with preceding topical anesthesia, with local nerve blocks, with mild preoperative sedation or anxiolytic medications, or a combination of any of the above. For full-face peels in anxious patients, it is useful to give preoperative sedation (diazepam 5–10 mg orally) along with meperidine 50 mg (Demerol—Winthrop, New York) and a mild sedative such as hydroxyzine hydrochloride 25 mg intramuscularly (Vistaril—Lorec, New York). The discomfort from this peel does not typically last beyond the procedure, so short-acting anxiolytics and analgesics are appropriate [14]. To ensure patient safety, patients who take sedatives or pain medications for the procedure are not allowed to drive post-procedure.

Application Technique

The removal of sebum, scale, and thickened stratum corneum is particularly important for even penetration of the solution and peel efficacy.

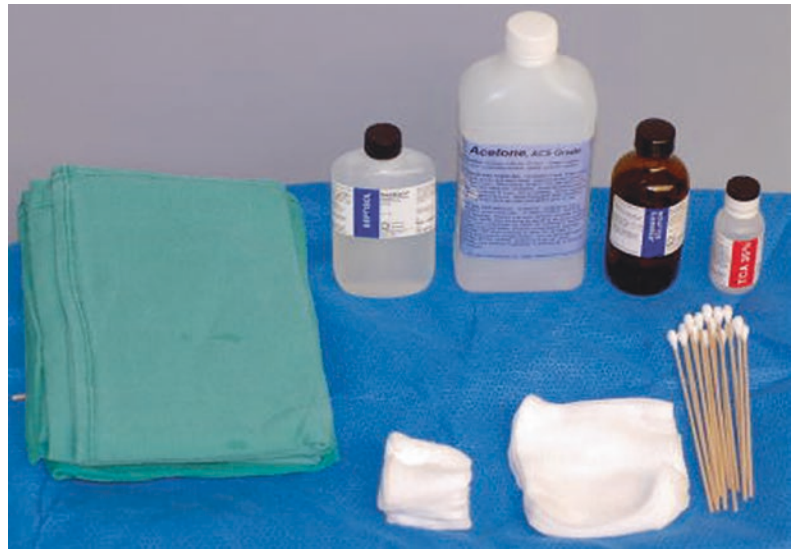

Fig. 3.3 A standard setup includes a facial cleanser such as Septisol, acetone, Jessner's solution, 35% TCA, cotton-tipped applicators, and 2 × 2- and 4 × 4-inch gauze pads

Vigorous cleansing and degreasing of the skin prior to application of the active peeling agent are essential and often overlooked steps in the peeling protocol.

The face is washed with an antibacterial cleanser in glycerin (Septisol—Vestal Laboratories, St. Louis, MO) applied with 4 × 4-inch gauze pads and then rinsed with water. Acetone is then applied with 4 × 4-inch gauze pads to remove residual oils and debris. The skin is thus debrided of loose stratum corneum and excessive scale. The necessity for thorough degreasing in order to achieve reliable and even penetration cannot be over emphasized. Prior to application of the active peeling agent, one should assess the thoroughness of degreasing. If oil or scale is felt, the degreasing step should be repeated. Particular attention to the hairline and nasal areas is required in order to obtain an even peel over the entire face.

Next, Jessner's solution is evenly applied, either with cotton-tipped applicators or 2 × 2-inch gauze pads (Table 3.10). Jessner's solution alone constitutes a very light peel and will disrupt the epidermal barrier allowing a subsequent TCA application to penetrate more deeply and evenly. Only one coat of Jessner's solution is usually necessary to achieve a light, even frosting on a background of erythema. The expected Jessner's frosting is much lighter than that produced by the TCA. The face is treated in sequential cosmetic zones progressing inferiorly from the hairline. Even strokes are used to apply the solution to the forehead, each cheek, the nose, and the chin. The perioral area should follow, and the eyelids are treated last, creating the same erythema with focal, light frosting.

As with the application of Jessner's, cosmetic units of the face are then peeled sequentially with TCA applied to the forehead, temples, cheeks, nose, and, finally, to the cutaneous lips and eye-

Table 3.10 Jessner's + TCA medium-depth chemical peel procedure

1. The skin should be cleansed thoroughly with Septisol to remove oils
2. Acetone is used to further debride oil and scale from the skin surface
3. Jessner's solution is applied with 2 × 2-inch gauze in an even coating, region by region
4. 35% TCA is applied with cotton-tipped applicators until a light frost appears
5. Cool saline compresses are applied for patient comfort
6. Post-peel regimen begun with 0.25% acetic acid soaks and a mild emollient cream

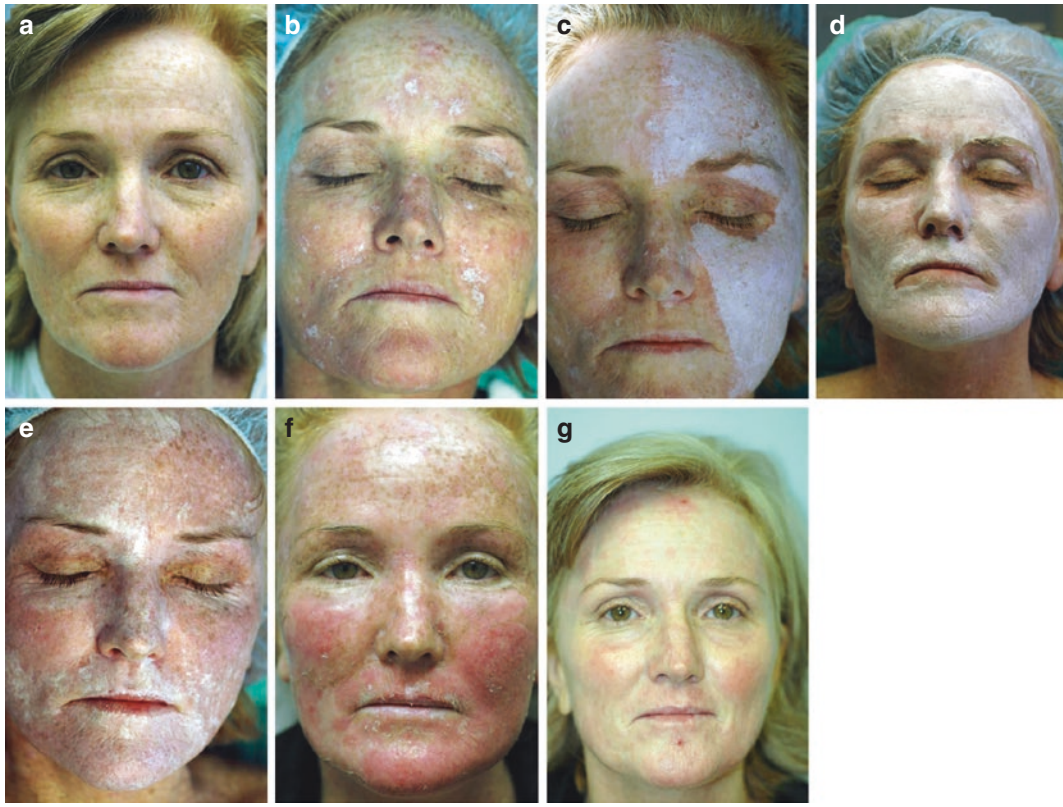

Fig. 3.4 (**a**) A 48-year-old female just prior to medium-depth chemical peel with Jessner's/35% TCA combination peel for multiple actinic keratoses and actinic damage. (**b**) After cleansing with Septisol and acetone and application of Jessner's solution, 35% TCA has been applied directly to actinic keratoses as evidenced by focal frosting of the lesions. (**c**) 35% TCA is applied regionally in a stepwise manner, allowing time for evidence of frosting. Level II frosting is achieved. (**d**) Level II frosting after full-face application. (**e**) Five minutes after completion of TCA, frosting has significantly decreased. (**f**) Three days later. (**g**) Thirteen days later. Note focal residual healing of actinic keratoses on forehead and mental crease

lids (Fig. 3.4a–g). The 35% weight-to-volume TCA is applied evenly with one to four cotton-tipped applicators rolled over different areas with lighter or heavier doses of the acid. Four well-soaked cotton-tipped applicators are used with broad strokes over the forehead and the medial cheeks. Two mildly soaked cotton-tipped applicators can be used across the lips and chin and one damp cotton-tipped applicator on the eyelids. The amount of acid delivered is thus dependent upon both the saturation of an individual cotton-tipped applicator and the number of cotton-tipped applicators used. In this manner, the application is titrated according to the cutaneous thickness of the treated area.

The white frost from the TCA application, which represents the keratocoagulated endpoint, should appear on the treated area within 30 s to 2 min after application. An even application should eliminate the need for a second or a third pass, but if frosting is incomplete or uneven, the solution should be reapplied to these areas. TCA takes longer to frost than a deep phenol peel, but less time than the superficial peeling agents do.

After a single application of TCA to an area, the surgeon should wait at least 3–4 min to ensure that frosting has reached its peak before considering further application.

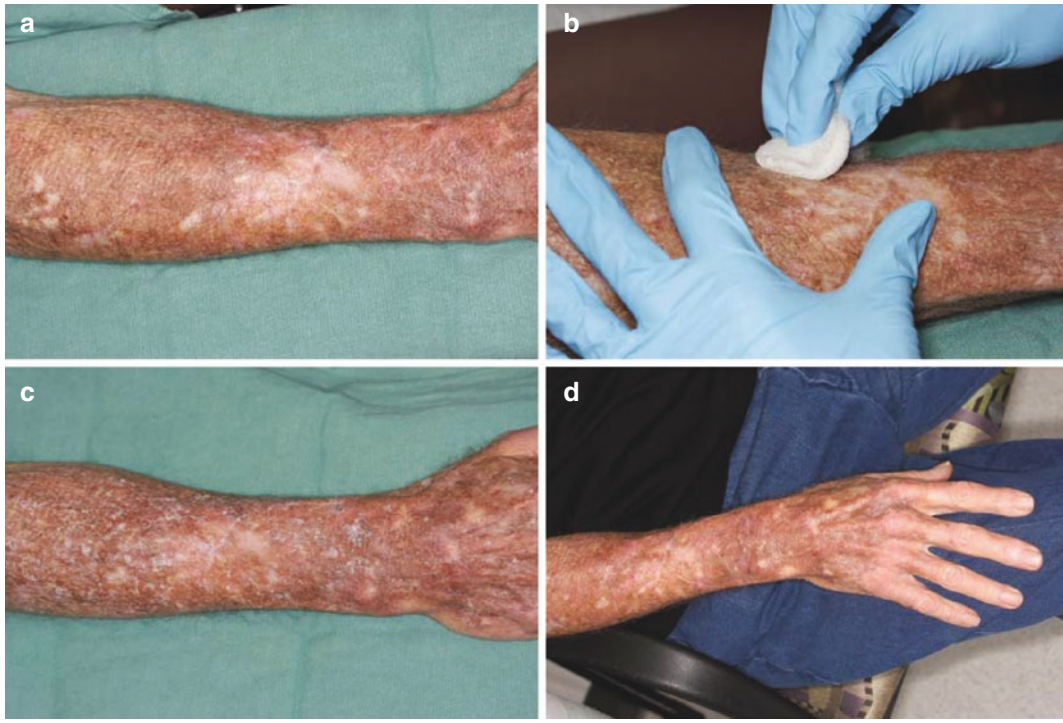

Fig. 3.5 (**a**) A 74-year-old male with a history of numerous non-melanoma skin cancers presents for a chemical peel of numerous actinic keratoses on his arms. (**b**) Following application of Jessner's solution, 25% TCA is applied. (**c**) Frosting is apparent. (**d**) At follow-up 1 month later

The thoroughness of application can then be analyzed, and a touch-up, or less commonly another pass, can be applied as needed. Areas of poor frosting should be retreated carefully with a thin application of TCA.

The physician should seek to achieve a level II to level III frosting. Level II frosting is defined as white-coated frosting with a background of erythema [20]. A level III frosting, which is associated with penetration to the reticular dermis, is solid white enamel frosting with no background of erythema. A deeper level III frosting should be restricted only to areas of heavy actinic damage and thicker skin. Most medium-depth chemical peels should strive to obtain no more than a level II frosting. This is especially true over eyelids and areas of sensitive skin. Those areas with a greater tendency to scar formation, such as the zygomatic arch, the bony prominences of the jawline, and chin, should only receive up to a level II frosting. Overcoating trichloroacetic acid with multiple passes or highly saturated cotton-tipped applicators will increase its penetration, so that a second or third application will create further damage. One must be extremely careful to retreat only areas where the amount of solution taken up was not adequate or the skin is much thicker. One should never overcoat a fully frosted area.

Certain facial features require special attention. Careful feathering of the solution into the hairline and around the rim of the jaw and brow conceals the line of demarcation between peeled and non-peeled areas. The perioral area has fine, radial rhytides that require a complete and even application of solution over the lip skin to the vermilion border. This is best accomplished with the help of an assistant who stretches and fixates the upper and lower lips as the peel solution is applied. Alternatively, the TCA may be applied

along the rhytide to the vermilion border with the wooden end of a cotton-tipped applicator. Deeper furrows such as nasolabial and labiomental folds, midfacial rhytides, and dynamic rhytides will not be eradicated by a medium-depth peel and thus should be treated like the remaining skin.

Thickened, focal keratoses do not pick up peel solution evenly and thus do not frost evenly. Additional applications rubbed vigorously into these lesions may be needed for penetration.

Eyelid skin must be treated delicately and carefully. A damp, rather than saturated, applicator should be used. This is accomplished by draining the excess TCA on the cotton tip against the rim of the bottle or onto a dry gauze pad before using it for application. The patient should be positioned with the head elevated at 30° and the eyelids closed to avoid corneal contact.

> Be cautious when peeling periocularly. Dry cotton-tipped applicators should be used at the lateral and medial ocular commissures to prevent spread of acid by capillary action of tears.

The applicator is then rolled gently on the lids and periorbital skin within 2–3 mm of the lid margin. Never leave excess peel solution on the lids, because the solution can roll into the eyes.

The patient will experience an immediate burning sensation as the TCA is applied, but this subsides within minutes as frosting is completed. A circulating fan may be placed beside the patient for comfort. Cool saline or water compresses also offer symptomatic relief for a peeled area. The compresses are placed over the face for 5–6 min after the peel until the patient is comfortable. The burning subsides fully by the time the patient is ready to be discharged. At that time, most of the frosting has faded and a brawny desquamation is evident.

Post-procedure

Postoperatively, edema, erythema, mild pruritus, and desquamation are expected. Mild to moderate edema in treatment areas should resolve within a few days [21]. With periorbital peels and even forehead peels, eyelid edema can be severe enough to close the lids, and the patient should be advised of this possibility. For the first 2–4 days, the patient is instructed to soak the peeled area four times a day with 0.25% acetic acid compresses made of one tablespoon white vinegar in one pint of warm water. A bland emollient is applied to the desquamating areas following soaks. After 4 days, the patient can shower and clean the area gently with a mild facial cleanser. Erythema will intensify as desquamation becomes complete within 4–5 days and healing is completed within 7–10 days. At this time the bright red color has faded to pink and has the appearance of a sunburn. This erythema may be covered by cosmetics after 1 week and will fade fully within 2–3 weeks.

Complications

While medium-depth chemical peels are generally safe when appropriately performed, complications do exist. The most common are prolonged erythema, infection, pigmentary alteration, and scarring.

Seven to ten days of desquamation and erythema are to be expected, yet prolonged erythema occasionally occurs. This is common in patients with an underlying diagnosis of rosacea, where the chemical peel serves as a trigger for inflammation. The event is limited, however, and should resolve within several weeks to a few months. Erythema associated with pain should prompt consideration of and investigation for an infection, particularly with herpes simplex virus. All patients with a history of herpes simplex virus of the facial area should take an antiviral agent such as acyclovir or valacyclovir and remain on prophylactic therapy for 10 days. Cultures and empiric, broad-spectrum therapy covering bacterial and candida infection are prudent as well in patients who demonstrate increasing pain and erythema.

Permanent hypopigmentation of Fitzpatrick skin types III–VI is a potential complication, although the risk is not as great as that seen with carbon dioxide laser resurfacing. If hypopigmen-

tation is a concern, a test spot is warranted prior to full-face application.

Scarring may occur as a result of various factors. Fifty percent and higher concentrations of TCA commonly lead to scarring, so lower concentrations should be used. Isotretinoin therapy within the previous 6 months has also been associated with an increased risk of scarring, and medium-depth peels should be delayed until 6 months following cessation of therapy. A history of keloid formation should also be screened for prior to chemical peeling.

Finally, eruptive keratoacanthomas have also been reported following medium-depth peels to the arms and hands, with all lesions resolving spontaneously in the two cases reported in the literature [22, 23].

Summary

Chemical peeling continues to be one of the most common procedures performed today by dermatologists for improving acne, reversing actinic damage, and rejuvenating the texture and appearance of aged or damaged skin. Furthermore, the medium-depth chemical peel remains the peel of choice for the treatment of actinic damage and precancerous lesions, as it demonstrates the greatest risk/benefit ratio. While the potential for permanent complications exist, medium-depth chemical peels remain a safe procedure for the treatment of precancerous lesions when adherence to well-established protocols occurs.

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Chapter 4
Photodynamic Therapy

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Photodynamic therapy (PDT) involves the use of a light source to activate a compound (photosensitizer) within precancerous or malignant cells. Generation of reactive oxygen species ultimately leads to cytotoxicity to malignant cells [1].

PDT has been shown, after years of research, to successfully treat actinic keratoses (AKs), squamous cell carcinoma in situ (SCCis), superficial basal cell carcinoma (sBCC), and thin nodular basal cell carcinoma (nBCC). It is a non-invasive treatment modality with good to excellent cosmetic outcomes in addition to higher levels of patient satisfaction and patient preference when compared to most standard treatments [2–4].

As a field therapy, PDT can be an effective treatment for patients presenting with multiple cutaneous lesions. Immunosuppressed patients, and organ transplant recipients (OTR) in particular, are at an increased risk for AKs, SCCis, and invasive skin cancers. These cutaneous malignancies are frequently numerous, occasionally widespread, and can be responsible for significant morbidity and mortality in OTRs [5] (see Chap. 17). Treatment with regular PDT sessions has shown promising results in this patient population to reduce AK burden and decrease the risk of SCC development. There is also evidence for the use of cyclic PDT for the prevention of AKs and NMSCs in transplant recipients [5, 6]. Patients with multiple BCC, such as those with basal cell nevus syndrome, may also benefit from treating simultaneously many lesions with PDT.

Several PDT protocols for the treatment of NMSC and precancerous cutaneous lesions have been developed and approved by major regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In addition, there are many published protocols in the literature that vary for the different PDT parameters including photosensitizers, incubation period, light source, irradiance, and illumination duration.

This chapter is designed to serve as a practical user's guide for providers involved in the management of precancerous lesions and skin cancer with PDT. It will emphasize some of the more commonly used techniques and treatment algorithms that have been associated with positive patient outcomes. In addition, this chapter discusses methods to improve outcomes with combination therapies and using PDT as a preventive modality.

Photosensitizers and Light Sources

The most common photosensitizing agents used in PDT are 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). An ALA 20% solution, a nanoemulsion 10% gel, and a self-adhesive 5-ALA patch are all available formulations [7]. Systemic photosensitizers, such as porfimer sodium, offer deeper tumor penetration,

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but their prolonged photosensitivity has limited their use in dermatology. Aminolevulinic acid (ALA) is an intermediate in the heme synthesis metabolic pathway. When applied to the skin, it is selectively absorbed by skin cancer cells and converted into protoporphyrin IX (PpIX). PpIX is activated by light of several wavelengths in the blue- and red-light spectrum with notable absorption peaks at 410, 505, 540, 580, and 630 nm [7].

A fluorescent blue-light with a peak emission at 417 nm (BLU-U), as well as several narrow band LED red-lights (BF Rhodo LED, Aktilite, Omnilux), are commercially available with activation peaks at 630–635 nm. Depth of tissue penetration is related to wavelength; red-light, with a longer wavelength, will penetrate deeper than blue-light and may be more suitable for deeper lesions. Other light sources such as coherent light sources (e.g., lasers), incoherent sources (e.g., broadband lamps), intense pulse lights, and natural sunlight or daylight can be used for PDT. Protocols using daylight PDT (dPDT) are approved by the European Medicines Agency in select European countries, and in several other countries around the world [7–9].

In the United States, the FDA has approved the use of ALA in combination with specific light sources for the treatment of AKs. ALA 20% solution with the BLU-U lamp is approved to treat AKs of the face, scalp, and upper extremities. In May 2016, the FDA approved ALA 10% (Ameluz) gel with the BF-RhodoLED lamp for the treatment of lesional and field-directed therapy of mild to moderate AKs of the face and scalp. Approval was based on the results of three randomized, double-blind, placebo-controlled multicenter trials [10]. Methyl aminolevulinate (MAL), the methyl ester cream derived from ALA, is a prodrug. Treatment of AKs with MAL and red-light PDT was approved for use in the United States in June 2008 by the FDA but is not currently available on the US market. In Australia, several European countries, South Africa, and Canada, MAL and a red-light source or daylight are approved for the treatment of AKs on the face and scalp.

Photodynamic Therapy for Actinic Keratoses

PDT is a clinician-directed field therapy and is therefore suitable for patients who present with multiple AKs. A variety of other treatment modalities exist for the treatment of AKs, including cryotherapy, imiquimod cream, 5-fluorouracil cream, ingenol mebutate gel, diclofenac 3% gel, and medium depth chemical peels [11, 12].

Patient Selection, Education, and Consent

The risks and benefits of each technique are discussed with the patient, and the choice of treatment is made on a case-by-case basis. Practitioners should also consider the possible contraindications to PDT before prescribing treatment (Table 4.1) Providers are encouraged

Table 4.1 Contraindications to the use of photodynamic therapy

Inability to avoid or block light exposure to skin on which the photosensitizer has been applied for 48 h after application
There is a theoretical risk of excessive phototoxicity when treating patients using medicines that predispose to phototoxicity, including griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines
Patients with preexisting photosensitivity or porphyria should not be treated with PDT
ALA PDT and MAL PDT are pregnancy category C according to the FDA. Therefore, ALA and MAL PDT should not be given to pregnant women only if clearly needed, according to the FDA label
According to FDA labels, caution is advised when considering the use of ALA and MAL PDT in nursing women, since it is unknown if ALA or its metabolites are excreted in milk
Consider delaying PDT if expected post-treatment erythema, crusting, and edema would interfere with the patient's social plans during the healing period
Avoid PDT if the patient has an allergy to porphyrins, soybean, or any of the ingredients of ALA or MAL. MAL cream contains peanut and almond oil and has a high rate of contact sensitization
ALA and MAL PDT are contraindicated for use on the mucous membranes and the eye. Consider avoiding PDT if ALA or MAL cream could accidentally be applied to the mucous membranes or eyes

to consult the product's FDA label for the most up-to-date list of contraindications. Prior to treatment, patients are thoroughly educated about the procedure and provided with an educational handout. Patients are also asked to read and sign a consent form (Fig. 4.1).

Before starting PDT, a physical exam is performed to evaluate for the presence of skin cancers in the expected field of treatment. Lesions suspicious for melanoma, invasive squamous cell carcinoma, and aggressive basal cell carcinoma should be biopsied and treated by other modalities.

CONSENT FOR PHOTODYNAMIC THERAPY

Procedure, or Treatment to be performed. Your doctors have recommended the following procedure(s) or treatments(s).

Photodynamic Therapy (PDT)

1. **I authorize and direct** my physician _____ and assistants of their choice, including resident physicians to perform the following procedure: PDT-Photodynamic Therapy

2. **I recognize** that I may withdraw my consent for this treatment at any time. Other treatment options have been presented to me.

3. During the procedure, if your physician believes that other procedures are needed for your health or safety; those other procedures will be performed at his/her direction. If your physician cannot perform or complete your procedure, a trained substitute practitioner will do so.

4. **I understand** that each condition and patient will vary in the number of treatments needed and time it will take for my skin to reach clearing stage is different for each patient. I understand that I will be required to come to _____ _____ office for the treatment time as directed by my physician. I understand that my skin may improve, I may have a reduction in new skin lesions or I may not experience any improvement in my skin.

5. **I understand** the following information regarding my treatment:

- Aminolevulinic acid (ALA) will be applied to my skin and depending on the physician orders and body area, the incubation time will vary from 15 minutes - 3 hours. The area will then be treated with a blue or red light according to physician's orders for approximately 10-30 minute per area to activate the ALA medication. I may experience unequal or variable results depending on how my skin reacts to the ALA and the area treated may not all respond the same way.
- I must **avoid the sunlight for 48 hours** following the treatment due to increase photosensitivity.
- I should wear sunscreen, a hat, a scarf and sunglasses after treatment to face and should return directly home after treatment. I must diligently use sun protection and sunscreen containing zinc oxide following this treatment.
- The anticipated effects following the use of ALA and PDT include discomfort, burning, swelling, lightening or darkening of skin tone and spots. The peeling may last several days, possibly weeks, as a temporary response to treatment.
- I consent to the taking of photographs of my skin before and after treatment sessions for my medical record, teaching and/or educational purposes. I understand that I may require several treatment sessions spaced weeks apart to achieve optimal results.
- PDT may cause a flare of fever blisters and mouth sores in susceptible people and I will need to inform medical staff if I routinely get these sores so I can be prescribed an antiviral medication.
- If I am female of childbearing potential, I may be asked to have a pregnancy test performed before starting treatment.

6. **Acknowledgment and Signature.** By signing this form, you are indicating that:

- You have read and understand the information in this form;
- Your doctor has discussed with you your procedure and explained the risks and benefits;
- Your doctor has alternative methods of treatment available, their risks and benefits, and what would happen if you did not have your procedure;
- You authorize and consent to the performance of your procedure.

Printed Patient Name: _____ DOB: _____

Signature: _____ Date: _____ Time: _____AM/PM
(patient/parent/legally authorized representative)
If signed by other than patient, indicate name and relationship: _____

Witness Signature:_____ Print Name: _____

Interpreter Signature: _____Print Name: _____

Fig. 4.1 A sample consent form for photodynamic therapy

Technique of Application for Actinic Keratoses

The ALA 20% preparation is applied to the skin as a solution with the Levulan Kerastick. Levulan Kerasticks are sold as single units, or in cartons of 6 units, and stored at 25 °C. Two glass ampoules are housed within the Levulan Kerastick. One ampoule contains the vehicle, which is comprised of ethanol, water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampoule contains ALA HCL in a dry solid form. Ampoules are housed within a common plastic tube, and the plastic tube itself is housed within a cardboard sleeve [13].

The Levulan Kerastick is prepared in four steps. Step 1—The device is held with the applicator tip pointing up. Step 2—The bottom ampoule containing the vehicle solution is crushed by applying finger pressure to the cardboard sleeve. Step 3—The top ampoule containing ALA HCL is then crushed with finger pressure to the cardboard sleeve. Step 4—The stick is shaken with the applicator tip pointing away from the face for 30 seconds in order to completely dissolve the ALA powder into the solution vehicle. Alternatively, the Kerastick Krusher can be used in lieu of steps 2 and 3. Once prepared, the stick should be used within 2 hours [13].

Immediately before applying ALA, the skin is degreased with an alcohol-soaked gauze pad, and AKs and surrounding sun-damaged skin are then gently debrided with medical-grade sandpaper (3M trace preparation tape) to enhance ALA penetration (Fig. 4.2). Care should be taken to avoid causing bleeding while preparing the skin. Other suggested methods to enhance the cutaneous penetration of ALA that have been discussed in the literature include mild curettage, micro-needling, salicylic acid or urea cream, 5-fluorouracil cream, heat, and fractional lasers [14].

The applicator tip is then pressed onto AKs and surrounding sun-damaged skin until the treatment area appears uniformly wet (Fig. 4.3). If desired, the contents of the device can be applied directly onto the skin, or into a gloved hand, and then uniformly spread over the skin. Care is taken to avoid the orbital and periorbital areas. After the ALA solution appears dry (about 1–2 min later), a second application may be performed with the same stick.

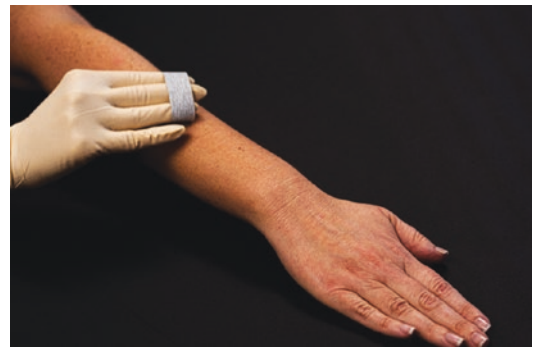


Fig. 4.2 To enhance the absorption of ALA, the skin may be abraded with medical-grade sandpaper (3M Red Dot Trace Prep)

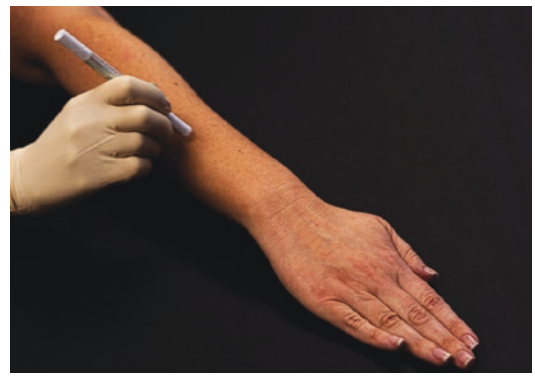


Fig. 4.3 The contents of the Levulan Kerastick (ALA 20% preparation) can be applied directly onto the skin, or into a gloved hand, and then spread with a gloved hand

The FDA label does not recommend occlusion of the face or scalp during incubation [13]. In addition, the treated area should not be washed during the incubation period, and patients should be instructed to protect the treated areas from sunlight and direct light exposure until treatment. For treatment of the extremities, we recommend occluding the skin with a transparent occlusive dressing (Fig. 4.4).

According to the FDA label, the ALA solution should be allowed to absorb for 14–18 hours when treating the face and scalp, and for 3 hours when treating the extremities [13]. It has become common for practitioners to use shorter incubation times, which enhances patient convenience

Fig. 4.4 Occlusion of the upper extremities with a transparent dressing prior to covering the area with a light-blocking layer

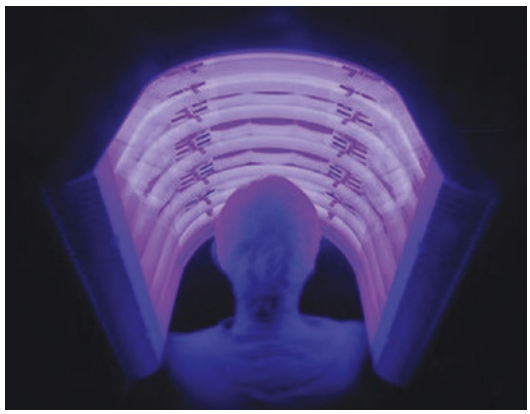


Fig. 4.5 Treatment with ALA 20% and the BLU-U blue-light for actinic damage involving the scalp and temples

and reduces pain. Typically, incubation periods of 1 to 3 hours are used for most sites. PpIX accumulation is linear in AKs and has been shown to be significant at 2 hours [15]. Studies have also reported similar therapeutic efficacy between 1, 2, and 3-hour incubation periods [16, 17].

Directly before light treatment exposure, AKs and surrounding skin may be rinsed with normal saline and patted dry. Before the light is activated, the patient and all personnel in the room are provided with blue-blocking protective glasses. AKs are then exposed to the BLU-U for 16 minutes 40 seconds for a total light dose of 10 J/cm^2 (Fig. 4.5). The patient's skin can be cooled with a stationary and/or handheld fan during the treatment. Patients are also given a stress ball to squeeze to help distract them from the discomfort they may be experiencing during the PDT treatment. Music generally enhances the patient's experience.

Fig. 4.6 A patient undergoing treatment with ALA 10% and red-light PDT for diffuse actinic keratoses

The technique for ALA 10% gel or MAL is similar to the one for the ALA 20% solution. Curettage or medical grade prep tape may be used after degreasing the area with alcohol-soaked gauze scrub. The FDA recommends a 3-hour incubation period for ALA 10% gel [18]. In our practice, we allow the ALA 10% gel to incubate for 1 hour to 1.5 hours. After removing the occlusive dressing and wiping off any excess gel, the built-in ruler is used to position the lamp at a distance of 5–8 cm from the treatment site. The patient and the personnel must use red-blocking protective eyewear while the light is on. The treated skin is then exposed to the red-light lamp for 10 minutes for a total light dose of 37 J/cm^2 (Fig. 4.6). Treatment areas larger than the lamp's active treatment area can be treated one after the other during the same treatment visit [19].

Following treatment, the skin is gently rinsed with normal saline. Cool wet towels can also be applied to the area to provide additional relief. Sun protection factor (SPF) 50 sunscreen or higher is applied to the site. Instructions are provided, and patients are instructed to avoid intense sunlight for 48 hours and to use sun-protective clothing. Patients are also instructed to avoid blue lights such as digital screens or electronic devices and tanning booths for 2 days after PDT treatment. Patients are contacted by a health-care professional within a week of treatment to evaluate for adverse reactions.

Of note, as of January 2018, a Healthcare Common Procedure Coding System (HCPCS) code was assigned for 1 unit (10 mg) of Ameluz: J7345. Ameluz is sold as a 2000 mg tube, which is equivalent to two-hundred 10 mg units; 200 units should be reported in the claims form when the entire tube is used. Any open and unused tube of Ameluz may be kept refrigerated up to 3 months [18–20].

Daylight PDT (d-PDT) uses natural sunlight as the light source and has been shown to be effective in the treatment of mild to moderate AKs [9, 21]. Consensus recommendations for MAL d-PDT have been developed for Europe, Canada, Australia, and Latin America [10, 21–23]. Protocols generally involve an approximately 30-minute incubation period followed by a 2-hour illumination phase with daylight. Prior to illumination, a chemical sunscreen with an SPF 20 should be applied to the treatment area to prevent sunburns, without blocking visible light. Products containing physical filters should not be used [24]. Advantages of d-PDT include significantly reduced pain levels, treatment of large areas, improved patient comfort, and reduced clinic time [21, 25–27]. Factors such as ambient temperature and cloud cover may impact the efficacy of d-PDT. Protocols with ALA are generally similar to the MAL protocol described above [10]. A 2018 randomized phase III trial comparing d-PDT with ALA 10% gel to MAL cream in 52 patients found that d-PDT with ALA 10% gel was non-inferior to d-PDT with MAL cream for the treatment of mild to moderate AKs on the face and scalp [26]. Few studies have looked at simulated alternatives to dPDT, but early reports suggest that these alternative light sources offer good efficacy with minimal treatment-related pain [24].

Treatment Schedule for Actinic Keratoses

Generally, only one cosmetic field—such as the face, scalp, or extremities—is treated during a visit. The recommended treatment protocol for ALA 20% solution PDT with the BLU-U blue-light is one initial PDT session followed by a second PDT session at 8 weeks if the lesions have not fully cleared [13]. In the clinical trials that led to FDA approval of ALA PDT with the BLU-U light for the treatment of AKs, patients were treated at week 0 and then at week 8 if needed [13]. Upon evaluation 3 months after treatment, 72% of patients achieved complete clearance. Physicians should discuss with patients the need to return for return visits as well as the potential need for alternative forms of treatment or for biopsies for non-responding AKs.

The FDA label protocol for the treatment of AKs of the face and scalp with ALA 10% gel with red-light recommends an initial treatment followed by additional treatments at 3 months if lesions have failed to completely respond [18]. In the clinical trials leading to the approval of ALA 10% gel with the BF-RhodoLED lamp, patients were treated with PDT once or twice depending on if their lesions did not completely resolve by 3 months after the initial treatment [10]. Forty-two percent of the patients required a second treatment at 3 months. In the three trials, clearance rates of mild to moderate AKs 3 months after the last PDT were 85%, 84%, and 91%. In patients who had previously achieved a complete clearance at 3 months, recurrence rates in the three trials were 40%, 22%, and 37% at 12 months [10].

In clinical trials using MAL red-light PDT for the treatment of AKs, patients received two treatments 1 week apart. Upon evaluation 3 months after the second treatment, 79–81% of patients were completely cleared [28]. Per the label protocol, one treatment session should be administered and lesion response should be assessed 3 months after the last treatment.

In our practice, patients treated with PDT are generally seen and assessed 4 weeks after the initial treatment. If fewer than 80% of AKs have completely responded, patients may be scheduled for another PDT session. If more than 80% of AKs have completely responded, the remaining AKs are treated with other modalities such as cryotherapy. Regardless of treatment response at the 4-week follow-up, patients are generally also seen 3 and 6 months after treatment to evaluate for AK recurrence and the need for additional PDT treatments.

Illustrative Case 4.1

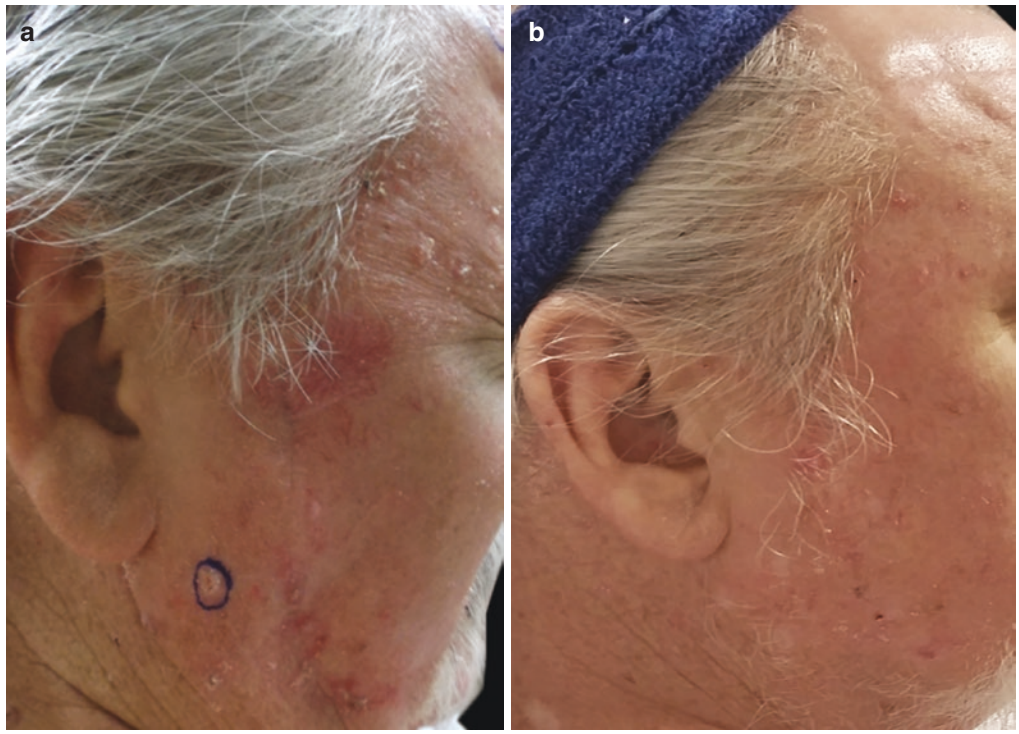
A 62-year-old male who presented for photodynamic therapy of AKs.

His past medical history was remarkable for facial AKs treated in the past with cryotherapy and 5-fluorouracil 5% cream. In addition, he has had multiple cutaneous squamous cell carcinomas and basal cell carcinomas treated with surgery.

Physical examination revealed more than 15 AKs on the forehead, cheeks, nose, and temples (Illustrative Case 4.1a).

The area was degreased with alcohol-soaked gauze, and AKs were gently debrided with medical grade prep tape. Two coats of ALA 20% solution were then applied to the area. After an incubation period of 1 h, he was treated with the blue-light for 16 min 40 seconds. The patient reported mild stinging and burning during the treatment, a 2–3 on the VAS scale. Sunscreen was applied and post-procedure instructions were reviewed with him.

After a total of two PDT treatments, physical examination revealed approximately 80–90% clearance of his AKs (Illustrative Case 4.1b). Patient was treated with Mohs surgery for the invasive SCC.



Illustrative Case 4.1 (**a**) Multiple AKs of the right forehead, temple, cheek, and chin prior to PDT treatment. (**b**) Clinical resolution of AKs on the face after two blue-light PDT treatments with ALA

Combination Therapies for Actinic Keratoses

Optimizing efficacy of photodynamic therapy has led to the use of various modalities to increase drug penetration and PpIX synthesis. In a randomized clinical trial comparing the relative potential of several physical pretreatments, curettage, microneedling, microdermabrasion, and ablative fractional laser (AFLX) prior to PDT were found to significantly increase intraepidermal PpIX [29]. Thermal PDT has been shown to be well tolerated and increase PDT efficacy at 1-year follow-up with a medium clearance rate of 90% [30]. A systematic review and meta-analysis of laser-assisted PDT for AK found significantly higher clearance rates in patients treated with laser-assisted PDT than PDT alone. Laser-assisted PDT was not more painful than either monotherapy PDT or laser treatment [31].

Topical neoadjuvant therapies, including 5-FU cream, retinoids, imiquimod, and most recently, vitamin D, have also been investigated in combination with PDT [30, 32]. Clearance rates of AKs in one study were improved with serial pretreatment of 5-FU for 6 days in a group of immunocompetent and transplant patients. After 3 and 6 months, the group with pretreatment followed by PDT had clearance rates of 75% and 67%, respectively, versus PDT alone with 45% and 39% clearance rates, respectively [33] (Fig. 4.7). Since both 5-FU cream and PDT are FDA-approved therapies, the combined regimen can be incorporated in clinical practice. Pretreatment with 5-FU cream has also been used to increase the efficacy of dPDT for AK [24]. In other studies,

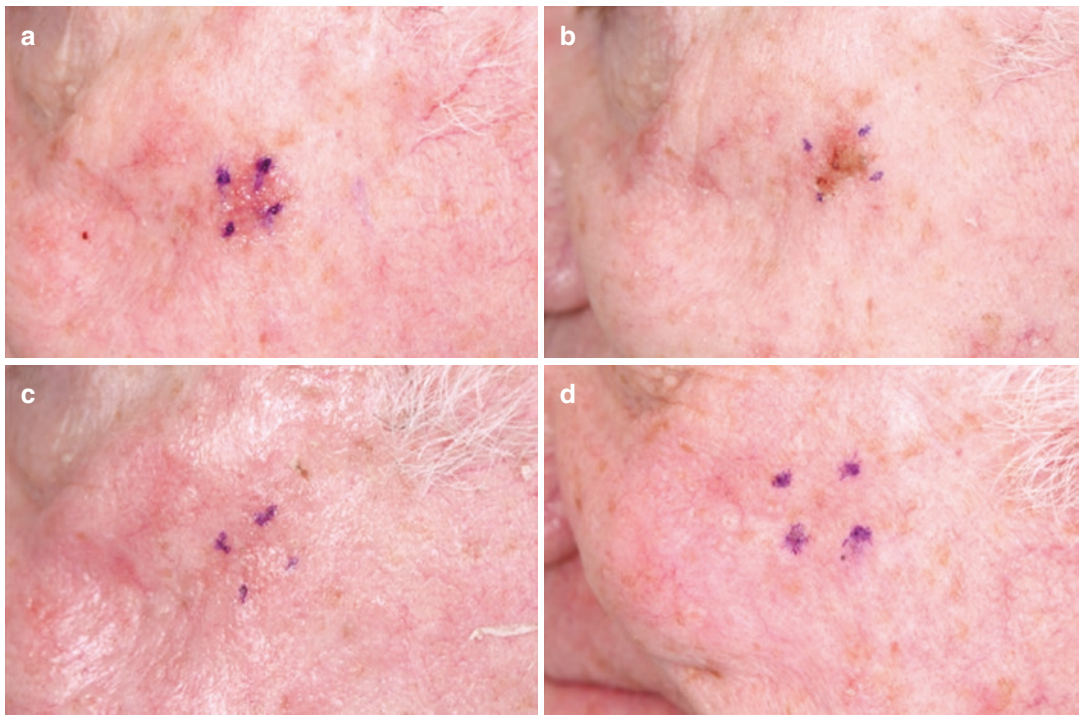


Fig. 4.7 (**a**) Patient with AC on left cheek at screening. (**b**) Treatment day. (**c**) 2 weeks post-PDT. (**d**) 3 months post-PDT. (Image Courtesy of Edward Maytin, MD)

topical vitamin D has also been shown to promote preferential accumulation of PpIX and increase efficacy of PDT for AK and BCC [34]. In a randomized clinical study, daily topical calcipotriol pretreatment for 15 days was combined with PDT for scalp AK. After 3 months, overall AK lesion clearance rates were 92.1% for the combination therapy versus 82.0% for conventional PDT [35]. A recent meta-analysis that included results from ten randomized controlled trials in which PDT was combined with another topical drug found improved AK clearance rates in the combination groups compared to monotherapy alone [36].

PDT can also be use prior to, or following, surgery. Following Mohs surgery, patients with clinical and/or histological evidence of actinic keratoses surrounding the area may undergo field therapy PDT 1–2 weeks after surgery. Postoperative PDT has also been described in a case of residual superficial BCC following Mohs surgery [37]. Patients with extensive actinic damage, AK, and/or superficial NMSC, may first undergo PDT for 1–2 sessions. Non-responding lesions and recurrent lesions should be biopsied to assess for invasive disease, and if positive, treated with surgery. Preoperative PDT has been shown to decrease tumor size prior to Mohs surgery [38] (Table 4.2).

Table 4.2 Clinical pearls

Increase PDT efficacy with neoadjuvant use of topical 5 FU cream or topical vitamin D cream
Minimize treatment-related pain with use of simultaneous PDT protocol
Biopsy recurrent or non-responding lesions to assess for invasive disease
Consider AK prevention with cyclic or regular PDT sessions q 3–6 months for high-risk patients

PDT as a Prevention Modality

Organ transplant recipients, who are at high risk for developing actinic keratoses, field cancerization, and multiple skin cancers, may benefit from regular PDT sessions either as monotherapy or in combination with other treatment modalities.

A recent systematic review and meta-analysis of 12 studies (prevention, $n = 4$; treatment, $n = 5$) was published on the use of PDT for both AK and SCC in organ transplant patients. PDT was associated with a lower incidence of new lesions and pooled risk difference (RD) of 0.14 (95% CI [0.08–0.19]) [39]. The complete response was also higher in patients receiving PDT as a treatment, with a pooled risk difference of 0.77 (95% CI [0.6–0.94]) and 0.50 (95% CI [0.22–0.79]) in predivided lesion areas and number of lesions, respectively [39]. Consecutive treatments of dPDT showed potential for preventing new AK and keratinocyte carcinoma in one study on transplant patients. Field cancerization-treated areas showed significantly fewer new lesions and a higher patient preference compared to the cryotherapy control [40]. As a prevention modality, a single PDT treatment may not be enough; rather frequent, regular, or cyclic sessions may be necessary for any benefits to be seen. Currently a primary prevention of AK and NMSC clinical trial is investigating the long-term safety and efficacy of cyclic ALA-PDT in patients who have recently undergone solid organ transplant (ClinicalTrials.gov: NCT03110159).

Photodynamic Therapy for Squamous Cell Carcinoma In Situ, Superficial Basal Cell Carcinoma, and Nodular Basal Cell Carcinoma

Studies have demonstrated efficacy of ALA PDT in the treatment of SCCis, nBCC, and sBCC [7]. The use of ALA 10% gel with red-light PDT for the treatment of thin (<2 mm) nBCC and sBCC was approved by the European Medicines Agency (EMA) in patients unsuitable for surgical treatment due to potential treatment-related morbidity and poor cosmetic outcome [9]. MAL is also approved in several countries for the treatment of SCCis, sBCC, and nBCC in patients deemed less appropriate for alternative therapies [9]. PDT is not recommended for cutaneous invasive SCC nor for the use in high-risk BCC [9]. In addition, ALA 20% solution and blue-light PDT may be used off-label to treat select thin nBCCs and sBCCs [41, 42]. A study comparing treatment with blue-light and red-light PDT in three patients with basal cell nevus syndrome reported similar tumor clearance rates and that treatment with blue-light was non-inferior to red-light [42]. After a 4-hour incubation period with ALA 20% solution, 50% of the patient's tumors were illuminated with red-light, the other 50% with blue-light. Patients were treated with six PDT sessions over the course of 4 months. Clearance with blue-light was 98% and clearance with red-light was 93%. Less pain was reported with blue-light PDT. Side-effect profiles were otherwise similar for both light sources.

Photodynamic therapy for SCCis has been shown to be useful in non-surgical candidates, in patients who cannot tolerate conventional therapies, and in patients with extensive disease or multiple lesions [43]. A recent retrospective review of primary SCCis lesions treated with ALA-PDT, and blue-light illumination found an initial complete response rate of 77.9%. Effectiveness in this study was related to tumor location on the face, smaller tumor diameter, and longer ALA incubation time [44].

The senior author completed a safety and efficacy study using ALA 10% gel and red-light PDT for the treatment of SCCis of the trunk and extremities. Twelve subjects underwent one or two PDT cycles with a 3-hour incubation period under occlusion. One PDT cycle was two PDT treatments spaced 10 (±3) days apart. All subjects achieved both a complete clinical and histological response after one or two PDT cycles. Patients tolerated the procedure well, and there were no significant adverse reactions. The majority of subjects rated cosmesis as excellent or good (manuscript submitted for publication).

Patient Selection, Education, and Consent

Approval of red-light PDT with ALA or MAL for nBCC, sBCC, and SCCis varies by country, but remains off-label in the United States. In our practice, lesions suspicious for SCCis, sBCC, and select thin nBCC are biopsied prior to performing PDT on these lesions. Patients referred for the treatment of basal cell nevus syndrome may present with numerous basal cell carcinomas. In these cases, select lesions can be biopsied. Before patients are treated with PDT, they are thoroughly educated about the procedure and an educational pamphlet is provided. They are also asked to read and sign a consent form.

Illustrative Case 4.2

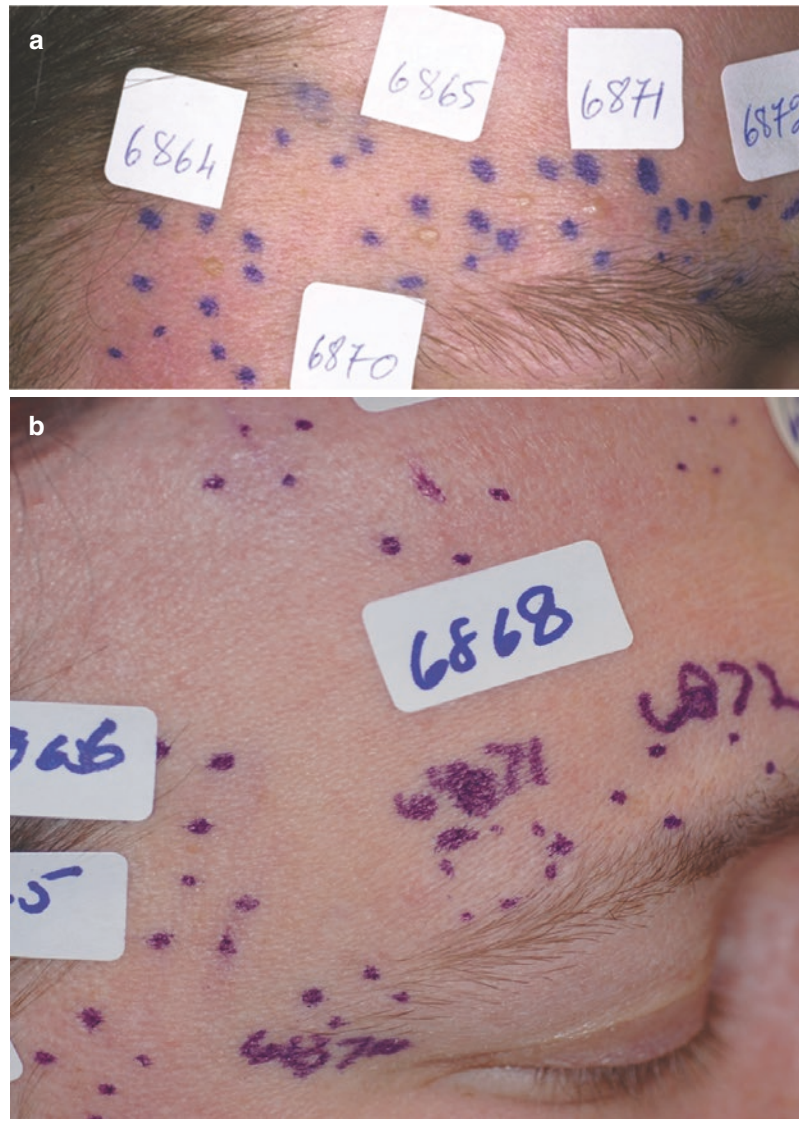
A 44-year-old man with nevoid basal cell carcinoma syndrome who presented for photodynamic therapy. This is a historical case from Roswell Park Comprehensive Cancer Center treated many years ago.

The patient had a history of more than 100 basal cell carcinomas treated by a variety of modalities.

Physical examination revealed multiple 2–4 mm pearly, telangiectatic papules—consistent with basal cell carcinomas—on the face (Illustrative Case 4.2a).

PDT was performed on 29 basal cell carcinomas using topical ALA and argon and diode lasers under monitored anesthesia care. ALA was applied to lesions for 18 h. Area 6871, described as two "skin-colored papules," was treated with the argon laser with the following parameters: 150 mW/cm^2, 200 J/cm^2, 633 nm, 1,333 s, and treatment field of 1.8 cm. There were no complications.

The patient was seen at 9 months and 10 months following treatment, and on both dates a complete clinical response for all lesions was noted (Illustrative Case 4.2b).



Illustrative Case 4.2 (**a**) Forehead of patient with multiple pearly, telangiectatic papules consistent with BCCs prior to PDT treatment. (**b**) Clinical resolution of the forehead BCCs 10 months after PDT treatment

Technique of Application for Superficial Non-Melanoma Skin Cancers

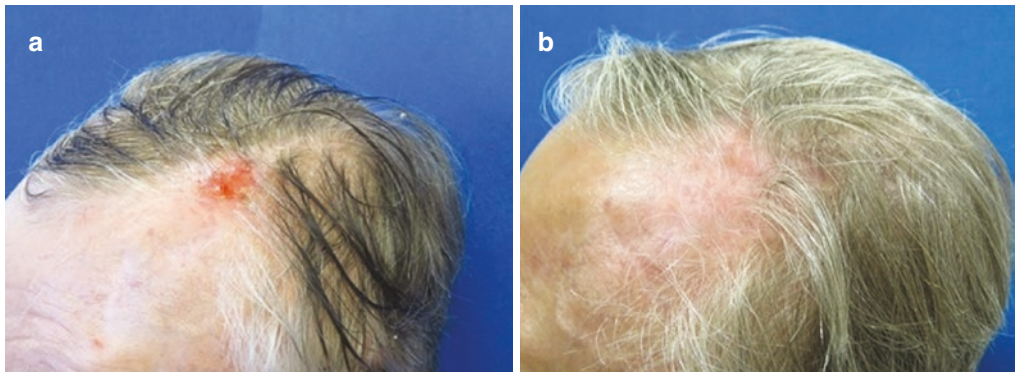
Prior to light exposure, photographs are taken and a circular 5 mm margin of normal skin is demarcated around the lesion using a marking pen. The target lesion is degreased with an alcohol-soaked gauze scrub followed by light curettage or debridement with medical grade sandpaper. Using gloves, topical ALA (or MAL) is applied ~1 mm thick to the lesion in question with a 5 mm margin of normal. The area is then covered with an occlusive dressing for a 3-hour incubation period.

After the incubation period, the tumor is cleansed with saline and may be infiltrated with 1% plain lidocaine if requested. The light is positioned at the appropriate distance from the treatment field, correct eye protection is worn by the patient and all staff, and the area is illuminated. In our practice, we generally use a red-light source for illumination of superficial non-melanoma skin cancers. After the procedure, treated skin is covered with SPF 50 (or higher) sunscreen. Wound care instructions are given, and a post-procedure instruction sheet is provided to patients. Finally, patients are contacted by a health-care professional within a week of treatment to evaluate for side effects.

Illustrative Case 4.3

A 78-year-old man with a history of AKs, BCCs, SCCs, and recurrent desmoplastic stage IIB melanoma of the right temple treated with wide local excision, radiotherapy, and adjuvant immunotherapy, presented for treatment of a left scalp SCCis. Patient elected to treat his left scalp SCCis with red-light PDT due to the lesion's large size (3 cm × 3 cm) (Illustrative Case 4.3a). He was treated with ALA 10% gel and red-light PDT.

ALA 10% gel was applied to the treatment sites for a 90-min incubation period under occlusion. At the 1-month follow-up visit, physical exam revealed notable improvement with complete clinical clearance of the patient's left scalp SCCis (Illustrative Case 4.3b). The patient remained clear at 12-month follow up.



Illustrative Case 4.3 (**a**) SCCis of the left scalp prior to PDT treatments. (**b**) Clinical resolution of the left scalp SCCis 1 month after two red-light PDT treatments with ALA 10%

Treatment Schedule for Superficial Non-Melanoma Skin Cancers

Patients are generally evaluated 7–10 days after PDT at which point they may be treated a second time [20]. Per European guidelines, nBCC and sBCC are generally treated with one PDT cycle. One cycle corresponds to two PDT sessions, 1 week apart. Patients are re-evaluated 3 months after the second PDT session, and lesions that have not fully responded may be re-treated at this point. In clinical trials, patients with SCCis were treated with MAL and red-light PDT using the same protocol as described above for nBCC and sBCC [10]. If the lesions have completely cleared at 3 months, the patient is thereafter monitored every 3–6 months. Patients with SCCis should be followed long term to evaluate for recurrences or possible development of invasive SCC [10]. Ultimately, response to treatment in patients with nBCC, sBCC, or SCCis should be confirmed by histopathology. Non-responding lesions and recurrent lesions should be biopsied, and close long-term follow-up of these lesions is recommended.

Combination Therapies for Non-Melanoma Skin Cancers

Patients with multiple BCCs may benefit from combination therapies to increase the overall efficacy of PDT. In 2018, Rizzo et al. published an open-label, pilot study on the combination of red-light photodynamic therapy (PDT) with vismodegib for the treatment of multiple nodular basal cell carcinomas (BCCs). Participants received oral vismodegib 150 mg daily for 3 months and red-light PDT with topical application of ALA 20% for a total of 3 monthly sessions. Overall initial treatment response rate was 90%. Cosmetic results were graded as excellent with no scarring and minimal change in pigmentation [45]. Long-term results of this pilot study showed high efficacy rates with no recurrence of disease at a mean of 19.2 months at follow-up [46].

Another strategy to optimize outcomes for patients with multiple BCCs may be to incorporate the use of neoadjuvant oral vitamin D with PDT. Dr. Maytin from the Cleveland Clinic and the authors are currently investigating the role of oral vitamin D with PDT for BCC (ClinicalTrials.gov Identifier: NCT03483441).

Extramammary Paget's Disease

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma that arises in apocrine-rich areas. Photodynamic therapy has been reported to be a therapeutic option for patients with EMPD. In a recent review of the literature, which included 177 patients with 211 lesions, an overall complete response rate of 59.7% was found with the use of PDT. Lesion size was shown to correlate with the efficacy of ALA PDT. Combination therapies using PDT with either surgery, imiquimod, or laser ablation increased the overall treatment efficacy. PDT was also found to be effective in previously treated sites and recurrent lesions [47].

Adverse Reactions and Pain Management

PDT is generally a well-tolerated treatment modality. Some of the main phototoxic effects seen are erythema and edema, which may be accompanied by crusting, hypo- and hyperpigmentation, and a tingling and burning

sensation post treatment [48]. One of the main limitations of conventional PDT is treatment-related pain. Pain typically peaks at the onset of illumination, and it tends to improve over the remaining duration of the treatment [49]. During the procedure, pain can be monitored and measured using the 0–10 Visual Analogue Scale (VAS) score.

Various pain-controlling interventions have been studied including inhalational analgesia, nerve blocks, oral analgesics, cold air analgesia, water spray, transcutaneous electrical nerve stimulation, topical analgesia, among others [48]. A 2017 systematic review of the literature concluded that protocols using continuous activation of low levels of PpIX such as daylight PDT or with short contact incubation, or bi-level irradiance, were associated with reduced pain while maintaining PDT efficacy [48]. Daylight PDT has been a game changer with regard to treatment-related pain. Studies have found that dPDT is associated with no to minimal pain and has similar efficacy to conventional PDT [8]. In addition, large fields can be treated, while reducing office visit time and minimizing cost and equipment [8]. Zeitouni and colleagues had previously introduced a two-step irradiance PDT protocol with red-light, which demonstrated efficacy in preserving clinical outcomes while minimizing patient discomfort [50–52]. The in-office "painless" PDT protocol has also been shown to result in little to no pain, with an AK clearance rate of 52% after a 15-minute ALA incubation followed by 60 minutes of blue-light exposure [53]. Recently a modified protocol of simultaneous or metronomic PDT (30-min prolonged illumination after immediate ALA application) was found to be significantly less painful than conventional PDT with similar efficacy [54]. In our office, we have regularly been using the simultaneous PDT protocol as described above with excellent patient satisfaction and outcomes (Table 4.3).

Table 4.3 Recommendations for pain relief

Supportive measures:
Fans
Short breaks
Music/talking
Monitor with VAS
Alternate protocols:
Daylight PDT ALA 30-min incubation followed by 2-h illumination
Simultaneous ALA application followed by blue-light illumination for 30 min
"Painless" PDT: 15-min ALA incubation followed by 60-min blue-light illumination
Two-step irradiance: 1–3 h of ALA incubation followed by initial red-light low irradiance of 35 mW/cm^2, then high irradiance of 70 mW/cm^2 (total light dose 75 J/cm^2)

Summary

Photodynamic therapy, when performed appropriately for precancerous lesions and superficial skin cancers, is effective and particularly useful in patients who need field therapy or those with multiple select non-melanoma skin cancer sites. The use of PDT in combination therapies as well as its use as a preventive modality continues to evolve as do effective pain-controlling protocols.

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Chapter 5
Intralesional and Perilesional Treatment of Skin Cancers

Christopher J. Arpey, Nicole M. Annest, Stephen B. Tucker, Erik T. Petersen, Ronald P. Rapini, and Deborah F. MacFarlane

In this chapter, various intralesional and perilesional agents that have been used in the treatment of skin cancers are presented by practitioners familiar with their use. The four medications reviewed—methotrexate, interferon, 5-fluorouracil, and bleomycin—have been in widespread use for many years in the treatment of cutaneous neoplasms and extracutaneous neoplastic and inflammatory conditions. Therefore, the efficacy, toxicity, delivery, indications, and costs for these agents are well established, and they are widely available. However, the most common routes of administration for such medications are oral, intravenous, and topical. An intralesional and perilesional approach to therapy is less often utilized, leading to less familiarity in clinical practice. It is our hope that a detailed review of these agents delivered in such a manner, along with a variety of clinical examples, will facilitate their use in practice and increase the variety of treatment options available to patients with cutaneous tumors.

METHOTREXATE

Methotrexate (MTX) possesses multiple ideal mechanisms of action for the treatment of rapidly growing cutaneous tumors. MTX has long been known to halt tumor growth by irreversibly binding to the enzyme dihydrofolate reductase, thus preventing the downstream formation of the purine nucleotide thymidine necessary for DNA synthesis in the dividing tumor cell. MTX also functions as a "magic bullet," selectively targeting and concentrating inside malignant cells via binding to the cell surface folate receptor, an overexpressed biomarker in tumor cell populations. Lastly, MTX mediates tumor cell death through an apoptotic pathway involving mTOR (mammalian target of rapamycin) and WWOX (tumor suppression WW domain-containing oxidoreductase) receptors. Interestingly, the mTOR pathway is one of the most common pathways implicated in epithelial tumor development and progression and has been specifically demonstrated to be involved in the development of keratoacanthoma (KA) tumors [1–4].

Historically, MTX has been administered through oral, intravenous, intra-arterial, or intrathecal routes, with demonstrated activity against a number of cutaneous malignancies including malignant melanoma, squamous cell carcinomas, and basal cell carcinoma [5–10]. Its use in most of these settings, however, has been both systemic and in combination with other chemotherapeutic agents. Intralesional use of MTX for tumor treatment is less common.

Intralesional injection of methotrexate (IL-MTX) is a well-established primary treatment modality for keratoacanthoma (KA) tumors [11–15]. More recently, neoadjuvant IL-MTX has been utilized for treatment of invasive cutaneous squamous cell carcinoma (cSCC) prior to definitive surgical excision [16]. IL-MTX as monotherapy or as an alternative to surgery

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for biopsy-proven cSCC is not recommended. Though this chapter section will largely focus on IL-MTX treatment for KA, we will briefly review the use of IL-MTX in the treatment of cSCC as well. The relationship between KA and cSCC is enigmatic and has long been debated [17–23].

The clinical presentation of solitary KA is often a rapidly growing, firm, dome-shaped lesion on sun-exposed skin in older patients; however, aggressive cSCC can present in an identical fashion. KA is typically considered to be a "benign tumor," clinically mimicking the hair cycle, with Wnt/beta-catenin-mediated phases of tumor proliferation, rest, and spontaneous tumor regression [24]. Though KA tumors may eventually involute spontaneously, the timing of involution is unpredictable and uncertain to occur at all. Given the potential of KA tumors to cause significant local tissue destruction with permanent functional or aesthetic compromise, deferring treatment and waiting for tumor involution are not recommended. The exception is the rare situation in which the tumor is clearly already in a phase of involution, although there is some risk in observation alone even in this setting [25]. Though metastasis of KA has been reported in the literature, it is unclear whether this truly represents metastatic KA versus misdiagnosed metastatic cSCC [16, 17, 21, 22].

Despite recent molecular support for KA and cSCC as separate entities, in the clinical setting it can be difficult to distinguish these two tumors [26]. The distinction is based upon both clinical presentation and histopathologic evaluation of an adequate biopsy specimen. The cellular characteristics of these tumors are often similar and therefore the overall architectural tumor features are critical in distinguishing KA from cSCC. Histologically, KA is characterized by a symmetric, keratin-filled crater lined by a proliferating, atypical squamous epithelium, sharp demarcation between the tumor and surrounding stroma, and an overhanging "lip," rim, or "buttress." By contrast, a diagnosis of cSCC is favored by the presence of mitoses, ulceration, and extension of the deep tumor margin beyond eccrine glands [27]. The architectural attributes needed to histologically distinguish KA versus cSCC require an adequately deep biopsy to allow visualization of the tumor base. Inadequate biopsy can lead to a high rate of misdiagnosis between these two tumor types. Thus, studies that report on treatments and clinical outcomes for both KA and cSCC, including treatment with IL-MTX, may include tumors that are in reality misdiagnosed.

More recent molecular studies suggest distinct mutational signatures in KA versus cSCC, providing support that these tumor types are likely separate entities [24–26, 28–31]. Gatekeeper mutations in the transforming growth factor beta (TGF-beta) pathway are often seen in KA, with TGF-beta receptor 1 mutations identified as the cause of the autosomal dominant Ferguson-Smith multiple self-healing epithelioma (MSSE) KA phenotype, while cSCC is characterized by very low rates of TGF-beta signaling pathway mutation. By contrast, NOTCH1/2 receptor mutations are more commonly observed in cSCC but are not observed in KA.

Multiple keratoacanthomas may present as a familial subtype, including the aforementioned multiple self-healing epithelioma of Ferguson-Smith, generalized eruptive keratoacanthomas of Grzybowski, and the less well-elucidated entity of multiple familial KA of Witten-Zak. Keratoacanthomas also occur in the setting of genodermatoses, including Muir-Torre and xeroderma pigmentosum, secondary to iatrogenic or traumatic Koebnerization, or in the setting of systemic treatment with BRAF inhibitors or hedgehog pathway inhibitors [19, 20, 26, 32–37].

Surgical excision, including standard excision and Mohs excision, is considered first-line treatment for KA, offering both prompt definitive treatment and providing a complete specimen for histologic evaluation [17, 18, 38, 39]. Surgery may not be appropriate, but appropriate in certain situations, such as tumors that are very large, tumors in difficult anatomic locations, recurrent or multiply recurrent tumors, or in patients who cannot tolerate surgery. Surgical intervention may lead to sizable defects in some cases, along with significant functional or cosmetic morbidity.

In cases where surgery may not be appropriate, treatment of KA with intralesional MTX has been demonstrated to be both effective and safe and is therefore considered an effective second-line treatment option [26, 39, 40]. IL-MTX offers the advantage of being less invasive, quickly

administered, and tissue sparing and is also cost-effective. Cosmetic results for KA treated with MTX are typically quite good. Recurrent or multiple-recurrent KA, particularly when multiple tumors develop within the surgical scar in a classic Koebner phenomenon, can be effectively treated with IL-MTX rather than endure the morbidity of additional surgical excision [34].

In addition to IL-MTX, additional local treatment options for KA include intralesional 5-fluorouracil (5-FU), intralesional bleomycin, and intralesional interferon alfa-2b [40–51]. The utility of intralesional interferon, 5-fluorouracil, and bleomycin for cutaneous tumors will be discussed later in this chapter. Intralesional 5-FU has been demonstrated to be an effective treatment for KA and is a worthy alternative. Intralesional corticosteroids have also been a controversial treatment option for KA, while more widely accepted additional local treatment options include electrodessication and curettage and cryotherapy [52–55]. Field treatment options include radiotherapy, photodynamic therapy, and topical imiquimod [56–60]. Active surveillance, or observation, can be considered for select patients with KA tumors that have already clinical begun the process of involution [25].

In patients with multiple diffuse keratoacanthomas, systemic retinoids are a first-line option either as monotherapy or in combination with local treatment modalities [34–36, 61–63]. Systemic retinoids have demonstrated efficacy for both treatment and chemoprevention (see Chap. 21).

Though this section focuses predominantly on the use of IL-MTX for the treatment of KA, it is worth noting that more recently IL-MTX has been described as a neoadjuvant therapy to lessen surgical morbidity and to decrease surgical scope in cases of large cSCC [16, 64]. In a recent comparative cohort study, patients with histologically confirmed infiltrative cSCC were treated with weekly neoadjuvant IL-MTX. Mean time between diagnosis and definitive surgical excision was 17 days in the IL-MTX + surgery group, with surgical excision performed in all patients within 1 month of initial diagnosis. The neoadjuvant treatment group demonstrated a significant decrease in the presurgical size of cSCC, with a trend toward a decrease in complex surgical reconstructions in this group as compared to the surgery-only group. In this study, IL-MTX 25 mg/ml was administered weekly using the identical injection technique described below. Of note, neoadjuvant treatment did not introduce a delay between the time of diagnosis and definitive surgical treatment and IL-MTX as monotherapy for treatment of cSCC was not considered due to the metastatic potential of this tumor.

Indications and Contraindications

An adequate biopsy should always be performed to confirm diagnosis prior to determining a treatment plan. KA tumors that are most amenable to treatment with intralesional MTX include solitary tumors where surgery would lead to excessive morbidity or local tissue destruction or in cases when the individual patient cannot tolerate surgery. These situations include tumors located in difficult anatomic locations such as the periorbital or perioral regions, nose, and ears. In addition, very large tumors in which surgical excision would result in excessive wound tension, necessitate large flap or graft repair, or require protracted wound healing are strong candidates for treatment with intralesional MTX. IL-MTX is also an excellent treatment option for patients who are poor surgical candidates, including decompensated patients with poor functional status who may not tolerate a lengthy surgery. Additionally, IL-MTX can be ideal for patients with comorbidities such as significant cardiovascular disease, pulmonary disease with a high supplemental oxygen requirement, significant dementia, anticoagulation, diabetes, liver disease, or significant tobacco use.

Contraindications to administering methotrexate include patients with severe active infection, severe hepatic disease, hepatic fibrosis, cirrhosis, pulmonary fibrosis, patients who are pregnant, and patients who are breastfeeding.

In larger, more recently published case series, adverse events associated with IL-MTX treatment for KA include one case of mucositis [14] and one case of pain persisting at the treatment site for 1 week after injection [15]. Two cases of pancytopenia occurring in patients with hemodialysis-

dependent renal failure treated with single 25 mg doses of IL-MTX have also been reported [65, 66]. Care should therefore be exercised when using IL-MTX in patients with renal impairment. These patients presumably lacked sufficient renal excretion after systemic absorption of the injected MTX, leading to transient bone marrow suppression. Cytopenias have not been reported to date in patients with normal renal function, but given the potential for subclinical cytopenia and possible previously undiagnosed renal disease, obtaining a baseline and 1 week post-injection complete blood count (CBC) and serum creatinine for all patients is reasonable. In patients with known renal dysfunction, baseline and 1 week blood counts are strongly suggested.

IL-MTX may be less ideal for some patients based upon social or geographic factors. Treatment with intralesional injection typically requires multiple treatments over multiple visits; therefore, IL-MTX may be suboptimal for patients who live very far away from the treatment clinic or patients with transportation or mobility limitations. Additionally, patients who have difficulty with several weeks of wound care or who are intolerant to a more prolonged clinical course may opt for other treatment modalities. Successful treatment with IL-MTX leads to tumor cell death, friability, and resultant tissue sloughing. This requires ongoing wound care both during and immediately after the course of treatment.

Pre-treatment Considerations

Clinical judgment is critical in treating patients with suspected KA. We recommend suspected KA be confirmed histologically with an adequate biopsy prior to any non-excisional therapy, given the proclivity for high-risk, rapidly growing cSCC to present in an identical fashion to KA.

In addition, even in cases when the diagnosis of KA is made with an adequate initial biopsy, a tumor that does not respond after two MTX injections should be re-evaluated. The failure to respond to intralesional or other nonsurgical approaches should prompt consideration of repeat biopsy to rule out aggressive cSCC or other aggressive tumors that can mimic KA [67, 68]. Treatment courses with intralesional MTX for KA are fortunately brief, spanning less than 2 months, thus allowing caregivers to establish an alternative therapeutic path in the case of possible intralesional treatment failure.

Injectable MTX is relatively inexpensive [69]. At most institutions, MTX solution is ordered from the hospital pharmacy at a cost of ten dollars or less, for a 2 ml vial at a concentration of 25 mg/ml. The brevity of time required to administer the injection also contributes to the overall low therapeutic expense.

Preparing MTX for Injection

Since MTX is a chemotherapeutic agent, most pharmacies require more stringent precautions for preparation than for agents commonly used in the clinical setting such as corticosteroids or local anesthetics. Advance communication with a local pharmacy or community hospital pharmacy several days in advance of the planned injection will ensure an efficient treatment session. The medication is prepared at the pharmacy and placed in a Luer-lok™ 3 ml syringe with a secure cap before delivery. Refrigeration is not required, but the medication should be administered within 24 hours of preparation. A concentration of either 12.5 or 25 mg/ml should be chosen—typically the lower concentration for smaller tumors (less than 1 cm) or the higher concentration for larger diameter tumors. Depending on clinical response after the first injection, the dose can be maintained or changed if a second injection is required. If the tumor becomes substantially necrotic and nearly resolves after the first injection, the lower dose may be chosen for the next injection. If the tumor responds minimally, then a higher dose should be strongly considered for the next injection.

Description of Technique

Our standard practice for injection is as follows: using a 27-gauge or 30-gauge needle, a total of

0.3–2.0 cc of MTX in a concentration of either 12.5 mg/ml or 25 mg/ml is injected at each treatment session. We favor the lower concentration for smaller tumors. Small KAs, less than 1 cm, are typically injected in a single central point at the base of the lesion whereas larger KAs are injected in each of the tumor's four quadrants, as well as at the central lesion base. Very large KA may require more than four injection points, working around the tumor circumferentially and aiming toward the center. The skin is prepped with an antiseptic swab and MTX is injected until an endpoint of uniform tumor blanching or yellowing is achieved. Given the poor cohesion between tumor cells, roughly 50% leakage of the total injected MTX volume typically occurs and can be wiped away with clean gauze. The procedure is well tolerated in most patients without the use of local anesthesia, though injected or topical lidocaine may be utilized to optimize patient comfort without loss of efficacy.

The overall approach to MTX injection for KA is highly analogous to injecting keloids with corticosteroids, though the pressure on the plunger required to inject a KA is less than that needed for the typical keloid. The volume instilled, the depth of injection, and the attempt at uniform distribution through the quadrants and base are quite similar.

Patients often feel discomfort at the time of injection, but as with triamcinolone, the discomfort afterward is minimal.

Treatment Pearls

1. Review all alternative treatment options and treatment outcomes, including possible treatment failure and the likely need for multiple injections with the patient before injection. In organ transplant recipients or other immunosuppressed patients, review the treatment plan with the patient's care team prior to commencing IL-MTX injections.
2. Consider obtaining a serum creatinine at baseline and at 1 week after the first injection. This is our standard practice for patients with underlying chronic medical conditions, given the rare reports of cytopenias in patients with renal insufficiency.
3. Local anesthesia is a reasonable option prior to MTX injection, especially for larger KA or anxious patients. Anesthesia can be administered prior to IL-MTX treatment or MTX can be mixed in a 1:1 ratio with lidocaine solution to yield a MTX concentration of 12.5 mg/ml.
4. Expect leakage of MTX through the tumor surface. This should not reduce clinical efficacy.
5. Always perform injections with eye protection and Luer-lok™ syringes. We use 30-gauge 0.5″ length needles for most KA. A longer 1″ needle may be needed for larger KA.
6. KA smaller than 1 cm can usually be injected with a single well-placed needle insertion from a peripheral site with the target for the needle tip located at the deeper central portion of the lesion. Larger KA benefit from several injections placed serially around the periphery and directed toward the center. The technique is highly analogous to injecting corticosteroids into hypertrophic scars.
7. Crusting, ulceration, and tumor breakdown are typical 7–10 days after each injection. Gentle debridement of necrotic tissue prior to the next injection assists in delivering the agent to viable residual neoplastic tissue as opposed to injection into the superficial crust.
8. KA tumors that respond to IL-MTX typically demonstrate a decrease tumor thickness before a significant decrease in tumor diameter is observed.
9. Tumor cure can be assessed based upon clinical assessment and does not require re-biopsy to confirm histologic clearance.
10. Tumors that do not respond with a decrease in tumor thickness or diameter after two treatments should be considered treatment failures and alternative treatment should be pursued.

Post-injection Care

1. A nonadherent dressing with a small amount of petrolatum centrally is sufficient to protect the recently injected KA. Thereafter patients may cleanse the area daily with dilute acetic acid or dilute hydrogen peroxide before applying a clean dressing.
2. Soaking the dressing surface first with a clean damp cloth or in the shower may help with removal of adherent dressings if the crusting is significant.

Expected Course of Treatment and Follow-Up

Based upon multiple case series, including our own, overall reported cure rates for treatment of KA with IL-MTX are approximately 90%. However true treatment response rates may differ based upon the lack of histologic confirmation of KA tumor type in a significant subset of patients in these studies, selection bias in treatment choice, as well as reporting bias in cases that are presented in the literature. These factors make comparison of relative response rates between IL-MTX and other treatments difficult. A randomized study comparing IL-MTX to surgery or other treatments would provide the best evidence of relative cure rates.

KA tumors successfully treated with IL-MTX in published cases have ranged in diameter from 0.5 cm to 4.0 cm. Smaller tumors tend to be more amenable to successful treatment [11, 14]. In our own case series, mean tumor diameter of nonrespondent lesions was 2.8 cm, whereas the mean diameter of successfully treated tumors was 1.9 cm. Similar results were noted by Moss and colleagues [14]. It is unclear whether the poorer response rate of larger tumors is due to user error, with difficulty in administering drug to all of the target tissue in a larger tumor, or alternatively may be due to the larger tumors being more likely to be in a later and less susceptible phase of growth. Tumors are known to be more sensitive to IL-MTX treatment during the early stages of growth [70].

There is wide variation in the total cumulative dose of MTX administered in published series, as seen in Table 5.1. It is noteworthy that treatment regimens with smaller cumulative doses of MTX are associated with a lower overall tumor response. Injection interval can vary as well; treatment interval flexibility is considered an advantage of MTX over other intralesional agents. In our clinics, we typically follow the 2-week injection interval initially described by Melton and colleagues [40].

Table 5.1 IL-MTX treatment for KA case series

	Number of tumors	Average tumor diameter (range)	Average patient age (range)	Total cumulative dose of MTX administered	Total number of injections (range)	Average injection interval (range)	Overall response rate
Annest, et al. [11]	38	1.9 cm (1.0–4.0)	66 years (31–94)	36 mg	2 (1–4)	18 days	92% (35/38)
Patel and Cervino [15]	9	2.3 cm (1.4–3.0)	65 years (35–92)	Not reported	2.5 (1–4)	7 days	89% (8/9)
Yoo and Kim [13]	11	2.1 cm (0.5–4.0)	62 years (34–89)	54 mg	4.2 (2–7)	10 days (4–28)	91% (10/11)
Moss, et al. [14]	73	1.5 cm (0.6–3.4)	78 years (47–91)	8.2 mg	2 (1–3)	Not reported (14–28)	88% (64/73)
TOTAL	122						89% (117/131)

With the exception of a single published series, all published case series include a significant proportion of tumors located on the face, with all other case series reporting a majority of treated KAs located on the face. In our own series, approximately 75% of KA treated with IL-MTX were located on the head and neck. In fact, large tumors located on cosmetically sensitive areas of the face are considered excellent candidates for IL-MTX, as surgical excision would lead to significant functional and aesthetic morbidity. By contrast, Moss and colleagues note avoidance of intralesional treatment for facial KA due to concern regarding increased metastatic potential of facial KAs; however, it is noted that 29% (21/73) of the tumors treated with IL-MTX in this study were treated without an initial diagnostic biopsy. KA tumor resolution in most published cases was determined by physical examination and clinical behavior while histological confirmation was obtained for very few tumors. There were no reported cases of tumor recurrence in any case series, with most published cases observed for at least 1 year after treatment completion. In all published cases, KA tumors that did not resolve with IL-MTX were treated with surgical extirpation.

A summary of our own experience with IL-MTX for KA over several decades as well as other published case series is summarized in Table 5.1.

Several case examples follow that illustrate the typical clinical course for patients treated with intralesional MTX for KA.

Illustrative Case 5.1

A 70-year-old Caucasian woman presented with a 1-month history of a rapidly enlarging, mildly pruritic nodule on the right forehead. Her general health was excellent and she was on no medications. Her examination revealed a solitary keratotic 1.5 cm nodule on the right forehead with no lymphadenopathy (Fig. 5.1). Wedge biopsy demonstrated a keratoacanthoma-like squamous cell carcinoma.

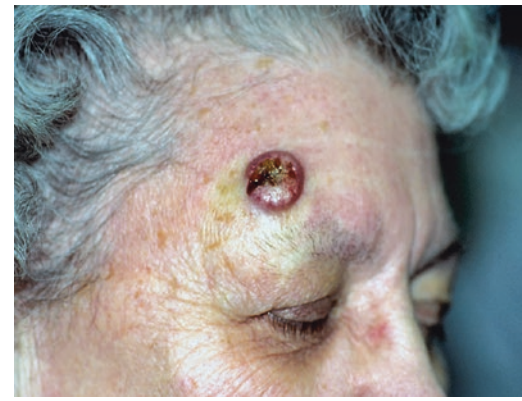

Fig. 5.1 A 70-year-old woman with biopsy-confirmed 1.5-cm keratoacanthoma of the right temple prior to initial intralesional injection of 1.0 ml methotrexate at 25 mg/ml concentration. The tumor developed over 1 month

Three days later she underwent injection of 1 ml of 25 mg/ml concentration MTX. She developed additional crusting over the surface of the nodule, with partial resolution noted 3 weeks later (Fig. 5.2). At that time, she underwent a second injection at the same concentration and volume. One month subsequently, there was minimal residual eschar, and no remaining nodule (Fig. 5.3). She continued to heal well over the next month (Fig. 5.4) with moist occlusive wound care and remained free of recurrence 1 year later, with an excellent esthetic result (Fig. 5.5).

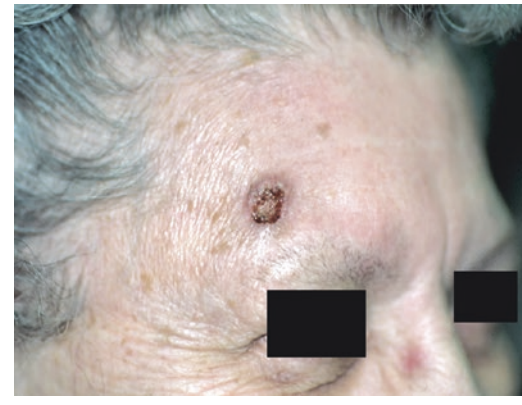

Fig. 5.2 Central and inferior crusting of the keratoacanthoma 3 weeks after initial injection, and prior to the second injection of methotrexate at the same concentration and volume

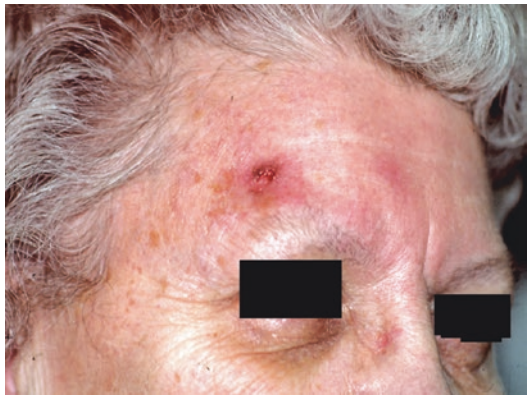

Fig. 5.3 Minimal clinically evident residual keratoacanthoma and eschar 1 month after the second injection

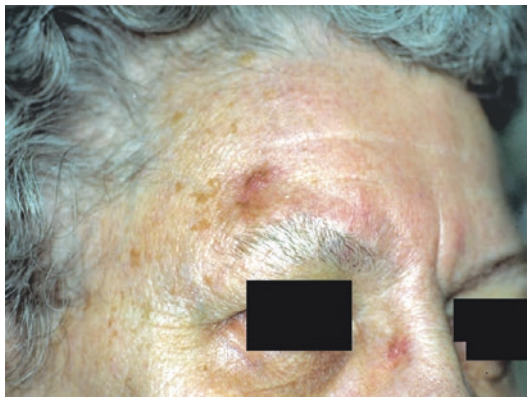

Fig. 5.4 Nearly complete healing 10 weeks after the initial injection of methotrexate

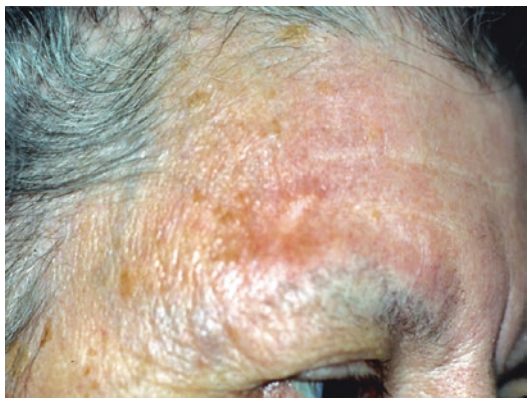

Fig. 5.5 Right temple 1 year after injection with excellent clinical and esthetic results

Illustrative Case 5.2

A 48-year-old Caucasian woman, with no prior medical conditions and on no medications, developed a rapidly growing nodule of the left upper lip and melolabial fold over a 2-month time period. The lesion had failed to respond to a 10-day course of oral antibiotics prescribed by a previous health care provider. On examination, there was a 2.3 × 1.4 cm hyperkeratotic and crusted nodule with a central crater. A suture was in place at the inferior border at the site of a recently performed wedge biopsy (Fig. 5.6). There was no clinical lymphadenopathy. Biopsy revealed a well-differentiated squamous cell carcinoma with keratoacanthoma-like features.

After discussing surgical and nonsurgical options, she underwent injection of 1 ml MTX at a concentration of 25 mg/ml. At 3 weeks the lesion was approximately 50% of its prior height, though its peripheral dimensions were similar to baseline (Fig. 5.7). The size of the central crater was greatly diminished. The patient underwent a second MTX injection at the same concentration and volume that day. Four weeks subsequently, the overall size of the lesion was 1.5 × 1.0 cm (Fig. 5.8). A final

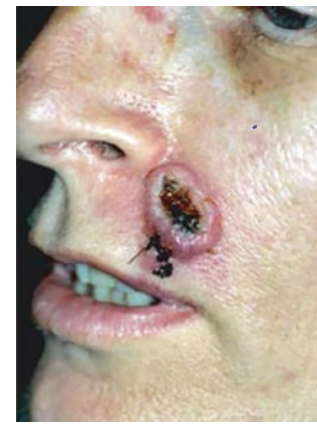

Fig. 5.6 A 48-year-old woman after wedge biopsy confirming well-differentiated squamous cell carcinoma with keratoacanthoma-like features of the left upper cutaneous lip, measuring 2.3 × 1.4 cm. The tumor rapidly evolved to this size over 2 months. She underwent initial methotrexate injection at 25 mg/ml concentration and volume of 1.0 ml at this time

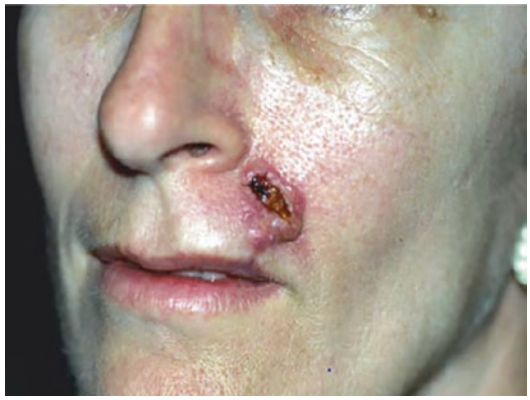

Fig. 5.7 Appearance of the tumor 3 weeks later at the time of the second injection. Note the additional crusting and central necrosis. Peripheral dimensions are similar, though tumor bulk is greatly diminished. She underwent a second injection of methotrexate at the same volume and concentration

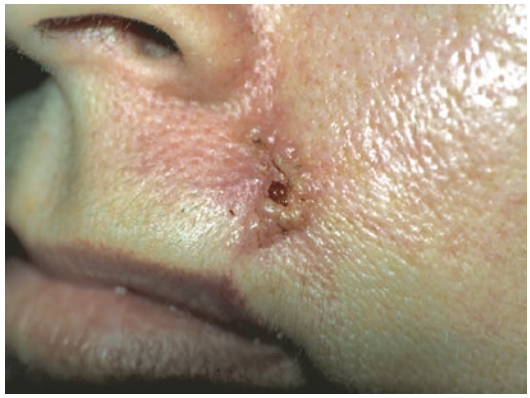

Fig. 5.8 After an additional 3 weeks, the keratoacanthoma continues to involute. She underwent a third and final injection of methotrexate, once again at a volume of 1.0 ml and concentration of 25 mg/ml

injection of MTX—once again at 25 mg/ml concentration and 1 ml total volume—was performed. One month later, a small, smooth 4 mm area of tissue remained inferiorly and clinically appeared to be a small scar (Fig. 5.9). This was confirmed by punch biopsy 6 weeks later, which also effectively smoothed the clinical residual. She had no recurrence of disease 2 years later, but did develop one additional small squamous cell carcinoma of the left shoulder in the interim, excised with clear margins and an uneventful postoperative course.

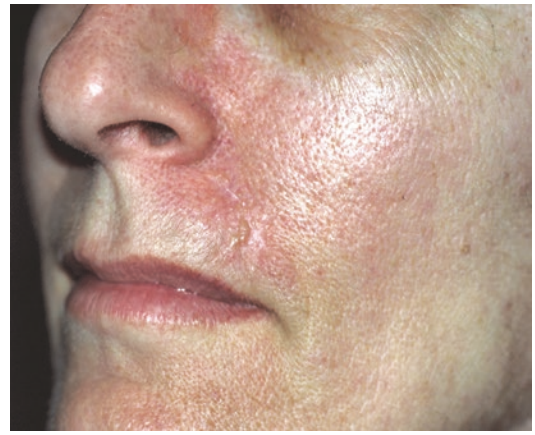

Fig. 5.9 Appearance of the upper lip 6 weeks later, showing a small fold of skin at the prior inferior border of the keratoacanthoma. A punch biopsy demonstrated scar and no residual tumor

Illustrative Case 5.3

An 87-year-old Caucasian female with multiple prior basal cell carcinomas developed a rapidly growing nodule on the right temple above the right eyebrow over a 3-month period. She noted occasional tenderness, crusting, and intermittent yellow drainage. The patient also had multiple underlying medical problems, including Parkinson's disease, a prior cerebrovascular accident, hypothyroidism, cervical cancer, and hypertension.

Examination revealed a 2.6 × 2.4 cm keratotic plaque on the right temple adjacent to the eyebrow (Fig. 5.10). There was no lymphadenopathy. A wedge biopsy demonstrated squamous cell carcinoma with keratoacanthomatous features.

Given her age and multiple comorbidities, she underwent injection of MTX 25 mg/ml concentration and a volume of 1 ml. She received 4 ml of 1% lidocaine with 1:100,000 epinephrine prior to MTX administration (Figs. 5.11, 5.12, and 5.13). Three weeks later, the center had become necrotic (Fig. 5.14) and was removed prior to injection of the base and periphery with an additional 1 ml of MTX at the same concentration (Fig. 5.15).

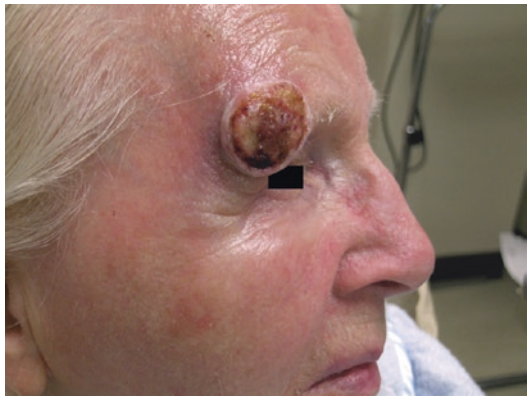

Fig. 5.10 An 87-year-old woman with a 2.6 × 2.4-cm nodule rapidly developing over 3 months on the right temple adjacent to the eyebrow. A wedge biopsy confirmed squamous cell carcinoma with keratoacanthomatous features

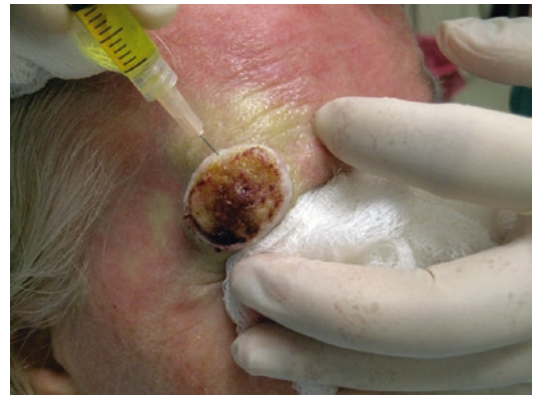

Fig. 5.12 Injection of methotrexate at 25 mg/ml concentration through the superior rim of the tumor with a 30-gauge 1-inch needle directed centrally and parallel to the skin surface. Approximately 0.2 ml was administered, with the remaining volume to be distributed around the periphery, sequentially. The 4 × 4-inch gauze serves both to protect the eye from extravasating methotrexate and to absorb any drug that extrudes through the crust

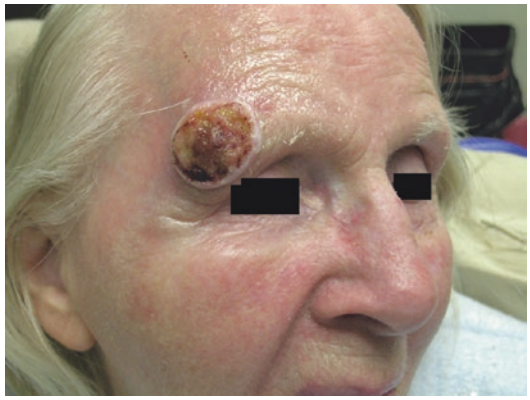

Fig. 5.11 Blanching of the skin surrounding the tumor resulting from administration of 4 ml of 1% lidocaine with 1:100,000 epinephrine prior to intralesional methotrexate injection

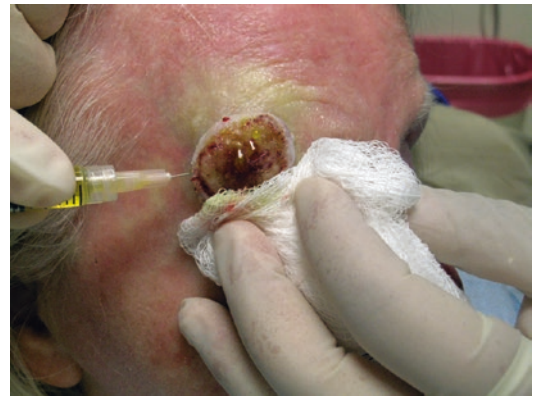

Fig. 5.13 Injection of an additional aliquot of 0.2 ml of methotrexate at the lateral aspect of the tumor. The inferior and medial injections followed, but are not depicted in this series

After three additional weeks, healthy granulation tissue was evident at the base, and no additional injections were required (Fig. 5.16). Twice-daily dilute acetic acid soaks followed by the application of white petrolatum and a nonadherent dressing were employed for the following month, with complete reepithelialization observed. She had no recurrence of the lesion or new lesions over the subsequent 3 years (Fig. 5.17).

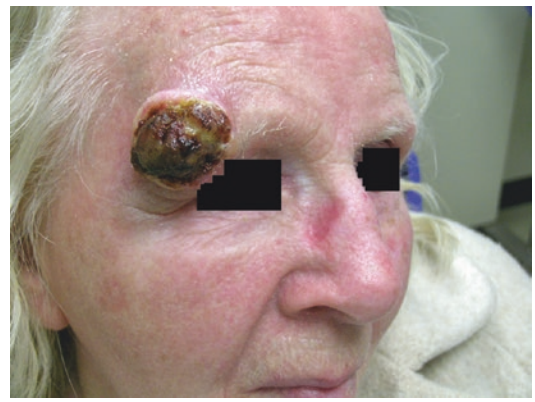

Fig. 5.14 Crusted and necrotic center of the keratoacanthoma 3 weeks later

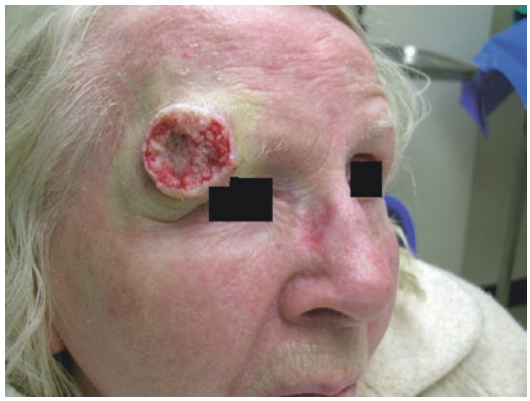

Fig. 5.15 The appearance of the base of the tumor with the crust debrided, and prior to the second methotrexate injection at the same volume and concentration, distributed evenly around the circumference of the residual tumor the same day

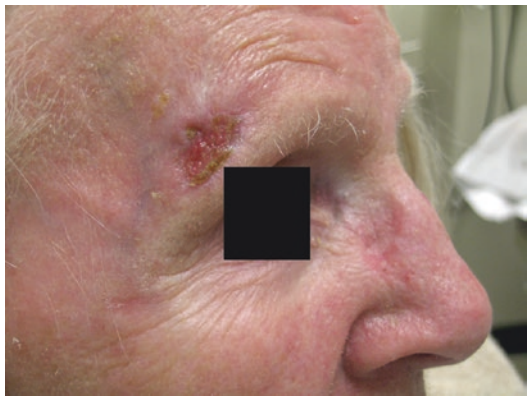

Fig. 5.16 Minimal erosion remaining at the site after an additional 3 weeks. The patient continued moist occlusive wound care without additional methotrexate administration. She completely healed 1 month later

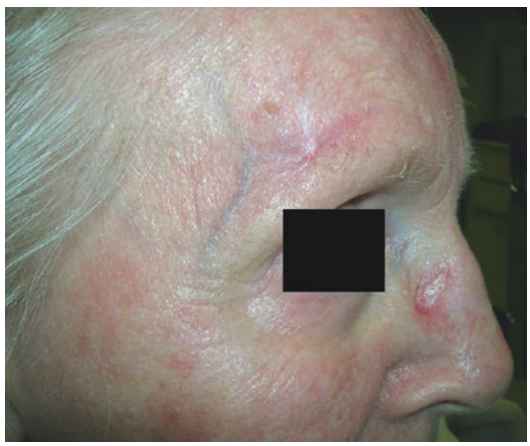

Fig. 5.17 Appearance of the site at 1 year, with excellent healing and no clinical evidence of recurrence. She remained disease-free at 3 years follow-up

Illustrative Case 5.4

A 59-year-old Caucasian male developed a rapidly growing nodule on the right pretibial leg over the course of 5 months. He was immunosuppressed (sirolimus and cyclosporine) secondary to renal transplantation 20 years prior. His medical history included type 1 diabetes mellitus, stage 2 chronic renal disease (most recent GFR 57 ml/min), hypertension, hyperlipidemia, atherosclerosis, and intermittent claudication. The patient also had a history of treatment noncompliance and chronic pain syndrome (Figs. 5.18–5.20). Figures 5.21–5.27 illustrate the use of MTX in the treatment of KA.

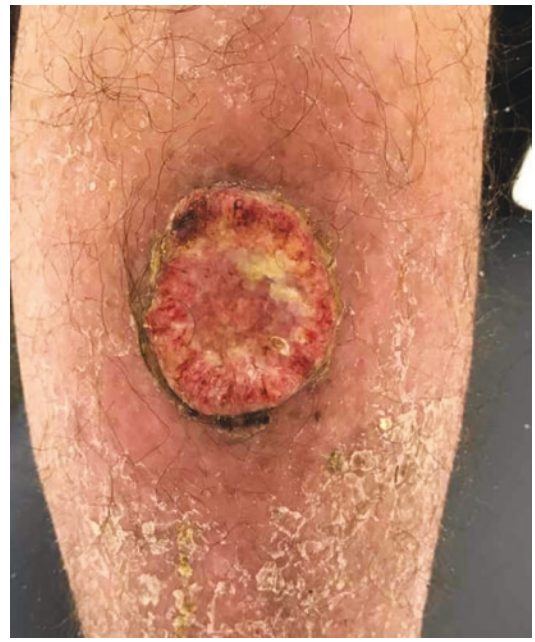

Fig. 5.18 Baseline examination revealed a 3.8 × 3.5-cm (10.4 cm^2) keratotic ulcerated nodule on the right pretibial leg. There was no adenopathy of the popliteal or inguinal nodal basins. Incisional biopsy revealed invasive well-differentiated squamous cell carcinoma, possibly consistent with keratoacanthoma. Given the patient's underlying immunosuppression, treatment with surgical excision was recommended with radiation therapy offered as a second-line treatment option. The patient refused both surgery and radiation. He agreed to a course of intralesional methotrexate injections as an alternative to refusing all treatment. Baseline blood counts and serum creatinine were drawn. 30 mg of IL-MTX was injected at a concentration of 25 mg/cc

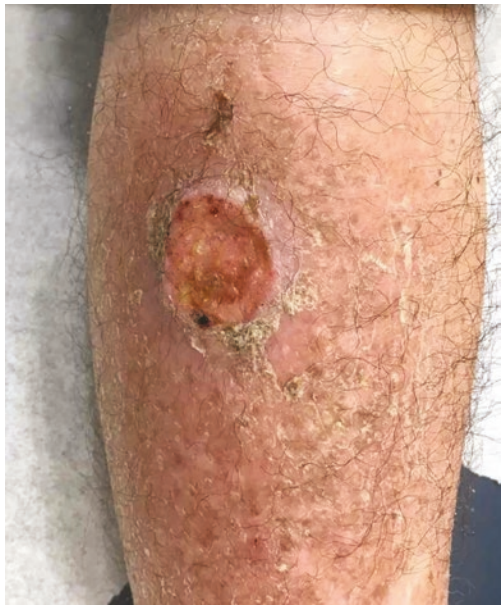

Fig. 5.19 Two weeks after a single injection of IL-MTX, the tumor measures 3.4 × 3.2-cm (8.0 cm^2), with a significant decrease in tumor thickness. CBC and serum creatinine are stable on recheck. 33 mg of IL-MTX was injected at a concentration of 25 mg/cc

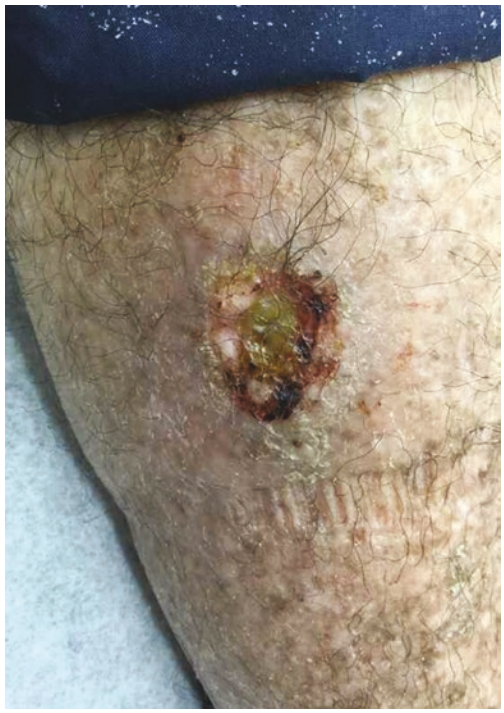

Fig. 5.20 After three injections of IL-MTX injected at 2-week intervals, the tumor measures 2.0 × 1.5-cm (2.4 cm^2). No injection was performed. CBC is stable on recheck. The tumor eventually completely resolved

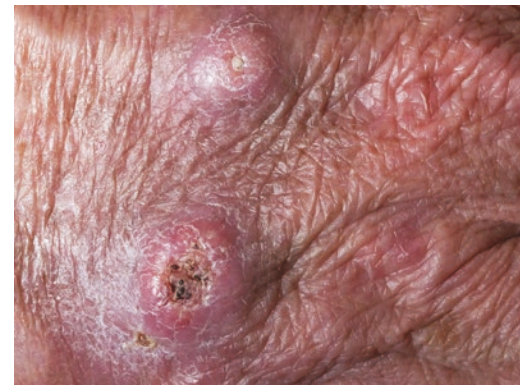

Fig. 5.21 Reactive keratoacanthomas (KA) on the right dorsal hand of a 70-year-old immunocompetent woman, 4 months after Mohs surgery with clear margins of a presumed squamous cell carcinoma. Each nodule was 1.1–1.5 cm and was injected via 30-gauge needle with 12.5 mg/ml concentration of methotrexate (MTX), 1.5 ml total, divided equally between the two lesions

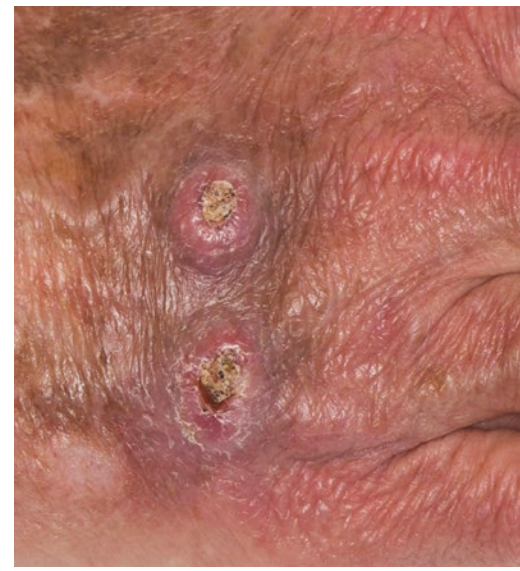

Fig. 5.22 One month post-injection, with some central necrosis and reactive erythema. Each KA was re-injected with MTX 25 mg/ml concentration, 1.0 ml total divided equally between the two lesions

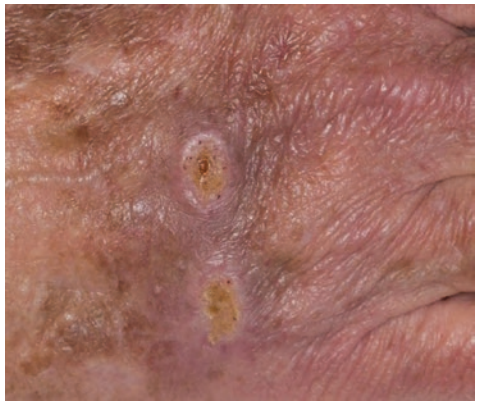

Fig. 5.23 Two months after initial injection, both lesions have crusted further and have nearly completely involuted. No additional injections performed

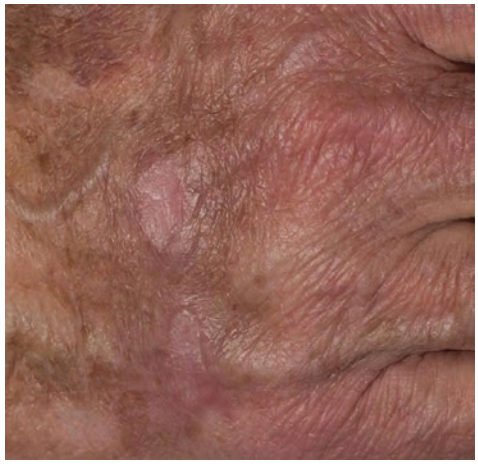

Fig. 5.24 Four months after initial injection, complete resolution has occurred, which has been maintained at 18 months follow-up

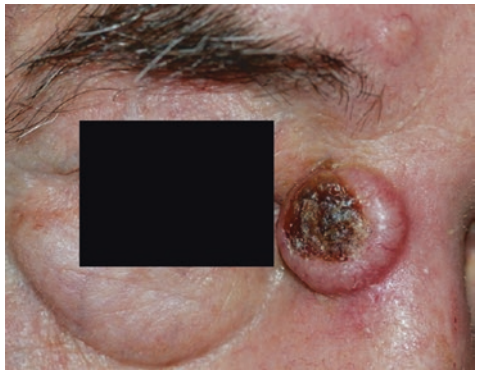

Fig. 5.25 Rapidly growing 2.0 × 2.0 cm KA of the right medial canthus in a 92 year-old man with multiple medical comorbidities. Injection of MTX 25 mg/ml concentration was performed, 1.0 ml total, via 30-gauge needle

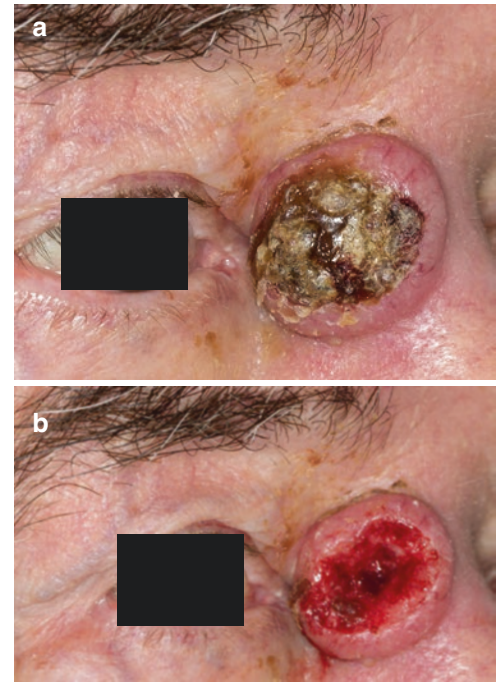

Fig. 5.26 One month later, with substantial central necrosis (**a**-top), gently debrided to a clean base (**b**-bottom) prior to a second injection performed at the same concentration and volume as the initial injection

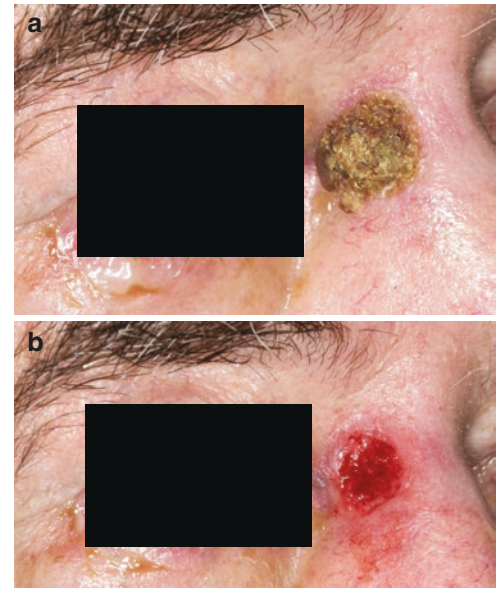

Fig. 5.27 Two months after initial injection with more extensive necrosis and crusting (**a**-top), more clearly evident after gentle debridement showing a clean but friable base and no remaining raised component (**b**-bottom). Complete healing occurred within another month with no additional injections necessary. The patient died of natural causes 7 months later with no recurrence of the KA

INTERFERON

Every epithelial carcinoma has been reported to have occasional total regression—stage and tumor burden not withstanding—brought about by immune attack. The immune system routinely kills neoplastic cells, and it is the overwhelming of this function that allows tumors to grow. In an immunocompetent individual, non-melanoma skin cancers are constantly attacked by tumor-infiltrating lymphocytes (TIL), and it is through stimulation of these cells that complete regression of skin cancer can occur [71–75].

Indications and Contraindications

Essential to the success of perilesional interferon treatment of skin cancer is screening of both the patient and the tumor. The patient should be an individual who understands that immune cells routinely kill cancer cells and one who is comfortable waiting 2–3 months for evaluation of efficacy. Since there are side effects of influenza-like symptoms, even though mild, it is important that this will not be of major concern to the patient. The physician must be comfortable and confident in recommending treatment and knowledgeable as to the mechanism of action and expected outcome.

The most beneficial treatment for skin cancer is that which eradicates the tumor and produces the least morbidity. Immunomodulatory IFN therapy, which is an alternative to destructive methods, meets these criteria for "most beneficial" with selected tumors.

Pre-treatment Considerations: Basal Cell Cancers

The tumors that respond virtually 100% to immunomodulatory treatment are superficial and nodular basal cell carcinomas (BCC) [75]. The location where there is a clear cosmetic benefit over destructive/excisional treatment is the trunk. Therefore, a physician who wishes to begin using this therapy should select a superficial or nodular BCC on the trunk. The experience gained will provide confidence and the opportunity to expand the range of tumors treated. Basal cell carcinoma, which is highly differentiated toward adnexal structures (hair follicle, eccrine sweat gland), does not respond to IFN treatment. Periorificial BCC tumors have a somewhat lower response rate, even with typical histology.

Pre-treatment Considerations: Squamous Cell Cancers and Malignant Melanomas

Because of the greater potential for metastatic spread of squamous cell cancer (SCC) and malignant melanoma (MM) great caution in selection of tumors for which injectable interferon (IFN) treatment is "most beneficial" is needed [76–78]. Generally speaking, the only SCC suggested for selection are those where the patient has refused surgery (Figs. 5.28 and 5.29) or a superficial or in situ SCC that has failed to respond to previous therapies (Figs. 5.30, 5.31, and 5.32). There are, however, two reported cases of recurrent squamous cell carcinoma of the head and neck responding to intralesional interferon. Both patients had recurrent lesions that had failed both surgery and radiotherapy [79]. SCC can invade deeply and be neurotropic—further factors for caution in tumor selection (Figs. 5.33 and 5.34).

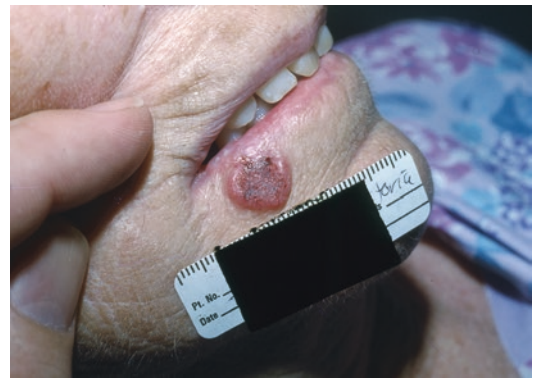

Fig. 5.28 Biopsy-proven large SCC on the lip of an elderly patient who refused surgical treatment

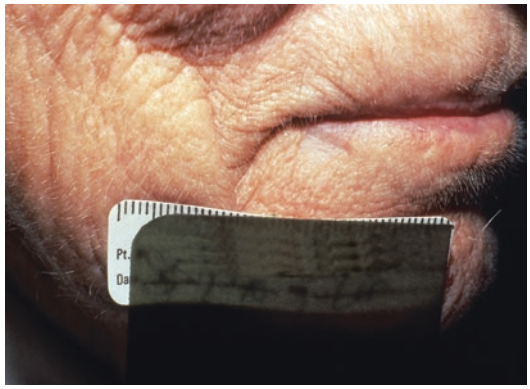

Fig. 5.29 Complete clinical resolution of the SCC on the lip 6 months later with slight delling at the tumor site, and skin markings present

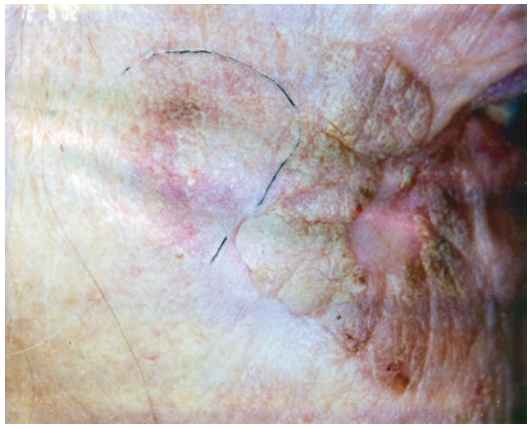

Fig. 5.30 Biopsy-proven verrucous SCC in situ near the lateral canthus with lateral extension outlined in ink. Previous treatments over 15 years included multiple cryotherapies, curettages, and curettage with electrodesiccation

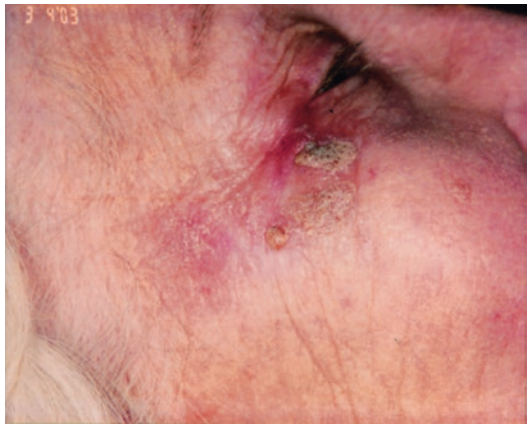

Fig. 5.31 Resolving tumor 1 week after the final IFN injection, typical for SCC but not seen with BCC

Malignant melanoma has great metastatic potential. The only melanoma suggested for selection are biopsy-proven melanoma in situ (MIS) for which surgery is deemed not to be a viable option (Figs. 5.33 and 5.34) [78].

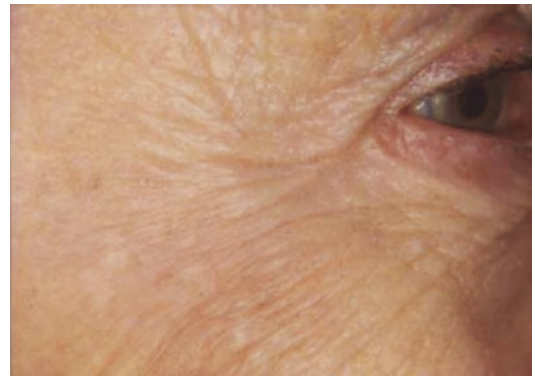

Fig. 5.32 Complete clinical resolution of tumor with intact skin markings. Photo taken 14 months after Fig. 5.31

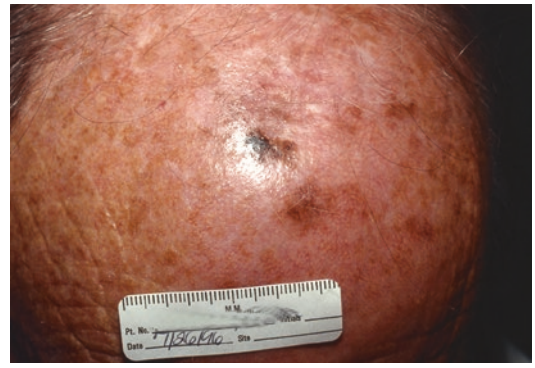

Fig. 5.33 Biopsy-proven recurrent MM MIS 2 years after wide excision

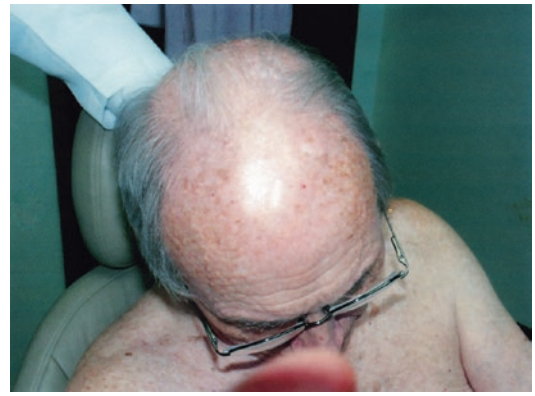

Fig. 5.34 Biopsy-proven and clinically seen complete resolution 7 years after IFN treatment

Obtaining Interferon α2b

Interferon alpha-2b (IFN) is not FDA approved in the United States but is approved in Europe and Canada. However, approximately one-third of patients may be able to get help from their insurance companies for purchasing IFN. A prescription is given for Intron A, 18 million units, NDC # 0085-1100-01. The manufacturer has labeled this as a "single-use vial," not for intralesional use. However, this is the same solution used in the early trials that showed great efficacy and does not have the risk of reaction to the preservative compounded in vials labeled "for intralesional use."

The diluent that comes in the package is used and additional bacteriostatic saline is further added to bring the concentration to 500,000 U per 0.1 ml (3.6 cc total volume). This vial is immediately and constantly refrigerated except when drawing up the injection. Routine sterile technique is used for multiuse vials. The reconstituted and diluted IFN retains its clinical efficacy when continuously refrigerated for up to 6 months.

The cost to the patient at a nationwide low-cost retail pharmacy is $270. Alternatively, the physician's office may purchase the medication and charge the patient for it. Since approximately 4 million units will be left over after giving all nine injections, the patient may be treated at a slightly reduced medication cost.

Description of Technique (BCC, SCC, MIS)

Administering Interferon α2b

The use of 1 cc syringes with plungers that push virtually all fluid into the 30-gauge needle is preferred (Norm-Ject, www.delasco.com). The site is prepared with alcohol and the end of an ice cube is placed on the specific small area where the needle will enter the skin for about 6 seconds to decrease pain.

Make Sure to Always

1. Inject into the dermis, not the subcutis, since the maximum local effect on the immune system depends on intradermal placement.
2. Inject perilesionally, not intralesionally. The solution, if properly placed, will cause swelling and blanching of the surrounding skin as well as the tumor (Figs. 5.35 and 5.36). Intralesional injection will cause loss of suspended IFN due to leaking of fluid from the less cohesive tumor tissue. It is the immune response in the normal surrounding dermis that attacks the tumor. Some IFN

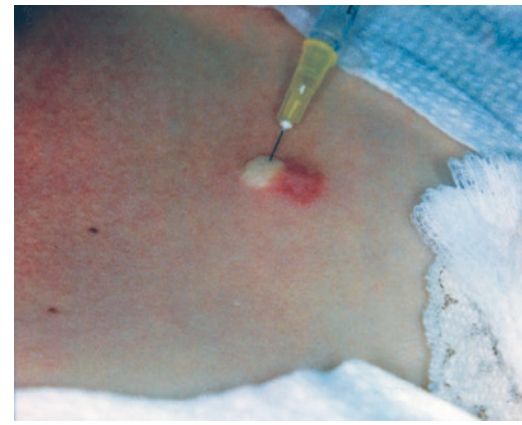

Fig. 5.35 Injection of IFN superior to the tumor with lightening and induration extending into the tumor

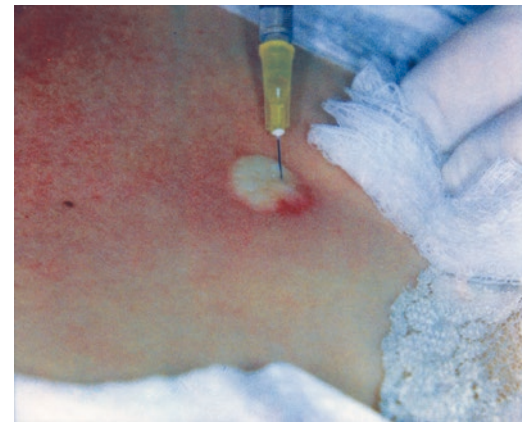

Fig. 5.36 Further extension of IFN into the tumor, complete infiltration of IFN solution with lightening of the area is desired

solution may leak out or come out in a spray from hair follicles; adjusting the depth of the needle point or injecting in a different area will correct the loss of medication. Any IFN solution that has leaked onto the skin may be sucked back into the syringe and reinjected.
3. Inject superior to the tumor.
4. Pre- and post-medicate individuals receiving IFN injections. The symptoms that an individual with a cold or flu experiences are due to the body's immune response to the virus, particularly interferon, not the virus itself. These same symptoms can be reproduced by the intradermal injections of interferon and are dose dependent.

Ibuprofen or acetaminophen—based on patient preference, medical history, and size—is recommended 1 hour prior to injection, 3 hour after injection (the time of onset of symptoms typically), the evening of the injection, and the following morning. Sensitivity to interferon-induced flu-like side effects varies among individuals. Tachyphylaxis of symptoms occurs if injections are given 2–3 days apart. However, after 5 days without an injection, symptoms are similar to the initial injection. Since symptoms may even vary between injections, the author highly recommends the use of the above regimen for all patients being treated with IFN.

The amount of IFN injected depends on the tumor size, the injection sequence, and the sensitivity of the individual to side effects. While the standard dose of IFN per treatment is 1.5×10^6 units (0.3 cc), using a lower dose for the first and second injections—such as 1×10^6 units (0.2 cc)—is recommended. The standard dose of 1.5×10^6 units is given by the third or fourth injection. For a small tumor (e.g., 1 × 1 cm), the lower dose may be used throughout. For larger tumors, larger doses may be given compatible with patient tolerance. In general, the effective dose range correlates with 1×10^6 units for tumor size 1 cm^2 and increases by 0.5×10^6 units for each additional cm^2. Dilution up to 0.25×10^6 units per 0.1 ml may be made for very large superficial BCC. This flexibility allows for individual variations based on tumor size and sensitivity to side effects. Higher doses have been reported in the literature for more aggressive tumors, including a case series of twelve basal cell carcinomas located on the nasal pyramid treated with intralesional interferon at a dose of 5×10^6 units thrice weekly for 4–8 weeks. Eighty percent of the treated tumors had an aggressive infiltrative growth pattern on initial biopsy, and 100% of lesions demonstrated a complete response confirmed by scouting biopsies [80].

Treatment Pearls

1. If 4 or 5 days have elapsed since the last injection, flu-like symptoms will be stronger, as with the first injection, so the dose may need adjustment.
2. It is the stimulation of the local immune system "over time," not the total dose that produces the desired results. Three large doses given over a week are not as effective as nine small doses given over 3–4 weeks.
3. The dilution of the IFN solution to 0.5×10^6 units per 0.1 cc increases efficacy over more concentrated solutions. When it is more concentrated, the ramifications of losing a small amount of the solution during transferring or injection are greater.
4. Less than 1% of patients treated with this regimen have no response. Another treatment modality is necessary in such cases.
5. Rare individuals will have only a partial response with marked tumor shrinkage. Since the tumor has responded partially, complete response can be obtained if retreatment with another course of IFN is desired by the patient.
6. The location where there is a clear cosmetic benefit of IFN over destructive/excisional treatment is the trunk.
7. The amount of IFN injected depends on the tumor size, the injection sequence, and the sensitivity of the individual to side effects.

Post-injection Care

As with any intradermal injection, local treatment is the placement of petroleum jelly, gauze, and pressure for 2–3 minutes and/or an adhesive bandage to protect clothing from seepage from the injection site.

Expected Course of Treatment and Follow-Up (BCC, SCC, MIS)

Three types of local responses may occur, typically between injections six to nine:

1. The tumor may become red and indurated, sometimes with slight surrounding erythema and rarely with a tender lymph node or folliculitis (Figs. 5.37, 5.38, and 5.39).
2. Slight erythema of the tumor occurs with little induration.
3. Little to no erythema is observed throughout the course, but slight induration occurs.

If local response 1 occurs, 100% tumor resolution has been the rule. However, in greater than 90% of tumors with responses 2 or 3, complete resolution also occurs.

The tumor often stops crusting after injection #6 and less leakage of interferon occurs. Following the ninth injection, the patient is instructed to return for evaluation in 3 months. Little to no regression of BCC is seen during the actual treatment of BCC but occurs weeks later once treatment has finished.

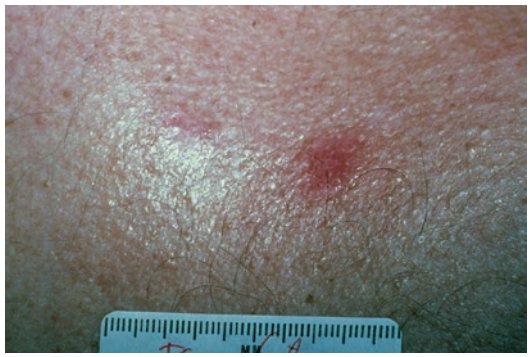

Fig. 5.37 Two superficial BCCs on the chest of a man with numerous truncal BCCs. The man sought treatment for these tumors that would not yield prominent scar formation (see Fig. 5.30)

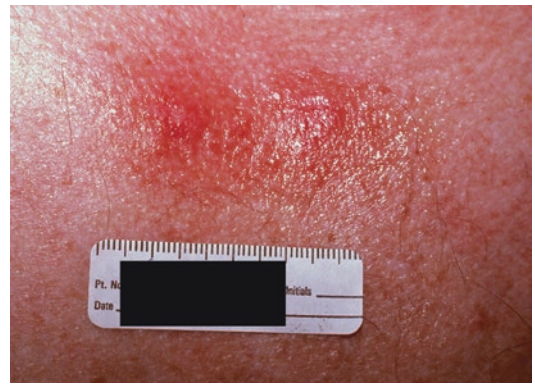

Fig. 5.38 Erythema and induration of the chest BCCs after the seventh IFN injection; typical for a type 1 response to treatment

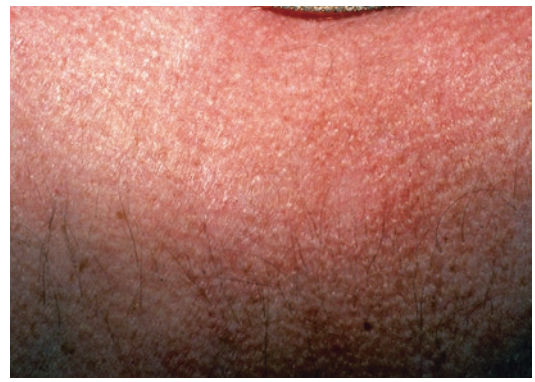

Fig. 5.39 Complete clinical resolution at 6 months posttreatment with slight hypopigmentation and normal skin markings

If no response of the tumor is observed (e.g., redness, swelling, induration), surgical removal should be performed. For the other 99% of BCC tumors, the 3-month posttreatment evaluation is sufficient.

SCC often show clinical partial resolution during the 3- to 4-week period of treatment (Figs. 5.30, 5.31, and 5.32). Occasionally, BCC or SCC will develop milia-like cysts, which resolve over the following 3–6 months [76].

MM resolve in a similar time period to SCC. For pigmented MM, resolution of the pigment, as well as the malignant melanocytes, is expected (Figs. 5.33 and 5.34).

The question of whether there is always a need to biopsy posttreatment is best answered (other

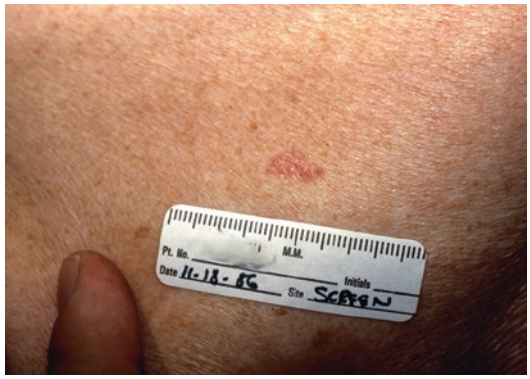

Fig. 5.40 Superficial BCC on back

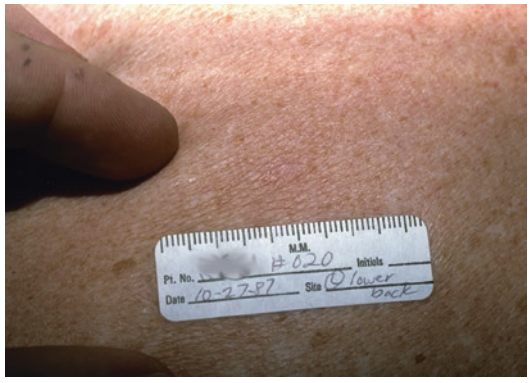

Fig. 5.41 Complete clinical resolution of superficial BCC with normal skin markings

than MM which should always be biopsied following treatment) with close evaluation of the treated site. Normal skin lines should return following treatment (Figs. 5.40 and 5.41) in contradistinction to curetted and electrodesiccated lesions (Fig. 5.42). Even with very large and deep tumors, where considerable posttreatment hypopigmentation and/or delling may occur, there is a return of normal skin lines (Figs. 5.43 and 5.44). This allows effective posttreatment clinical follow-up, making biopsy unnecessary.

In the largest double-blind, placebo-controlled study of IFN treatment of BCC, no subclinical tumor was found on excision of the treated site at 1-year posttreatment if no tumor was visible by clinical inspection [81]. Long-term follow-up for 10 years or longer has confirmed the extremely low incidence of persistent or recurrent tumor with this immunomodulatory treatment [75].

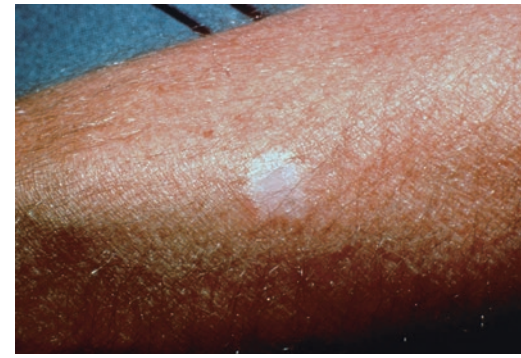

Fig. 5.42 Electrodesiccation and curettage scar for BCC on the arm of the patient whose chest BCCs are seen in Figs. 5.37, 5.38, and 5.39. Note lack of skin markings after 1 year

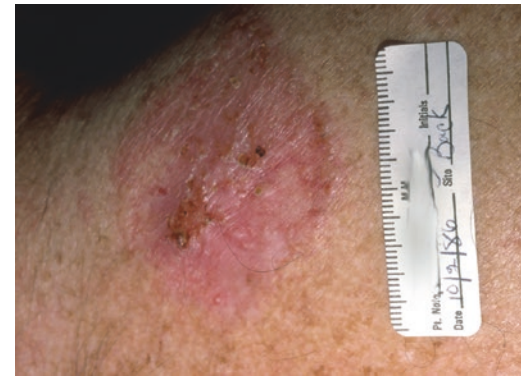

Fig. 5.43 Extensive nodular and superficial BCC on the shoulder prior to IFN treatment, note the hemangioma within the tumor

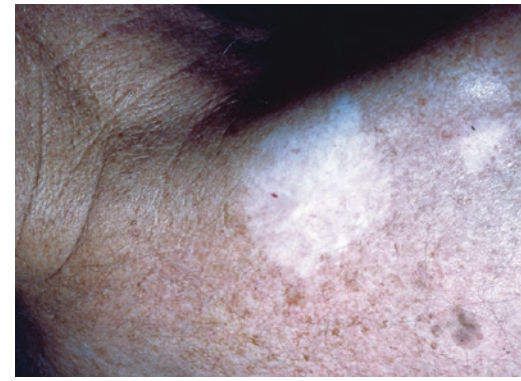

Fig. 5.44 Complete clinical resolution of the tumor photographed 20 years following IFN therapy. Skin markings are present despite the prominent hypopigmentation. The hemangioma was unaffected by IFN therapy as are all benign structures

5-FLUOROURACIL

5-Fluorouracil (5-FU) is a structural analog of thymidine that interferes with synthesis, resulting in the death of rapidly proliferating malignant cells. It has been used topically for years to treat actinic keratoses, Bowen's disease, and superficial basal cell carcinoma (Chap. 2). 5-FU has been used intralesionally in the treatment of keratoacanthomas, squamous cell carcinomas, and nodular basal cell carcinomas (Figs. 5.45, 5.46, 5.47, 5.48, 5.49, 5.50, 5.51, 5.52, 5.53, and 5.54) [82–91].

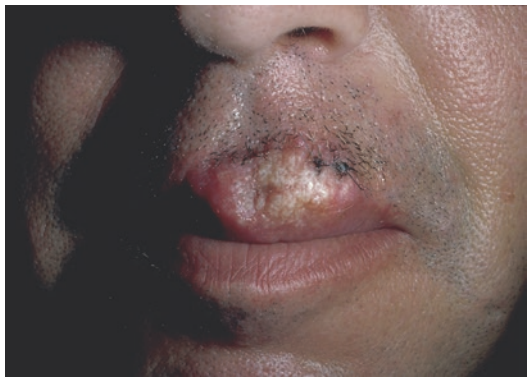

Fig. 5.45 Keratoacanthoma of the lip, pre-treatment

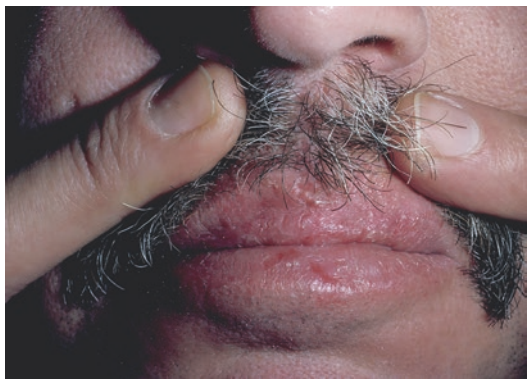

Fig. 5.46 Keratoacanthoma of the lip, 5 months after treatment with intralesional 5-fluorouracil and oral isotretinoin

Keratoacanthomas

Klein was the first to use intralesional 5-FU in 1962 to treat KAs [47]. Since then there have been many reports of KAs treated effectively with intralesional 5-FU [41, 42, 49, 83–86]. In two separate studies, 55 keratoacanthomas located on the face, head, and extremities were studied. Following an average of three weekly injections of 0.2–0.6 ml of an aqueous solution of 50 mg/cm^3 5-FU, 53 of the 55 lesions (96%) showed histologic clearing [83, 84]. In another case report, Eubanks et al. observed total clearing of all of a patient's 14 KAs treated with doses of IL 5-FU of 0.1–0.2 ml over five to nine weekly injections [41]. A more recent review of the literature published in 2016 by Metterle et al. reported a 97% cure rate for KAs treated with intralesional 5-FU [86].

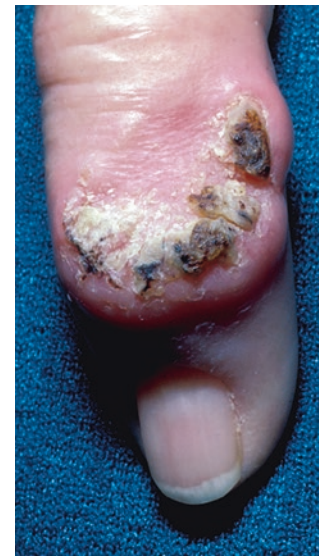

Fig. 5.47 Keratoacanthoma of the finger, pre-treatment

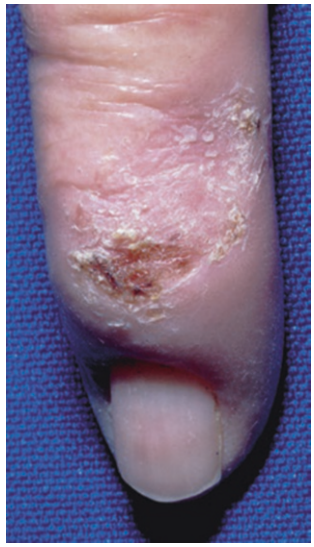

Fig. 5.48 Keratoacanthoma of the finger, 1 month after treatment with weekly intralesional 5-fluorouracil

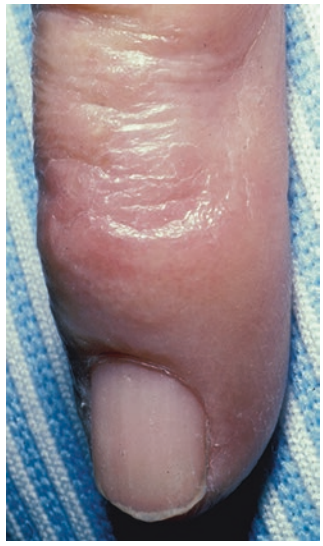

Fig. 5.49 Keratoacanthoma of the finger, 1 year follow-up

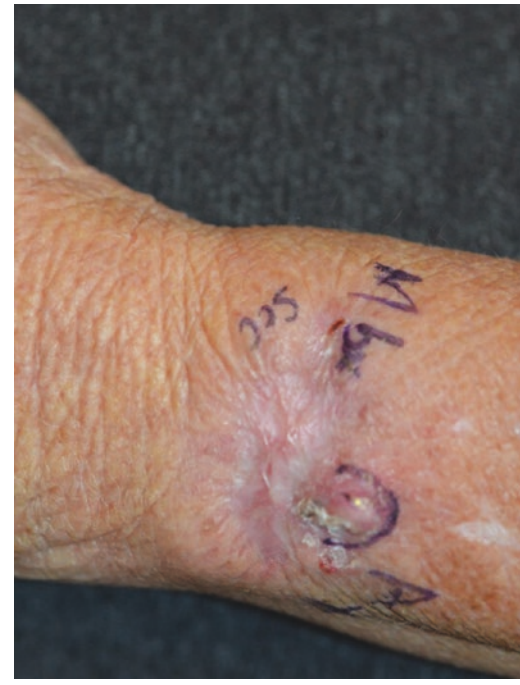

Fig. 5.50 Reactive keratoacanthoma within a prior excision site on the left forearm, pre-treatment

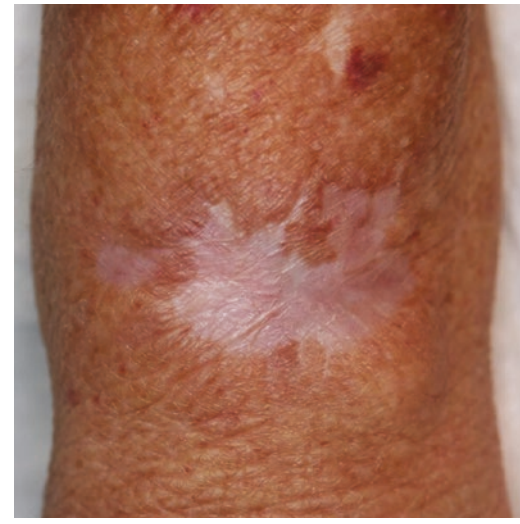

Fig. 5.51 Appearance at 9 month follow-up

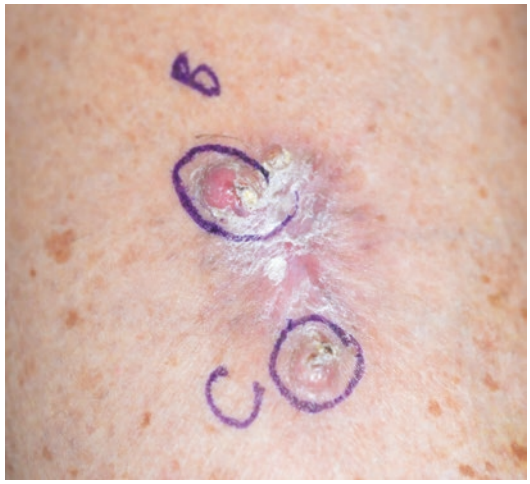

Fig. 5.52 Two reactive keratoacanthomas within prior ED&C site on the lower leg, pre-treatment

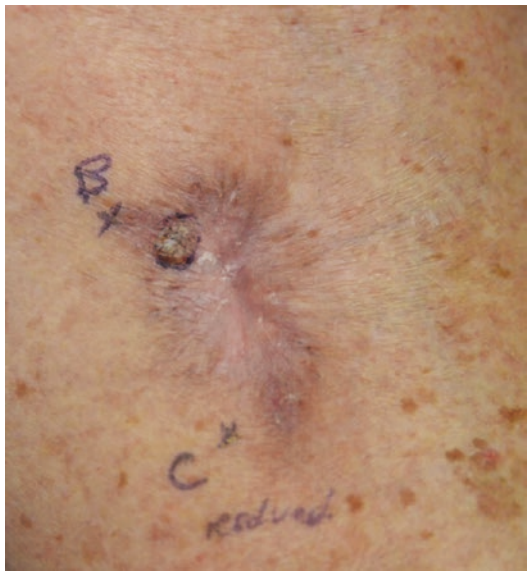

Fig. 5.53 Clinical resolution of one lesion after single injection of 5-fluorouracil

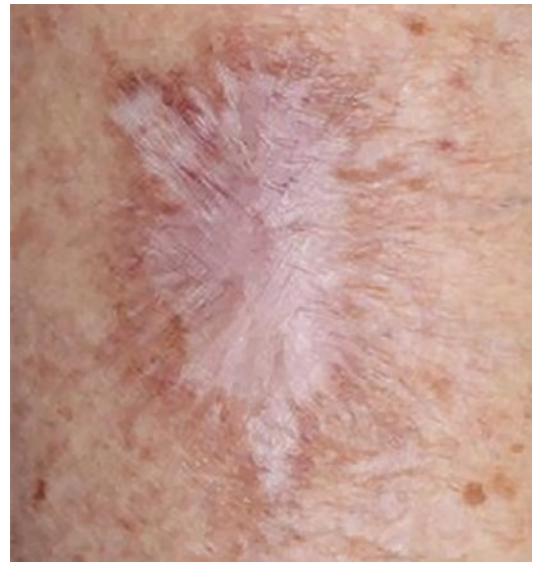

Fig. 5.54 Appearance at 11 month follow-up

Squamous Cell Carcinomas

Intralesional 5-FU has been used to treat SCCs [43, 85–88]. Twenty-three patients with biopsy-proven SCCs of less than 6 months' duration, located on the face, head, neck, arms, or hands and varying from 0.24 to 7.50 cm, were treated with intratumoral 5-FU/epinephrine gel. The patients received weekly injections of 1.0 ml or less of a combination of 30 mg/ml of 5-FU and 0.1 mg/ml of epinephrine gel for 4–6 weeks. Only one patient failed treatment and all had a good to excellent cosmetic result. The same review article by Metterle et al. published in 2016 reviewed intralesional 5-FU in SCC (distinct from KA) and reported a cure rate of 96% of published cases [86]. Morse et al. treated an SCC on the right nasolabial fold with eight weekly

injections of 5-FU with doses ranging from 0.8 to 2.4 ml. Histological clearance was achieved and the patient was tumor-free at 5-month follow-up [43]. Reisinger et al., following refusal of surgical treatment, treated a giant (3.8 cm) SCC located on a patient's dominant thumb with weekly injections of 5-FU at a mean per treatment dose of 100 mg. After six treatments there was complete resolution of the tumor confirmed by five scouting biopsies [88].

Basal Cell Carcinomas

Intralesional injection of 5-FU has been effective in nodular basal cell cancers [89]. At 2-year follow-up, intralesional 5-FU was successful for three keratoacanthomas and two of three BCCs. It was found that 5–6 injections were needed to treat the BCCs, a finding in agreement with an earlier study. An average of eight injections of 5-FU was required to treat the KAs. Odom et al. were able to treat them with 2.8 injections [83].

Indications

These are similar to MTX, used when a patient refuses surgical intervention, or in cases where a patient's medical condition contraindicates surgery, or in cases where the surgery will result in a large defect.

Contraindications

Hypersensitivity to 5-FU and difficulty with following the protocol are contraindications. Of note, there have been reports of acute cerebellar syndromes following treatment with topical 5-FU cream [90], as well as potentially life-threatening toxicities observed in patients with dihydropyrimidine dehydrogenase deficiency [91]. None of the cases were in the context of intralesional administration of the agent, but it is advisable to be aware of these reported outcomes.

Pre-treatment Considerations

These are similar to MTX.

Obtaining and Preparing

Use 5-fluoruracil commercially available for systemic chemotherapy (50 mg/ml). Local anesthesia can be used with it, as an option (1% lidocaine).

Description of Technique

Infiltrate in and around lesion once or twice weekly until neither palpable nor visible. Thorough and complete infiltration of the tumor with 5-FU is essential for efficacy [92].

Note on Technique

Compared with intralesional methotrexate, intralesional 5-fluorouracil is more painful. The authors have no strong opinion about the relative effectiveness, and we are not aware of a controlled comparison study. It is important to abort the therapy if it clearly is not working and resort to surgery, radiation therapy, or some other modality. One of the authors (RR) is aware of one case of treatment of a keratoacanthoma of the periorbital area with intralesional 5-fluorouracil that was ineffective, resulting in a lawsuit. The lesion had continued to grow despite the intralesional treatment, and eventually the patient had to have an ocular enucleation.

Post-injection Care

This is similar to intralesional MTX.

Expected Course and Follow-Up

If KAs do not demonstrate necrosis clinically after two to three weekly intralesional 5-FU treatments, alternative treatments should be considered [92].

Adverse Effects

Kurtis and Rosen reported the development of SCC within a BCC that was treated with intralesional injections of 5-FU [85]. Intralesional injections can result in pain, necrosis, and ulceration. Systemic effects similar to intravenous 5-FU therapy can occur, but generally only when the above doses are exceeded.

BLEOMYCIN

Originally isolated from the fungus *Streptomyces verticillus*, bleomycin is used as an antitumor agent for the treatment of various kinds of malignancy [93]. Other dermatologic uses include the treatment of recalcitrant warts, hypertrophic scars, and keloids. Bleomycin has been shown to block the cell cycle at G2, cleave single- and double-stranded DNA, and degrade cellular RNAs. Bleomycin forms a complex with metal ions such as Fe (II), which is oxidized to Fe (III), resulting in the reduction of oxygen to free radicals which in turn cause cell breaks, leading ultimately to cell death [94]. While systemic bleomycin is FDA approved for the treatment of SCC of the head and neck, cervix, penis, and skin, Hodgkin's and non-Hodgkin's lymphoma, testicular carcinoma, and malignant pleural effusion, there are no current FDA-approved indications for intralesional bleomycin [95]. The cytotoxic effect of bleomycin is enhanced considerably by coupling it with local anesthetics which increase its cellular uptake [96]. Electrical stimulation also disturbs the cell membrane and enhances bleomycin cytotoxicity in a process known as electroporation [97]. While bleomycin alone has not shown desirable outcomes for the treatment of cutaneous malignancies, when combined with electrocorporation, results have been very successful. In electrocorporation, a circular configuration of electrode needles is used to deliver brief, high-intensity, pulsed electrical currents directly into the target tumor [98]. The combined use of electrocorporation and a chemotherapeutic agent is termed electrochemotherapy (ECT).

Squamous Cell Carcinoma/ Keratoacanthoma

Keratoacanthomas have been treated with intralesional bleomycin without ECT. While no controlled, randomized studies have been conducted, in seven cases of KAs treated with intralesional bleomycin alone, a 100% cure rate and no side effects were reported [44, 45]. In these cases a 0.5% solution of bleomycin was used, diluted with saline and lidocaine. Using a 27-gauge needle, 0.2–0.4 mg of solution was injected. At most, four courses of treatment were needed at weekly follow-up sessions.

Basal Cell Carcinoma

In a case series of 20 patients with 54 tumors treated with ECT, Glass et al. noted a complete response rate of 94% and a partial response rate of 6%, no reports of nonresponse or disease progression [99]. There have been no reports on response rates for the different histologic subtypes of BCCs, cost-effectiveness or direct comparison between ECT and conventional treatment. There is one report of ECT and bleomycin used to treat a metastatic BCC with squamous differentiation [100].

Metastatic Cutaneous Malignant Melanoma

Of the studies performed, treatment protocols varied, with 0.5–1.0 U bleomycin per calculated cc of tumor, electrical amplitude between 560 and 15,000 V/cm/s. Complete response rates have been reported to range from 72% to 89%, partial response rates (greater than 50% reduction in calculated tumor size-5–10%). Long-term follow-up was not reported [98].

Indications

This is similar to MTX.

Contraindications

Those with Raynaud's phenomenon or peripheral vascular disease should not be treated with bleomycin. It should be avoided in the pregnant or nursing patient.

Pre-treatment Considerations

This is same as MTX.

Obtaining and Preparing

A common dilution of bleomycin is to take a vial of 15 international units of powder and dilute it with 15 ml of normal saline to make a solution of 1 unit per ml. Other authorities have used more dilute preparations.

Description of Technique

One of the authors (RR) generally injects less than 0.6 ml of this solution weekly into a lesion for up to 8 weeks (0.1–0.2 ml for smaller lesions). Care must be taken to inject it specifically into the dermis associated with the lesion, and not into the fat, where larger amounts become easily injected, with very little effect on the malignancy.

Post-Injection Care

This is similar to MTX.

Expected Course and Follow-Up

One of the authors (RR) used bleomycin in a case of a large verrucous carcinoma of the sole (Fig. 5.55), with the idea that human papillomavirus plays a role in this type of carcinoma. The intralesional bleomycin in the illustrated case did very well at eradicating the verrucous carcinoma (Fig. 5.56), but portions of it subsequently recurred (Fig. 5.57).

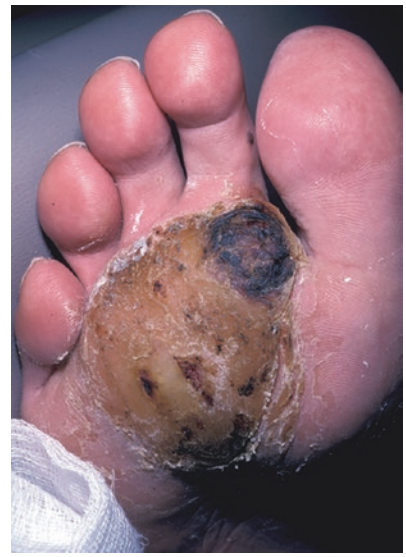

Fig. 5.55 Verrucous carcinoma on sole, pre-treatment

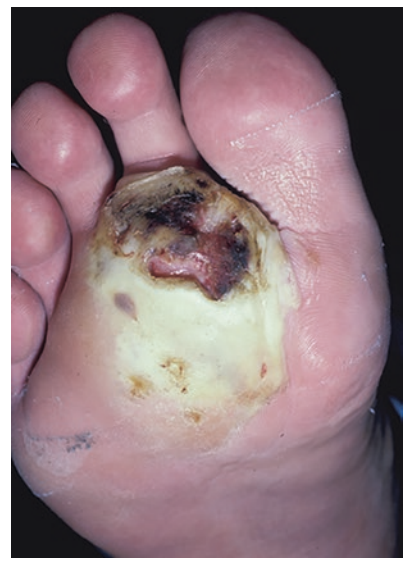

Fig. 5.56 Verrucous carcinoma 1 month after treatment with weekly intralesional bleomycin

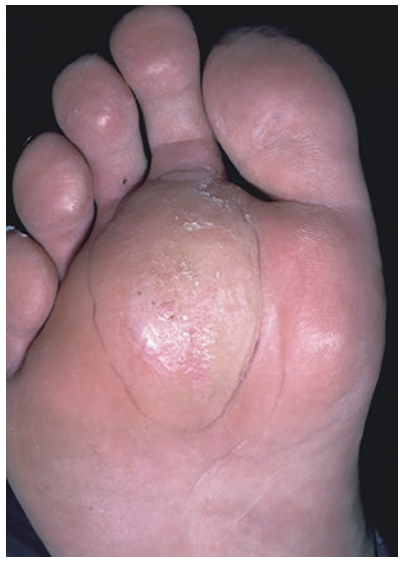

Fig. 5.57 Verrucous carcinoma 3 months after treatment with intralesional bleomycin. The tumor had an excellent response, but did have a partial recurrence later

Adverse Effects

The following reactions occur immediately after injection and include erythema with swelling [101], pain [102], and a burning sensation [103]. The pain usually lasts for 72 hours and is relieved with acetaminophen. Blackening of the skin and eschar formation have also been observed [104]. Rarely onychodystrophy [103], hypopigmentation [105], atrophic, and hypertrophic scarring [106] are reported. Raynaud's phenomenon, anaphylaxis, and flagellate hyperpigmentation have been reported [107]. If combined with electrical impulses to increase uptake (electrochemotherapy), patients may experience discomfort, local muscle contraction, skin burning, erythema and edema, and muscle fatigue [108].

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Chapter 6
Electrodesiccation and Curettage

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Indications

Curettage alone or in combination with electrodesiccation has been used for the treatment of skin cancer. While the curette was developed in the 1870s [1], electrodesiccation was first used in 1911 by Clark when a high-voltage, low-current electrode was applied to the skin and resulted in drying of tissue [2]. It was not until later that the combination of curettage and electrodesiccation gained acceptance for low-risk lesions such as superficial and nodular basal cell carcinomas [3].

Since there is impaired adherence between the tumor cells and the basement membrane and a mucinous stroma around the tumor, the soft tissue can be curetted easily. Other tumors such as warts, actinic keratoses, and keratoacanthomas may respond well to this technique. The differentiation between the healthy fibrous tissue from the softer tumor tissue provides a plane for defining the clinical border of the tumor [4]. Curettage has also been used prior to excision, cryosurgery, and Mohs surgery. Debulking the tumor and better establishing the clinical borders provide a defining step prior to these other procedures [5]. In general terms, electrodesiccation and curettage are used for smaller more superficial lesions and those in less critical locations such as the cheek, temple, forehead, ear, chest, and back. Curettage is widely used alone for biopsies in benign lesions as well as other types of malignant lesions. In some studies, curettage alone has been shown to be effective in over 96% of lesions that adhered to a specific protocol [6, 7].

The lower-risk sites for this procedure are the neck, trunk, and extremities. Moderate-risk sites include sites that are determined by depth and found on the scalp, forehead, around the ear, and the malar areas. Higher-risk areas are around the nose, nasolabial folds, eyelids, periorbital areas, lips, chin, and some tumors on the ears [8, 9]. Cure rates of greater than 96% have been found with this technique for lesions 2 cm or less in size.

Contraindications

Larger lesions that are not superficial or that are in high-risk sites are best treated by other techniques. Morpheaform basal cell carcinomas (BCCs) are difficult to remove by electrodesiccation and curettage and are best treated by Mohs micrographic surgery, as are infiltrative BCCs, which may be more aggressive and tend to recur more often. Recurrent BCCs extending into scar tissue from previous treatments are infrequently amenable to curettage and electrodesiccation. This technique is contraindicated for most lentigo maligna and for lentigo malignant melanomas, as cancerous cells may extend down the hair follicle and for several millimeters beyond the clinical edge of the tumor.

This technique is useful in patients on anticoagulants.

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Electrodesiccation should be avoided in those prone to hypertrophic scars and keloids and cryosurgery used instead [10–12].

Preoperative Considerations

A history of pacemaker, anticoagulants, or immunosuppressive drugs is important to note [13]. There are specific guidelines for the use of electrodesiccation for the treatment of basal cell and squamous cell carcinomas in patients with pacemakers [13]. The procedure, anticipated results, and complications should be explained to the patient and informed consent obtained prior to treatment. The borders of the tumor should be outlined in ink prior to beginning the procedure—include a safety margin of 4–5 mm. The skin should be cleansed with a nonflammable antiseptic solution or dried carefully if alcohol is used to avoid inadvertent fire. Local anesthesia is provided with 1% lidocaine with epinephrine using a 30-gauge needle.

Important considerations prior to making the decision to use electrodesiccation include flammable substances on the skin, oxygen flowing in the room, and elevation of the tumor from superficial nerves and tendons.

If electrodesiccation is used around the anal canal, a moist packing should be provided to prevent the ignition of methane [10–12].

Description of Technique

Remove the tumor when obtaining a biopsy by shave excision, and then perform curettage if the procedures are to be followed in sequence. Removal of the bulk of the lesion with the curette is followed by electrodesiccation, which removes persistent tumor cells at the base and rim of the lesion. A curette may be held like a pencil. Curettes vary in size from 1 to 7 mm, but a 3–4-mm diameter is most frequently used. The scooping motion involves holding the curette at a downward angle and vigorously scraping in all directions. After the obvious portion of the tumor is removed, the base and margins may be removed. Holding the curette like a pencil is effective for smaller tumors. With the nondominant hand, hold the skin around the lesion taut while holding the curette in the dominant hand, between the thumb, index, and middle finger, and resting the remainder of the hand on the skin. Starting at the more distal end of the lesion, firm strokes are carried through the tissue and repeated several times until the entire tumor has been removed. For larger lesions, the curette is held in a position similar to a potato peeler; the thumb stabilizes the movement and holds the skin taut as does the other hand. Curettage is continued until pinpoint bleeding is noted.

If the curette penetrates into subcutaneous fat, curettage should be stopped since the tumor may extend too deeply for removal by this technique [14].

Electrodesiccation using a hyfrecator is performed on the base and rim of the lesion for at least 2 mm around the rim of the tumor. For more intense tissue damage, the electrocautery mode using biterminal with low voltage and high amperage is carried out to a 4–6-mm margin and repeated at least three times to ensure that all tumor cells are removed. While electrodesiccation destroys tumor cells, it also aids hemostasis and seals lymphatic vessels [15]. The sequence of steps is illustrated in Figs. 6.1, 6.2, 6.3, 6.4, 6.5, and 6.6.

Variations of this basic technique include curettage alone [6], electrosurgery followed by curettage [4], curettage followed by cryosurgery [16], curettage followed by a course of imiquimod [17], or curettage and electrodesiccation followed by imiquimod [18].

One theory proposes that electrosurgery precede curettage. This is believed to cause more tissue destruction and to reduce the need for curettage, but may interfere with the curette's ability to differentiate normal from abnormal skin [15, 19].

Curettage with electrodesiccation cure rates ranges from 95% to 98% depending on size, depth, location, and tumor type [12]. A study of 361 BCCs and squamous cell carcinomas showed

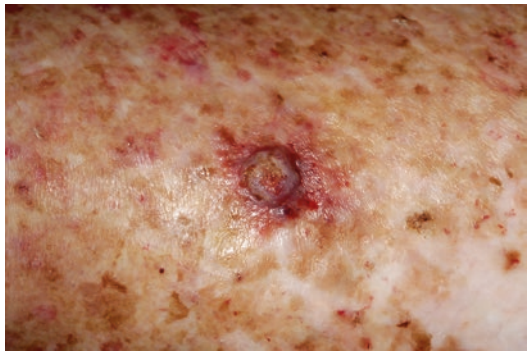

Fig. 6.1 Suspected SCC on the leg of a 46-year-old female with a past history of irradiation and numerous NMSCs

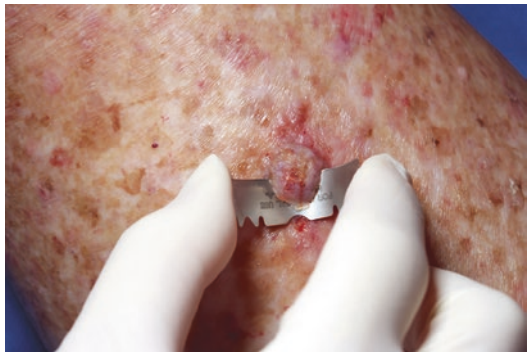

Fig. 6.2 Shave biopsy of suspected SCC

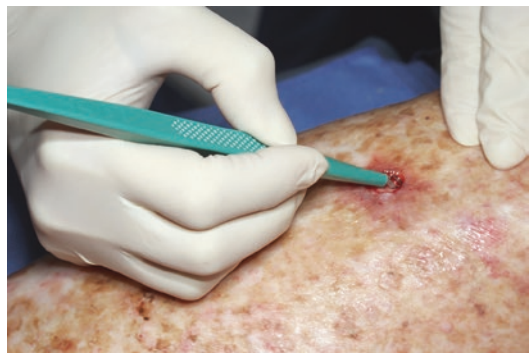

Fig. 6.3 Curettage of lesion base. Note how the curette is held and that the nondominant hand stabilizes the skin

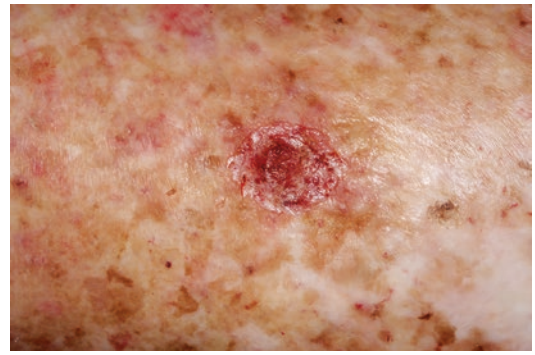

Fig. 6.4 Appearance following curettage

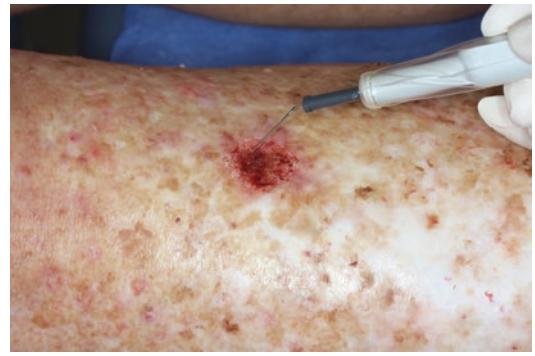

Fig. 6.5 Electrodesiccation to the base and rim of the lesion

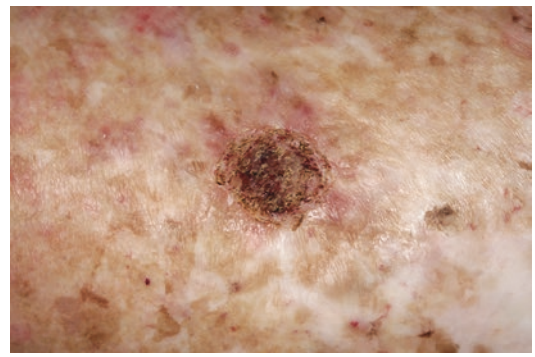

Fig. 6.6 Appearance of the lesion base following ED and C

that in appropriately selected patients electrodesiccation and curettage has a cure rate of 95.1% at 7-year follow-up [20]. Curettage alone will also be reviewed briefly and in select patients can give over 96% chance of cure [6, 7].

Spiller reported a cure rate of 99.4% for smaller tumors excluding those on the nose or nasolabial fold [21].

Higher recurrence rates have been reported in aggressive histologic types of BCC and high-risk anatomic locations. A study of 34 patients with primary aggressive BCCs including primary infiltrative, desmoplastic, morpheaform, or micronodular BCCs showed a 73% cure rate after treatment with electrodesiccation and curettage at 6.5 years follow-up [22]. A study of 257 patients with primary BCC located in medium- and high-risk facial areas treated with four or five cycles of electrodesiccation and curettage showed a cure rate of 79.4–98.8% at 5-year follow-up [9].

Daily application of imiquimod following curettage was found to be effective in treating primary nodular BCC on the trunk and extremities [17, 18]. Ninety-four percent of patients did not have a recurrence at 3 months and had an excellent cosmetic result [17]. Once-daily application of imiquimod for a month following curettage and electrodesiccation resulted in a decrease in the frequency of residual tumor [18].

Postoperative Care

The area should be cleansed daily with soap and water, hydrogen peroxide, or other cleansers and covered with the twice-daily application of an antibiotic ointment or white petroleum jelly. Leaving the wound open is also associated with excellent healing. Pain is minimal, but over-the-counter analgesics may be used if needed. If swelling of a treated lesion occurs on the lower extremities, a compression bandage or support hose may be used. Healing is accomplished within approximately 2–4 weeks with minimal scarring [10, 11].

Use of Curettage Alone

How effective is curettage alone? Curettage without electrodessication of basal cell carcinomas has been reported to be as effective as electrodessication and curettage [6, 23]. Barlow et al. looked at this in a study of 302 low-risk basal cell carcinomas and found a 5-year cure rate of 96% [6]. Curettage alone has been found to be effective for BCC meeting certain strict criteria. The criteria included only primary tumors with nodular or superficial histology, discrete borders, less than 6 mm, not in high-risk areas (nose, nasolabial area, eyelids, medial canthi, ear, or lips), and not more than 2 cm in size. Superficial BCCs of any size were included. Cosmetic results were considered better than when curettage and electrodesiccation were used, as the latter technique has been shown to increase the chance of hypertrophic scarring and hypopigmentation in some locations [6, 21, 24]. A recent study showed similar efficacy of curettage alone for invasive cutaneous squamous cell carcinoma. In this study treatment of 89 SCC lesions in 80 patients resulted in a cure rate of 97% [7].

Complications

A depressed scar with atrophy or even hypertrophic scarring may result and there may be hypo- or hyperpigmentation. Patients prone to keloids may have a greater tendency to develop one after electrodesiccation than after cryosurgery.

Summary

Curettage and electrodesiccation is an effective, simple, and cost-effective treatment for superficial as well as some nodular basal cell carcinomas in 95–98% of selected cases [15, 19]. Curettage alone has also been shown in several studies to clear more than 96% of selected lesions [6, 7].

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Chapter 7
Cryosurgery

Gloria F. Graham

The history of cryosurgery in dermatology dates back to the 1890s, when White, a New York dermatologist, dipped a cotton-tipped applicator into liquefied air in 1899 and successfully treated warts, keratoses, and skin cancers [1]. Torre [2] and Zacarian [3] both published their findings on the use of freezing for treating skin cancer in the mid-1960s. The Spillers first described its use with curettage and this is a technique that is often used today [4].

Basic Cryobiology

The physics of cryoablation has been elucidated by Baust and Gage [5].

Heat moves from warm to cold objects, so when a cold applicator (or "heat sink") is applied to a warm target a temperature differential results that drains heat from the tissue. As tissue is frozen, further thermal conduction is facilitated by the formation of what is known as an "ice ball." The size of the applicator as well as physical factors such as the temperature of the cryogen determines the size of the ice ball that can be created and how deep the thermal gradients develop within this ice ball. While the depth of freezing is less important in benign lesions, it is of crucial importance in the treatment of malignances. The rates of temperature fall, of rewarming, and of solute concentration, as well as the length of time the cells are exposed to below-freezing temperatures, are all important parameters [5].

If a tissue is frozen too slowly, the target tissue primarily produces extracellular ice crystals, whereas rapid cooling can produce intracellular ice, which is most destructive. Intracellular ice can shear the membrane of the cell and concentrate intracellular solutes. Repeating the freeze–thaw cycle produces additional destruction. The inflammatory response releases cytokines and may form useful antibodies to enhance an immune response [3, 5, 6].

Unassisted thawing to room temperature is preferable, but if excessive freezing has occurred in a location, thawing with a warmer object—even one's fingertip—can hasten thawing and lessen destruction. The solutes within tissue become more concentrated as the ice is forming, and this chemical insult adds to the destruction of cells and a greater oxidative insult to the tissue. During recrystallization a phenomenon occurs that is called "grain growth," which produces maximum damage to cells [6].

Maximum destruction occurs around −50 °C and is believed to be the preferred target temperature most used today, but in the 1960s it was felt that −20 to −25 °C was satisfactory for cancer cell destruction [6].

Varying degrees of apoptosis on the outer perimeter of tumors is observed at temperatures of −6 to −46 °C [7]. Liquid nitrogen is the preferred cryogen, capable of producing sufficient depth of freeze for cancer destruc-

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Table 7.1 Cryogens historically used in cutaneous surgery [4]

Agent	Temperature
Solid CO_2	−79.0 °C
Liquid N_2O	−88.5 °C
Helium	−185 °C
Liquid N_2	−195.8 °C

Adapted with permission from Abramovits [4]; © 2016.

tion [6]. Helium is also capable of this, but it is not readily available. Small superficial lesions may be removed with carbon dioxide and Freon gases, but these cryogens are not used in the United States for skin cancer treatment. Nitrogen oxide units available in Europe, and especially in France, have been engineered to develop low enough temperatures for the treatment of malignancies (Table 7.1).

Indications

Patients with multiple nonmelanoma skin cancers on the arms, legs, chest, face, and back have been successfully treated by cryosurgery or electrodesiccation, and a combination of the above with shave excision and curettage may prove most effective [8]. In general this involves electrodesiccation and curettage for lesions of minimal to moderate depth and cryosurgery for deeper lesions in the 3–4 mm range [9]. Excision or Mohs surgery is preferred for deeper lesions, especially around the nose, and for more aggressive subtypes such as micronodular, infiltrative, or metatypical basal cell carcinomas (BCCs). Immunosuppressed patients with multiple lesions respond well to both electrodesiccation and cryosurgery. Results vary depending on the tumor type, location, and skin color. It is important to consider the patient's preference once the techniques and potential outcomes have been explained to them. Patients who are keloid formers, have multiple cancers, are on anticoagulants, have a pacemaker, or are otherwise poor risks for more extensive surgery may be ideal candidates for cryosurgery [8, 10].

Contraindications

Cryosurgery should be avoided in patients with a history of cold anaphylaxis or cold urticaria if severe attacks have occurred. While cold urticaria is often not significant when small lesions are treated, a large tumor treated on the head or neck could produce severe periorbital edema or edema of the skin of the neck, and the patient must be forewarned. Contractures may develop around the eye, nose, and mouth, but in the author's experience these are rare. Relative contraindications include cryoglobulinemia, multiple myeloma, autoimmune diseases including pyoderma gangrenosum, Raynaud's disease, areas of vascular compromise, and darkly pigmented skin [6].

- Patient selection is of prime importance.
- Use excellent techniques for keloid formers.
- Discuss potential changes in skin: hypopigmentation, alopecia, uncommon numbness, scarring.
- Obtain informed consent.

The appropriate selection of patients and tumor sites is vitally important, as hypopigmentation and alopecia can occur. Transient numbness may also occur on the sides of the fingers, neck, or elbow. These potential side effects should be discussed before the patient signs an informed consent. A patient with pigmentary problems such as ephelides, lentigenes, or telangiectasia may be at greater risk for a less-than-satisfactory cosmetic result since the isolated area of pigment loss will be more obvious and

this should be discussed with the patient. Inform the patient that more scarring may result when treating a more extensive malignancy for palliation. Mohs surgery or excision may be a preferable option [9, 10].

Preoperative Considerations

A shave excision for biopsy may be performed prior to or at the time of freezing or electrodesiccation for diagnostic confirmation. The lateral margins may prove helpful in diagnostic considerations, especially in squamous cell carcinoma that is arising from an actinic keratosis. The shave, tumor type, and depth are all important in the final decision-making process. The shave followed by curettage allows an even better determination of depth and, with experience, one can make a reasoned judgment about whether a destructive technique, excision, imiquimod, or Mohs surgery would be the preferred method for definitive treatment. Another consideration in selecting a method is the proximity of a surgeon skilled in Mohs surgery. A long driving distance makes this selection more difficult for some older patients.

Discuss with patients the cure rates and potential side effects from cryosurgery. Since hypopigmentation is the most significant cosmetic change, explain to patients that this leaves the skin more like the color of sun-protected skin. If pigment is removed from photodamaged skin, a more obvious area is appreciated than if the skin is of lighter color. The same is true with telangiectasia in the malar region where freezing may leave a lighter area devoid of the finer superficial vessels. Atrophic scarring may be noted with deeper freezing. Caution patients regarding alopecia on scalp, eyebrow, and temple or other areas of cosmetic significance to the patient [10].

Equipment

The equipment primarily used in cryosurgery consists of a cotton swab, spray, and probe (Fig. 7.1). A swab with a large cotton reservoir may give a limited increase in depth of freeze but is not sufficient for the routine treatment of skin cancer. Since viruses can survive in liquid nitrogen, a change in swab between patients is recommended.

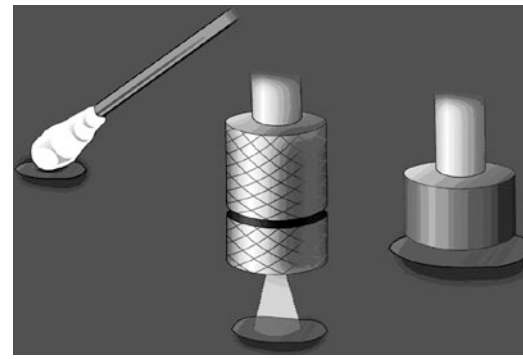

Fig. 7.1 Cotton swab, spray tip, and probe are all commonly used techniques in cryosurgery [11]. (Reprinted from Graham and Barham [11] © 2003, with permission from Elsevier)

While swab cryosurgery was used from the late 1940s for benign and precancerous tumors, it was never widely used for skin cancer because it reaches a depth of destruction of only 2–3 mm and is considered an inadequate heat sink for skin cancers [4]. Spray and probe freezing with liquid nitrogen are more effective and are used for skin cancers greater than 3–5 mm in depth. The most widely used instruments today are handheld spray and probe units that sit on table tops and are filled from a large Dewar holding liquid nitrogen. A 32-liter tank will last 2–4 weeks with moderate use, and the static holding time for the handheld sprays is 24 h and with moderate use during the day, 8–10 hours.

Techniques

With the spray technique, a central spray using intermittent pulses or spiral pattern starting at the center of a lesion and progressing to the periphery is customary.

A 1 cm lesion is best treated with an A tip or probe that fits the lesion. For larger lesions a paint brush pattern, passing back and forth over the lesion, is used. A 5 mm halo around the tumor is desired for skin cancer and a 2 mm halo for precancerous lesions. Spraying into an insulating cone using a cryoplate with openings of various diameters (4 mm, 7 mm, 9 mm, 12 mm) provides a deeper, more even depth of freeze similar to that obtained with a probe. The average spray time for a skin cancer 3 mm in depth is around *one minute*. Cryoprobe techniques are generally slower than sprays but result in a deeper depth-of-freeze to lateral spread-of-freeze ratio [11].

- Cryosurgery: field therapy.
- Three basic techniques are swab, spray, and probe.
- The three spray patterns are central, spiral, and paint brush.

Various sizes and shapes of cotton swabs, probe, and spray tips are available and can vary the shape of the ice ball produced in the target. While cotton swabs are not generally used for treatment of other than the most superficial skin cancers, probes are excellent where there is a well-defined small lesion, one in a difficult-to-reach location or one on the eyelid where there is a danger of getting liquid nitrogen sprayed into the eye. There are also large probes for the treatment of large deep tumors and in areas where palliation is the goal. An assortment of spray tips of varying sizes are available [12, 13, 14].

A plastic Jaeger retractor may be used to protect the eye as well as a plastic cone, but metal retractors should not be used around the eye when freezing due to possible adherence of the metal to the surrounding tissue [13]. (Fig. 7.3a)

Monitoring of Freeze Depth

Accurate assessment of freeze depth is critical in cryosurgery. An ice halo may be observed around the frozen tumor. The lateral progression of this halo corresponds to the depth of the freeze [14]. A 6 mm halo on the surface approximates a freezing depth of 6 mm. For most procedures, a single thermocouple needle is used and inserted at the border or under the tumor depending on tumor size (Fig. 7.2). This provides an accurate assessment of depth and quality of freeze and may be obtained from Brymill Cryogenic Systems. Clinical judgment determines the placement of the needles, but if in doubt the needle can

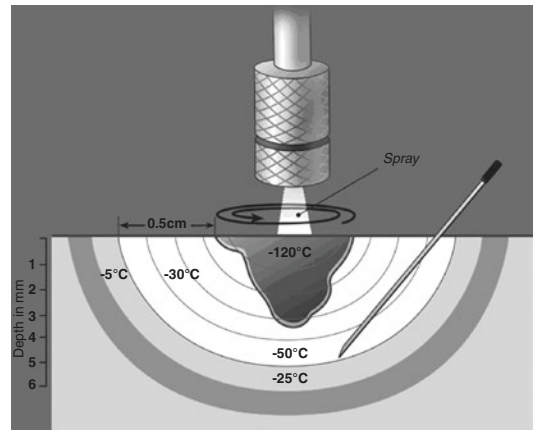

Fig. 7.2 Use of thermocouple needle allows clinician to monitor depth of freeze and clinically the extent of freeze around lesion by measuring the halo, which should be around 5 mm [11]. (Reprinted from Graham and Barham [11] © 2003, with permission from Elsevier)

be placed at the dermal subcutaneous border. With experience the need for the thermocouple becomes less [13, 14].

Basal Cell and Squamous Cell Carcinoma Cure Rates

Cryosurgery offers cure rates in the 96–98% [15, 16] range when appropriately selected lesions are treated. Proper selection and attention to detail will produce the highest cure rate. Reported cure rates of longer-term data for one experienced cryosurgeon utilizing this method on low-risk basal cell carcinomas reach 99% after a 5-year follow-up on 522 BCCs [17].

To obtain cure rates in the range of 96–98%, follow well-established criteria. Outline the border of the lesion with a marking pen so that the progression of the ice ball can be appreciated. When the area becomes white, the boundary of the tumor is no longer visible; so outlining the lesion with a surgical marking pen prior to infiltrating with local anesthetic is crucial. The elevated portion of the tumor is removed by shave or scoop biopsy and submitted for pathology. When cryosurgery is used, many cryosurgeons prefer to curette the base of the lesion prior to freezing.

If a novice at using cryosurgery, use a thermocouple needle implanted under the deepest part of the tumor and freeze using the spray or probe until a 5 mm halo of ice is obtained around the tumor. This will most often require a freeze time of approximately 60 s of intermittent freeze [18, 19].

Cryosurgery is a field therapy with a target temperature of −50 °C, which may be measured by monitoring depth of the freeze and temperature. For superficial basal cell carcinomas on the back, a single freeze is adequate unless the first thaw time is short of the 60 s, in which case a second freeze–thaw cycle should be utilized. Record the halo thaw time (HTT) and the clinical thaw time (CTT) of the entire site. The HTT ranges from 60 to 120 s, the CTT 2½–5 min [19].

Illustrative Case 7.1

A 67-year-old white male with a biopsy-proven basal cell carcinoma in the medial canthus 5 mm is treated by cryosurgery (Fig. 7.3).

Times used for *Case 7.1*:

- *Cycle 1*
- Freeze time (FT): 1′ 1″
- HTT: 1′ 28″
- CTT 3′ 12″
- *Cycle 2*
- FT: 1′ 2″
- HTT: 1′ 46″
- CTT: 3′ 32″

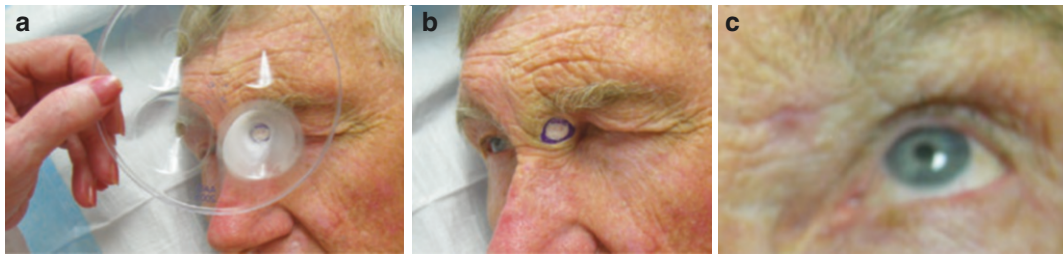

Fig. 7.3 A 67-year-old white male with a biopsy-proven basal cell carcinoma in the medial canthus is treated by cryosurgery. (**a**) A plastic cone is used to protect the eye and confine the spray. (**b**) A 5 mm halo of frozen tissue around the tumor after freezing. Caution patient regarding edema and weeping of the site as well as periorbital edema, which may be observed for 3–5 days postcryosurgery (**c**) At follow-up 3 months later, the site is well healed

Illustrative Case 7.2

A 69-year-old, white female with a biopsy-proven squamous cell carcinoma (SCC) is treated with shave excision, curettage, and cryosurgery (Fig. 7.4).

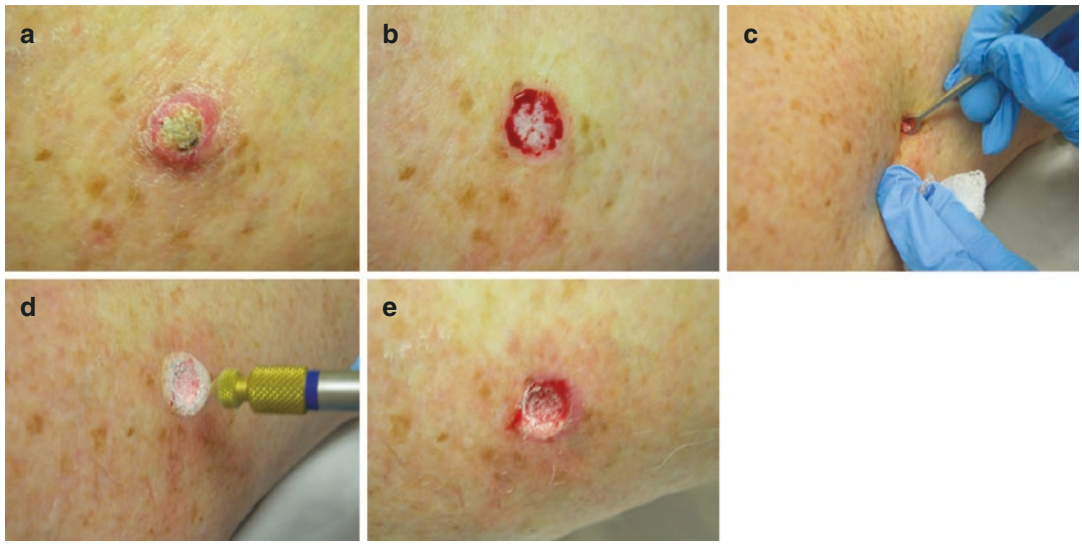

Fig. 7.4 A 69-year-old, white female with a biopsy-proven squamous cell carcinoma (SCC). (**a**) *Right thigh* shows an erythematous nodule with a keratin-filled center. (**b**) After shave excision, *white* base of center of tumor remains. (**c**) With curettage the rest of the friable part of the tumor is removed. (**d**) Area treated by cryosurgery. (**e**) Appearance after 1-min freeze time. Halo thaw time 1 min 33 s and clinical thaw time 4 min 32 s

Illustrative Case 7.3

A 79-year-old white male, with a biopsy-proven basal cell carcinoma on his right forehead (Fig. 7.5) is treated with cryosurgery.

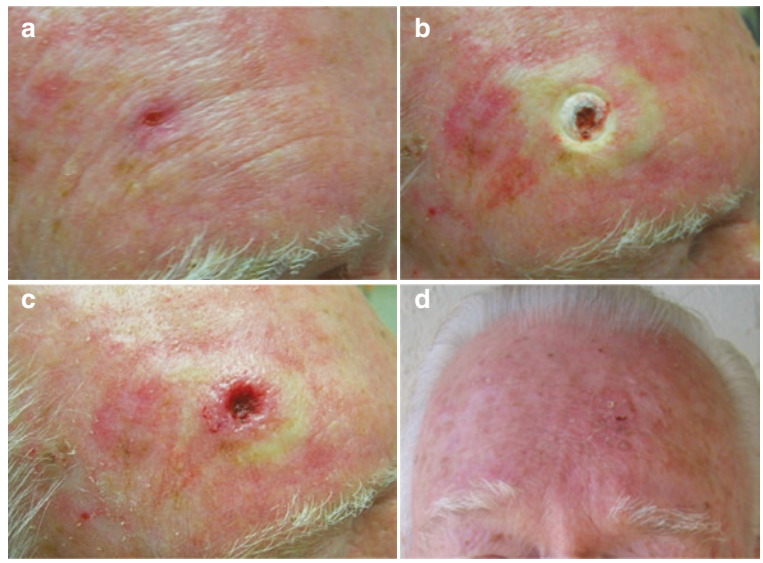

Fig. 7.5 (**a**) A 79-year-old white male, with a biopsy-proven basal cell carcinoma on his right forehead is treated with cryosurgery. (**b**) The tumor is frozen. (**c**) Appearance immediately after cryosurgery. (**d**) At follow-up 2 months later the area has healed well

Times used for *Case 7.3*:

- *Cycle 1*
- First FT: 1′
- HTT: 1′ 10″
- CTT: 2′
- *Cycle 2*
- Second FT: 1′
- HTT: 2′ 30″
- CTT: 5′

Illustrative Case 7.4

A lesion clinically suspicious for a BCC is noted on the upper back of a 55-year-old muscular male patient (Fig. 7.6). The area is treated with cryosurgery as the lesion looks superficial and surgery would necessitate a long scar, which would probably spread in this area.

For deeper tumors, most cryosurgeons recommend a double freeze–thaw cycle, with the second cycle following the thawing of the first cycle [18, 19]. Local anesthesia may allow longer treatment and thaw times. For a list of diagnoses that can be appropriately treated by cryosurgery see the guidelines of care for cryosurgery (Table 7.2).

Treatment Pearls

- "Fast Freeze, Slow Thaw."
- Repeat freeze–thaw for additional destruction.
- Monitoring of depth dose and temperature is important.
- Target temperature is − 40 to −50 °C.
- Hypopigmentation expected if freeze over 20–30 s.
- Alopecia may result following 20+ second freeze.

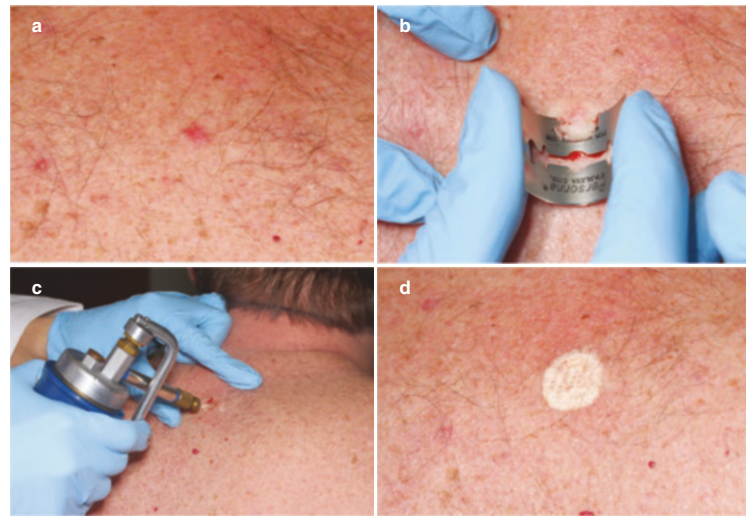

Fig. 7.6 A lesion clinically suspicious for a BCC on the upper back of a 55-year-old male. (**a**) Appearance prior to cryosurgery. (**b**) Shave biopsy is performed. (**c**) A single freeze is performed as the lesion is superficial and on the back. (**d**) Appearance following cryosurgery with 5 mm rim of freezing obtained

Table 7.2 Lesions that can appropriately be treated with cryosurgery [20]

Precancerous lesions or tumors of uncertain behavior	Malignant lesions
Actinic cheilitis	Basal cell carcinoma
Actinic keratosis	Bowen's disease (carcinoma in situ)
Keratoacanthoma	Kaposi's sarcoma
Lentigo maligna	Squamous cell carcinoma
Bowenoid papulosis	Actinic keratosis with squamous cell carcinoma, adenoid squamous cell carcinoma, de novo squamous cell carcinoma

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Leukoplakia and Actinic Cheilitis

Freeze with a spray applied in a paint brush manner.

> If the entire lip requires treatment, it is best to treat one half of the lip at each of two sessions, with a freeze time of 10–15 s [18].

Keratoacanthoma

First biopsy to exclude invasive squamous cell carcinoma by shaving the exophytic portion and then freeze the base for 30–60 s. Holt cleared seven of eight keratoacanthomas using a 30–60-s freeze time with a 5 mm halo around the lesion [21].

Postoperative Care

Shortly after the completion of freezing, an erythematous and/or urticarial response may be noted around the lesion. A deep blistering reaction may occur resulting in edema and, within 12–24 h, bullae formation followed by weeping of the wound for several days. An eschar forms in approximately 2 weeks. This may be adherent to the underlying tissue for up to 1 month in most locations and on the back or lower leg for 1–3 months. Before complete healing occurs, the eschar must separate and peel away. If delay in healing occurs debridement of the eschar can be performed. Daily cleansing with soap and water may be all that is necessary for most cryosurgical wounds.

- Cryosite acts as its own biologic dressing.
- Cleanse site with soap and water daily.
- Eschar present for up to 1 month—occasionally on the back and legs it may last 2–3 months.
- Debride eschar only if not separating after 4–8 weeks [18].

Patients may resume their daily activities as tolerated, including bathing and swimming. The site acts as its own biological dressing and does not usually need to be bandaged. In fact, bandaging can adhere to the wound, resulting in premature removal of the eschar and a longer healing time [19].

Patients should be followed carefully for 2 years postoperatively to check for recurrence.

Long-Term Follow-Up Studies

In addition to previous follow-up series [15–17], other more recent long-term follow-up series, with and without curettage, attest to the effectiveness of cryosurgery. These include follow-up studies of curettage and cryosurgery for midfacial BCC [22, 23] and auricular nonmelanoma skin cancers [24]. Follow-up series of cryosurgery for the treatment of periocular nonmelanoma skin cancers have also been reported [25].

Immunocryosurgery

In more recent studies of immunocryosurgery for non-superficial basal cell carcinomas $\leq$20 mm in maximum diameter, followed by 5 years by Gaitanis and Bassukas, an enhanced clearance rate felt to be due to the additive effect of imiquimod and cryosurgery was observed [26]. This combination has also been used to treat periocular basal cell cancers [27].

Summary

Cryosurgery is a safe, efficient, and effective procedure for the treatment of many benign, premalignant, and malignant skin lesions. Physicians must be able to distinguish normal reactions to

cutaneous freezing from sequelae that require intervention. Physicians who wish to train in cryosurgery are encouraged to do so under the supervision of a person experienced in this technique.

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Chapter 8
Optimizing Surgical Outcomes

Thomas Stasko, Deborah F. MacFarlane, and Amy S. Ross

To optimize outcomes associated with cutaneous procedures the surgeon must consider multiple factors. Many of these factors should be addressed prior to the start of surgery and others require attention during or after the procedure. Recognition of these factors can aid in the meticulous planning and attention to detail necessary to obtain the best outcome following surgical treatment of skin cancer.

> It must always be remembered that the primary goal of surgical skin cancer management is complete eradication of the tumor. An outstanding initial cosmetic result is of no avail if the tumor recurs.

There are several approaches to the surgical removal of skin cancer. The approach may differ depending on factors such as tumor type, tumor location, patient health, and health care system limitations. Because of the paramount goal of complete tumor removal, a commonly used method for removal of skin cancers is Mohs micrographic surgery (MMS) [1]. The appeal of this approach is its high cure rate and cost-effectiveness [2].

There are situations in which MMS may not be the most appropriate method of skin cancer removal (see Chap. 11). Tumors that require permanent histological sections for optimum evaluation or tumors that are well demarcated may be best approached with standard surgical excision. It is important to note that until there is pathologic confirmation that a malignant tumor is completely removed, it is inappropriate to repair the resulting defect with a complex flap or graft. If the pathology specimen turns out to be positive for tumor at the margins, closing a wound with a flap or graft may prevent the surgeon from identifying the location of residual tumor in subsequent surgeries.

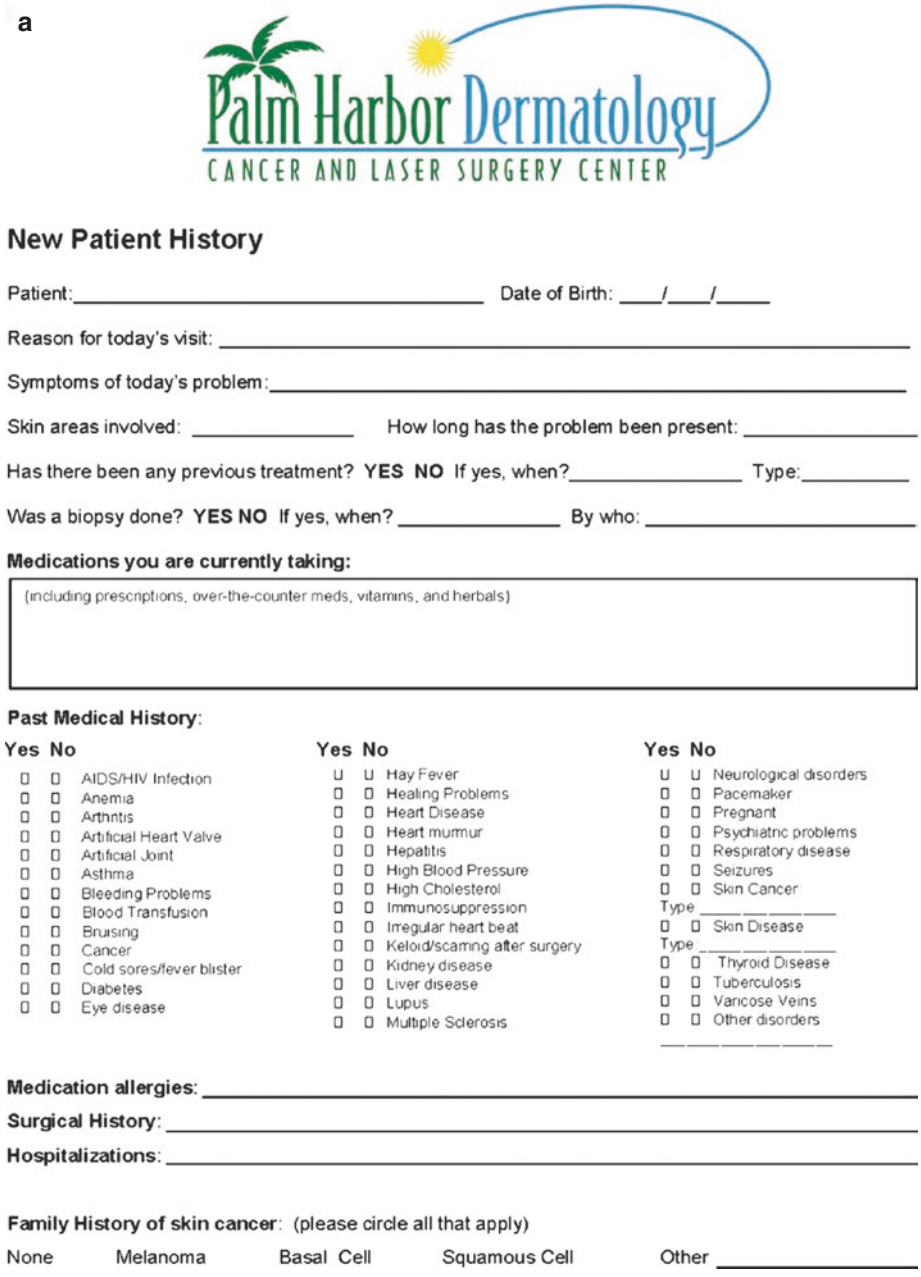
The dermatologic surgeon must also recognize that there are situations where he or she may not be the most appropriate physician to be treating the patient. The best outcome could be provided by another specialist (see Chap. 20). At some institutions, melanomas greater than 0.8 mm in depth and Merkel cell carcinomas are evaluated by the surgical oncologist for possible inclusion of a sentinel lymph node biopsy at the time of excision. In some circumstances radiation therapy may be the best option for a large tumor in an elderly patient or for an in-transit metastasis. The dermatologic surgeon must be well versed in all aspects of cutaneous oncology to select the proper treatment for the best possible outcome.

Once the dermatologic surgeon has determined that a surgical procedure is the best approach to the treatment of a tumor, there are several steps that will help to optimize the outcome of the procedure. A thorough preoperative assessment and appropriate surgical planning followed by excellent intraoperative technique and vigilant postoperative care are necessary to yield an optimal outcome.

D. F. MacFarlane (ed.), *Skin Cancer Management*, https://doi.org/10.1007/978-3-030-50593-6_8

Preoperative Considerations

All patients considered for dermatologic surgery should be questioned regarding pertinent medical history. Commonly this information is first recorded by the patient and then confirmed and elaborated on by a nurse or physician extender. The physician then utilizes this information to direct their history taking and examination. Figure 8.1a, b shows an example of a standard medical information form. This form may be customized to meet the needs of a specific practice population but should cover the historical factors relevant to all of the considerations listed as follows.


a

Palm Harbor Dermatology
CANCER AND LASER SURGERY CENTER

New Patient History

Patient:_____ Date of Birth: ___/___/_____

Reason for today's visit: _____

Symptoms of today's problem:_____

Skin areas involved: _____ How long has the problem been present: _____

Has there been any previous treatment? **YES NO** If yes, when?_____ Type:_____

Was a biopsy done? **YES NO** If yes, when? _____ By who: _____

Medications you are currently taking:

(including prescriptions, over-the-counter meds, vitamins, and herbals)

Past Medical History:

Yes	No		Yes	No		Yes	No	
☐	☐	AIDS/HIV Infection	☐	☐	Hay Fever	☐	☐	Neurological disorders
☐	☐	Anemia	☐	☐	Healing Problems	☐	☐	Pacemaker
☐	☐	Arthritis	☐	☐	Heart Disease	☐	☐	Pregnant
☐	☐	Artificial Heart Valve	☐	☐	Heart murmur	☐	☐	Psychiatric problems
☐	☐	Artificial Joint	☐	☐	Hepatitis	☐	☐	Respiratory disease
☐	☐	Asthma	☐	☐	High Blood Pressure	☐	☐	Seizures
☐	☐	Bleeding Problems	☐	☐	High Cholesterol	☐	☐	Skin Cancer
☐	☐	Blood Transfusion	☐	☐	Immunosuppression	Type _____		
☐	☐	Bruising	☐	☐	Irregular heart beat	☐	☐	Skin Disease
☐	☐	Cancer	☐	☐	Keloid/scarring after surgery	Type _____		
☐	☐	Cold sores/fever blister	☐	☐	Kidney disease	☐	☐	Thyroid Disease
☐	☐	Diabetes	☐	☐	Liver disease	☐	☐	Tuberculosis
☐	☐	Eye disease	☐	☐	Lupus	☐	☐	Varicose Veins
			☐	☐	Multiple Sclerosis	☐	☐	Other disorders
						_____		

Medication allergies: _____

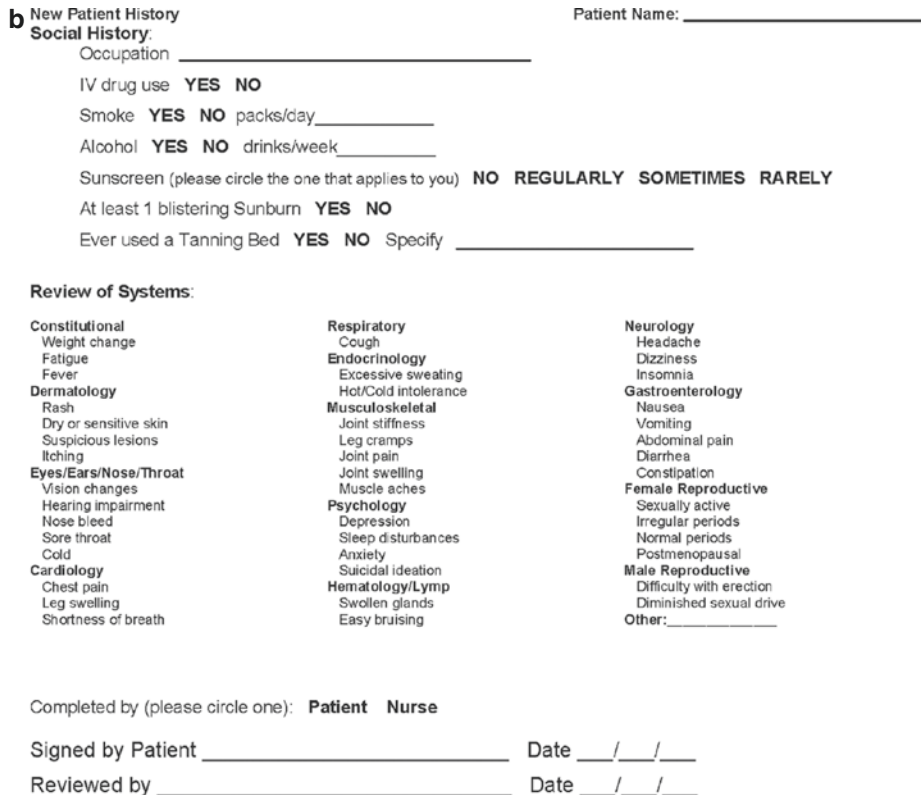
Surgical History: _____

Hospitalizations: _____

Family History of skin cancer: (please circle all that apply)

None Melanoma Basal Cell Squamous Cell Other _____

Fig. 8.1 Example of a medical information form: (**a**) page one and (**b**) page two



b New Patient History
Patient Name: _____
Social History:
Occupation _____
IV drug use YES NO
Smoke YES NO packs/day_____
Alcohol YES NO drinks/week_____
Sunscreen (please circle the one that applies to you) NO REGULARLY SOMETIMES RARELY
At least 1 blistering Sunburn YES NO
Ever used a Tanning Bed YES NO Specify _____

Review of Systems:

Constitutional
Weight change
Fatigue
Fever
Dermatology
Rash
Dry or sensitive skin
Suspicious lesions
Itching
Eyes/Ears/Nose/Throat
Vision changes
Hearing impairment
Nose bleed
Sore throat
Cold
Cardiology
Chest pain
Leg swelling
Shortness of breath

Respiratory
Cough
Endocrinology
Excessive sweating
Hot/Cold intolerance
Musculoskeletal
Joint stiffness
Leg cramps
Joint pain
Joint swelling
Muscle aches
Psychology
Depression
Sleep disturbances
Anxiety
Suicidal ideation
Hematology/Lymp
Swollen glands
Easy bruising

Neurology
Headache
Dizziness
Insomnia
Gastroenterology
Nausea
Vomiting
Abdominal pain
Diarrhea
Constipation
Female Reproductive
Sexually active
Irregular periods
Normal periods
Postmenopausal
Male Reproductive
Difficulty with erection
Diminished sexual drive
Other:_____

Completed by (please circle one): Patient Nurse
Signed by Patient _____ Date ___/___/___
Reviewed by _____ Date ___/___/___

Fig. 8.1 (continued)

Bleeding Tendency

Excessive bleeding during or after a surgical procedure may result in a less-than-optimal outcome. Identifying patients at risk for increased bleeding allows the surgeon to take corrective action prior to the procedure when possible and to be prepared to utilize additional tools to minimize any negative effects associated with excessive bleeding.

Exaggerated bleeding is most often related to extrinsic causes (medications and dietary supplements) but may also be related to intrinsic causes such as inherited deficiencies in coagulation factors or problems with platelet production, function, or survival.

Anticoagulant use in today's patient population is high. A new class of blood thinners referred to as NOACs (novel oral anticoagulants) have been increasingly utilized in place of or in addition to more traditionally used blood thinners [3–6]. Table 8.1 lists the more commonly prescribed anticoagulants, their mechanism of action, and duration of effect. Many of these anticoagulants are prescribed for use by physicians after cardiac events, DVT, pulmonary embolism, or stroke; however, many patients are on low-dose antiplatelet therapy for primary prevention. Historically, many surgeons were hesitant to operate on patients taking blood thinners; however, the literature supports the continuation of prescribed medications to prevent potentially deadly consequences [7–10]. There are numerous cases of thromboembolic stroke, pulmonary emboli, cerebral emboli, myocardial infarction, and deep venous thromboses reported after the discontinuation of anticoagulation therapy, with severe consequences in some cases [11–14].

Table 8.1 Prescription blood thinners

Medication	Mechanism of action	Recommendation	Treatment/reversal
Aspirin	Irreversibly blocks thromboxane A_2	If for secondary prevention, discontinue 10 days prior to surgery	None
Clopidogrel bisulfate	Irreversible blockade of the adenosine diphosphate (ADP) receptor on platelet cell membranes	Continue, with particular attention to intraoperative hemostasis	Platelet transfusion
Warfarin	Competitively inhibits vitamin K_1-2,-3 epoxide reductase	Continue. Confirm INR <3.0 within 48 hours of surgery	Vitamin K, fresh frozen plasma
Heparin	Inhibits factor Xa	Discontinue 6 hours prior to surgery	Protamine sulfate
NSAIDs (ibuprofen, naproxen, etc.)	Inhibit cyclooxygenase pathway and prostaglandin synthesis	Discontinue 3 days prior to surgery	None
Apixaban	Direct inhibitor of free and clot-bound factor Xa	Continue with particular attention to intraoperative hemostasis	Andexanet alfa [5]
Rivaroxaban	Binds directly and reversibly to factor Xa via the S1 and S4 pockets	Continue with particular attention to intraoperative hemostasis	Andexanet alfa [5]
Edoxaban	Selective inhibitor of factor Xa Inhibits free factor Xa and prothrombinase activity and inhibits thrombin-induced platelet aggregation	Continue with particular attention to intraoperative hemostasis	Andexanet alfa [5]
Dabigatran	Direct thrombin inhibitor that inhibits free and fibrin-bound thrombin	Continue with particular attention to intraoperative hemostasis	Idarucizumab [6]

The risk of intraoperative and postoperative bleeding must be balanced with the risk of the patient developing a thromboembolic event if anticoagulation is discontinued

If the patient can safely discontinue aspirin, it should be withheld for 10 days prior to surgery. Clopidogrel, warfarin, and NOACs are often found to be unsafe to discontinue. Unfortunately, in the case of clopidogrel and NOACs, there is no commonly performed blood test that will inform the surgeon of the degree of anticoagulation present.

For patients on warfarin, if the physician managing the anticoagulation therapy feels the patient can safely be without therapy for a short period, it is discontinued 48–72 hours prior to the procedure and restarted the evening of the procedure or the following morning. This most commonly occurs in patients on warfarin as prophylaxis for atrial fibrillation. For patients in whom discontinuation of warfarin therapy is not advisable, such as patients with mechanical heart valves or a recent history of embolic stroke, the authors usually ask that an international normalized ratio (INR) value be checked within 24 hours of surgery. In general, the authors will operate on individuals with an INR less than or equal to 3.0. In patients with a long-term history of stable anticoagulation a more remote INR may suffice. Although these patients still require extra precautions during and after surgery and may be subject to more extensive ecchymosis, cutaneous procedures can usually be successfully performed in these circumstances.

Many patients are on nonprescription supplements that may increase the chance of bleeding and subsequent complications. There are reports of patients on a variety of supplements developing bleeding complications such as subdural hematomas, hemorrhagic stroke, and vaginal or gingival bleeding unrelated to cutaneous surgery [15].

Some of these supplements and their reported indications for use are listed in Table 8.2. Given that well over 50% of the adult population has

Table 8.2 Nutritional supplements to avoid in dermatologic surgery

Supplement	Effect	When to discontinue
Vitamin E	Inhibits platelets	2–3 weeks before
Garlic	Inhibits platelets	At least 7 days before
Ginger (large doses only)	Inhibits platelets	At least 36 hours before
Ginkgo biloba	Inhibits platelets	At least 36 hours before
Ginseng	Inhibits platelets	At least 7 days before
Ephedra	May react with epinephrine (increases heart rate, blood pressure)	At least 24 hours before
Feverfew	Inhibits platelets	2–3 weeks before

reported supplement usage [16, 17] all dermatologic surgery patients should be questioned on the use of these products. Patients should, in general, be advised to discontinue these supplements in preparation for surgery.

One of the most frequently encountered supplements is vitamin E. It is commonly advocated for use in cardiovascular disease prevention, as well as for cancer prevention. It inhibits platelet aggregation and secretion and may cause bleeding [18]. Vitamin E is frequently taken with other supplements, such as garlic, ginseng, and *Ginkgo biloba*, which may also interfere with platelet function. These medications should be discontinued prior to cutaneous surgery [15].

Ideally, patients with intrinsic clotting problems should be identified preoperatively and managed in coordination with hematology. The etiology of intrinsic bleeding problems may range from conditions such as hepatic disease to inherited bleeding disorders such as Von Willebrand disease (VWD). An estimated 0.1–1% of the population is affected by VWD [19, 20], making it very likely that a patient with this problem will be encountered in the average practice. Although 20% of patients with VWD have postoperative bleeding as a complication of their disease, there are few standard guidelines for their perioperative management during dermatologic surgery [21, 22]. Consultation with the treating hematologist should be completed before there is any decision for surgery, and consideration of pretreatment with 1-desamino-8-arginine vasopressin (DDAVP) or plasma concentrates should be made.

Patients with low platelet counts secondary to idiopathic thrombocytopenic purpura, myeloproliferative disorders, or other extrinsic causes such as chemotherapy represent a special population. Although there is no data specifically addressing cutaneous surgery in patients with low platelet counts, informed decisions regarding care may be made by reviewing the surgical literature. Thrombocytopenia is strictly defined as a platelet count less than 140,000/μl. The otolaryngology literature suggests surgery with minimal anticipated blood loss may be performed with platelet counts as low as 20,000/μl. However, a platelet count greater than 50,000/μl should be present if more extensive surgery is anticipated. This count should be maintained for 3–4 days following surgery [23].

Wound Healing

There are three phases of wound healing (Fig. 8.2). Interruption of any of these phases of healing can result in a less-than-optimal outcome. Medications and chronic diseases are the most

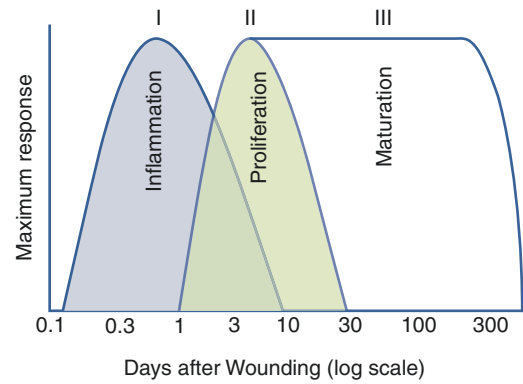


Fig. 8.2 Phases of wound healing

commonly encountered factors that influence wound healing. Anti-inflammatory medications including glucocorticoids are known to interrupt wound healing and are associated with infection and increased risk of dehiscence [24]. Despite the possibility of impaired wound healing and the need for prolonged wound care, these medications are continued during surgery because the risk of discontinuation is greater than the risk of continuation. Retinoids have been associated with keloidal scarring following some procedures. This outcome has not been found to be true following Mohs surgery, and retinoids may be continued through this type of surgery [25].

Several patient populations historically have increased difficulty with wound healing. Most commonly encountered are patients with diabetes and the frail elderly. Usually there is no reason to defer a needed procedure on these patients, unless they are simply unable to tolerate the surgery. In these patients attention to postoperative care is essential to optimize surgical outcome. For patients unable to care for their own wounds, nursing care should be arranged. In rare cases, hospitalization may be necessary following surgical removal of skin cancer. Most often this is following extensive Mohs surgery prior to repair; however, it may be reasonable to hospitalize frail elderly patients with risk factors for excessive bleeding following a long outpatient procedure. There is published data that suggest that dermatologic surgery on patients greater than 80, or even 90 years of age, is safe with few adverse outcomes [26, 27].

History of Hypertrophic Scar or Keloid Formation

Patients with a history of hypertrophic scar or keloid formation should be prepared for a possible similar outcome following skin cancer surgery. This is particularly true of the "V distribution" (Fig. 8.3) on the trunk (shoulders, central chest, upper arms, and upper back) where hypertrophic scarring and keloids tend to occur more often. Close postoperative follow-up and early intervention may allow the surgeon to minimize the adverse outcome of keloid formation following surgery. Strategies to minimize postoperative keloid formation include intralesional steroid injections, as well as pressure devices, and occlusive dressings [28]. Hypertrophic scars may be regarded in a similar manner preoperatively, with the recognition that the problem may be self-limiting and intervention less imperative.

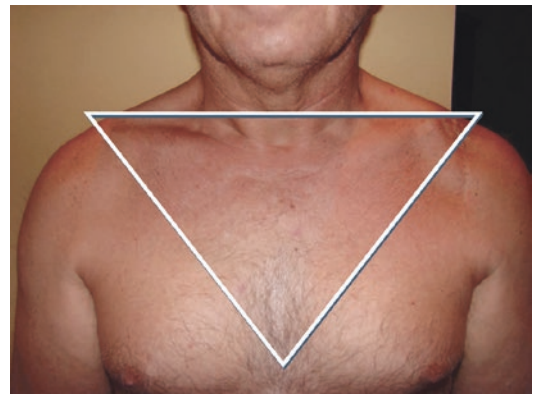


Fig. 8.3 "V" distribution at risk for keloid formation

Prophylactic Antibiotics and Antiviral Medication

Prophylactic antibiotics in dermatologic surgery are used for either prevention of endocarditis or prosthesis infection or for prevention of surgical site infection. Almost all the lesions cutaneous surgeons encounter are considered clean or clean contaminated and therefore do not require prophylaxis unless the patient has a prosthetic valve, an unrepaired congenital heart abnormality, or a history of endocarditis. It is important to consider the type of wound being manipulated when deciding whether or not antibiotics are appropriate (Table 8.3).

In 2017, the American Heart Association (AHA) revised the recommendations for antibiotic prophylaxis for endocarditis [29]. In the highest-risk patients, prophylaxis against endocarditis is reasonable for procedures involving oral sites, the respiratory tract, or infected skin

Table 8.3 Wound classification

Type	Class	Characteristics	Risk of infection
I	Clean	Noncontaminated skin Aseptic technique	1–4%
II	Clean contaminated	Location: gastrointestinal, respiratory, or genitourinary without gross contamination Minor breaks in aseptic technique	5–15%
III	Contaminated	Location: gastrointestinal, respiratory, or genitourinary with gross contamination Major breaks in aseptic technique	6–25%
IV	Dirty and/or infected	Foreign body contamination, wound with acute bacterial infection, ± pus	>25%

structures. The American Academy of Orthopedic Surgeons offers additional guidelines for antibiotic pretreatment for dental and urologic patients with total joint replacements [30]. Antibiotic prophylaxis is recommended for high-risk patients with joint prostheses undergoing procedures on oral sites.

In the most recent advisory statement of antibiotic prophylaxis in dermatologic surgery, coverage is recommended for patients with high-risk cardiac conditions and a defined group of patients with prosthetic joints at high risk for hematogenous infection when the surgical site is infected or when the procedure involves breach of the oral mucosa. While decisions regarding antibiotic prophylaxis should be made after consideration of each patient's specific case, there is recognition of the need to cautiously use these agents given the growing problem of bacterial resistance [31].

Regardless of the recommendations available in current published guidelines, some patients will request prophylaxis. Most often it is because they were once told to take the medication for a "murmur." Even with education, these patients feel very strongly they should take the medication and often do so with or without the dermatologic surgeon's advice.

Prophylactic antiviral therapy is frequently utilized in patients with a history of frequent flares of herpes labialis (greater than three per year) undergoing facial resurfacing procedures. The risk of reactivation of herpes with resulting spread in incisional surgery near the mouth is probably much less than would be inferred from case reports, and no randomized controlled studies exist to support or refute the use of prophylaxis. Oral acyclovir at a dose of 200 mg five times a day—starting 2–5 days prior to the procedure and continuing for 5 days postoperatively or until the skin has re-epithelialized—may be considered for patients considered at particularly high risk for complications from reactivation and spread; however, a herpes simplex eruption may also be effectively treated by the initiation of antiviral therapy at the first sign of reactivation [32, 33]. Alternatively, famciclovir or valacyclovir may be used to reduce dosing frequency.

Allergies

A comprehensive review of allergies is necessary for all first-time patients as well as return patients. Although all medication allergies are important, dermatologic surgeons are most interested in allergies to anesthesia, antibiotics, and pain medications. Patients often report a history of allergy to penicillin, epinephrine, and codeine, which are not true allergies, but adverse reactions. It is important to explore further and determine the nature of the reaction to the medication. Depending on the patient's ability to recall details of the allergic episode, the physician may use his or her judgment in administering the medication.

True allergies to lidocaine are rare, but do exist. They constitute less than 1% of the total adverse reactions to local anesthesia [34]. Despite this small population of truly allergic individuals, a study detailed that up to 69% of dermatologists report seeing patients presenting

with an alleged allergy [35]. These allergies are most often to the ester class of local anesthetics, which is metabolized to para-aminobenzoic acid (PABA), a highly allergenic product in some individuals. The commonly used anesthetic lidocaine is an amide and has a much lower potential to cause an allergic reaction. Patients who have developed a reaction to esters most often may be treated with amide anesthetics without problems (see Chap. 9).

Local anesthesia may be obtained in patients with allergies to amides and ester anesthetics by the injection of bacteriostatic saline. Benzyl alcohol, present as a bacteriostatic agent, acts as a local anesthetic. This relatively painless substitute may be sufficient for a quick punch or superficial shave biopsy; however, its duration is limited to a few minutes and the anesthesia is not profound. It is usually not sufficient for longer, more involved surgical procedures.

Diphenhydramine has been evaluated for its ability to produce local anesthesia. It does produce significant local anesthesia, but the duration is significantly less than that of lidocaine, it is more painful to inject, and necrosis has been reported after local infiltration [36]. Because of the lack of excellent alternatives to lidocaine for involved or extensive procedures, referral to an allergist for evaluation of an uncertain lidocaine allergy may be necessary. General anesthesia may be appropriate for extensive procedures in the lidocaine allergic patient.

Epinephrine, although reported by many patients to cause an allergic reaction, most often causes minor palpitations due to sensitivity to the drug. Diluting epinephrine to up to 1:500,000 limits such reaction in most patients but still provides a reasonable degree of vasoconstriction. For the very sensitive patient, especially those with concomitant cardiac compromise, total avoidance of epinephrine may be necessary.

Patients commonly voice an allergy to penicillin and other antibiotics. On questioning, again, many of these reactions turn out to be adverse reactions, not allergies. Obviously, drugs that have induced allergies or severe adverse reactions should be avoided, if possible, in that individual. Antibiotics are not routinely required in dermatologic surgery; however, if required, the most commonly utilized class of medications is the cephalosporins. Although the risk of cross-reactivity in patients with an allergy to penicillin is low, estimated at 4.4% in a recent review [37], it is prudent for the physician to avoid this class of antibiotics in patients with documented penicillin allergy.

Implantable Cardiac Devices

Implantable cardiac devices, including pacemakers and defibrillators, are becoming more common in the population of patients with skin cancer. An estimated 4% of Mohs surgery patients have implantable cardiac devices [38]. Electrosurgical instruments used for treatment and hemostasis in dermatologic surgery have the potential to interfere with cardiac devices, and therefore preoperative assessment is crucial in order to ensure that a safe method of hemostasis is employed during the surgery. Electrocautery has been shown to be safe in patients with pacemakers and implanted defibrillators [39]. Handheld disposable electrocautery pens are convenient and often sufficient for hemostasis in this patient population; however, the heat is not adjustable as with tunable, electrically powered thermal cautery units. As a result, the high temperature of disposable units may lead to sectioning of the tissue, increased tissue destruction, and poor hemostasis. Bipolar forceps are also considered safe; however, an electrical current is produced, and cardiac monitoring should be available.

Patient Expectations

Proper informed consent prior to beginning any surgical procedure is essential. Figure 8.4a, b demonstrates a standardized consent form that is reviewed by the nurse and confirmed by the physician prior to starting any surgical procedure. The review of the procedure by multiple team members and at multiple times helps ensure that the patient is well educated about the procedure and

a

Palm Harbor Dermatology
CANCER AND LASER SURGERY CENTER

INFORMED CONSENT: MOHS MICROGRAPHIC SURGERY& REPAIR

Patient Name: _____ **Patient Date of Birth**: _____

This form is designed to provide you with the necessary information that you will need to make an informed decision on whether or not you wish to have Mohs Surgery performed. All of the information provided in this form will be or has been reviewed with you by the physician. If you have any questions please do not hesitate to ask us. Do not sign this form until you are instructed to do so.

WHAT ARE THE POTENTIAL COMPLICATIONS AND SIDE EFFECTS OF SKIN SURGERY?

1. **PAIN:** Some mild discomfort is experienced when the area is first anesthetized with the numbing medication. You may experience some mild discomfort during the procedure if the numbing medication has worn off in a particular location. This is easily remedied by immediately giving more anesthetic in that area. After the procedure, some discomfort will be experienced at the surgical site. This is easily controlled with pain medications for a few days.
2. **INFECTION:** Any time that the skin is injured an infection is possible. The rate of infection is very low. Some patients will receive postoperative antibiotics to prevent an infection. If you feel that your wound is infected after surgery please call our office immediately.
3. **BLEEDING:** When you leave our office you will have a pressure bandage applied to your wound. Bleeding is always possible after surgery. Most cases of postoperative bleeding are easily stopped by applying pressure for 20 minutes over the site. If this does not work please call our office immediately.
4. **SWELLING:** After surgery you should expect some swelling where your surgery was performed and around the wound as well.
5. **HEMATOMA:** A hematoma is a collection of blood that forms under the skin. This results from bleeding that occurs after the surgery. A "lump" forms under the skin, which represents the dried blood. If this occurs call our office immediately.
6. **SCAR FORMATION:** Any time that the skin is injured a scar will form. Some scars are more noticeable than others, but a scar is always present. A scar will form after your surgery. Hypertrophic and keloidal scarring are possible. If you have a history of bad scarring please advise us at the time of your visit. The cosmetic appearance following surgery is unpredictable.
7. **WOUND DEHISCENCE:** This means that your wound has broken back open after it has been repaired with sutures. It is very important to take it easy after your surgery so that unnecessary strain is not placed on the wound. This is an uncommon complication.
8. **FAILURE OF FLAP OR SKIN GRAFT:** After your surgery is completed we will need to repair the wound. Some patients are repaired with either a flap or skin graft. A flap is when skin is borrowed from a nearby site to close the defect. A skin graft is when a piece of skin is taken from one site and transplanted to another. A possible complication is the failure of either of these to take at the new site. Smoking is a documented risk for this complication. If you are a smoker it is recommended that you discontinue smoking for one week before and after the procedure.
9. **TEMPORARY OR PERMANENT NERVE DAMAGE:** The primary goal of your surgery is to completely remove the tumor. In order to accomplish this, it is sometimes necessary to damage a nerve. Nerve damage can be temporary or permanent. Recovery usually takes 6 months or more, and rarely can require additional surgery. Nerve damage may be limited to a loss of sensation or may include paralysis.
10. **DISTORTION/ALTERATION OF SURROUNDING ANATOMIC FEATURES:** The repair or healing of surgical wounds may distort the appearance of adjacent structures. Our goal is to completely remove your skin cancer, and then concern ourselves with the function and appearance of surrounding anatomic structures.

Fig. 8.4 Example of a consent form for Mohs surgery: (**a**) page one and (**b**) page two

b **INFORMED CONSENT: MOHS MICROGRAPHIC SURGERY& REPAIR**

11. **TUMOR RECURRENCE:** No skin cancer treatment has a guaranteed 100% cure rate. However, Mohs surgery has been shown to have the highest cure rate for the treatment of skin cancer.

The complications of surgery are not limited to the above list.

I acknowledge that I have received and read a copy of the Palm Harbor Dermatology Mohs Micrographic Surgery Brochure. This brochure fully explained to me the procedure and what to expect during and after the procedure. I understand its contents, and all of my questions regarding the procedure have been answered.

I acknowledge that I have read the entire consent form. I understand its contents, and the doctor has adequately informed me of the risks, benefits, advantages, disadvantages, alternatives, and possible complications of skin surgery. I also understand that the postoperative size of the surgical wound after removing the skin cancer, and the method of repair cannot be predicted in advance, and I could require referral for additional closure or revision of the procedure site.

I further request the administration of such analgesia and/or sedative medication as deemed necessary or desirable for the completion of the procedure. I understand that the administration of medication carries risks separate and apart from the risks of the procedure.

I recognize that the results from the practice of medicine and surgery are not absolutely predictable, and I acknowledge that no guarantees or assurances have or can be made concerning the results of such treatment. I further acknowledge that there have specifically been no guarantees as to the cosmetic results from the procedure.

All of my questions and concerns have been answered, and I hereby consent to Mohs surgery and repair if necessary to be performed by Dr. Ross upon _____ (patient).

I have identified and confirmed the location(s) of my surgical site(s).

I also consent to the taking of photographs before, during, and after the procedure. I understand that these photographs are important to document and follow my progress after surgery. These photographs will belong to Palm Harbor Dermatology, and may be used for educational and scientific purposes. This may include presentation at lectures or publication in medical journals. In such an event, I will not be identified by name. I expect no compensation for any such use of these photographs, and I waive all my rights to any claims for payment or royalties. I also release Dr. Ross from any liability in connection with the use of such photographs.

I agree that any tissue removed during the course of the operation may be examined, documented, preserved and/or disposed of in a manner considered proper for diagnosis, study, and advancement of medical knowledge.

I understand that Palm Harbor Dermatology has recommended that a spouse, relative, or friend accompany me and drive me home following my surgery. If I decide to drive myself home, I understand and assume the risk involved.

Patient's/Guardian's Printed Name _____ Patient's/Guardian's Signature _____

Relationship, if other than patient _____

Date: _____ Time: _____ AM/PM

I confirm that this form has been completely reviewed with the patient. The potential risks, side effects, and complications were all discussed. All of the patient's questions have been answered.

Physician's Signature: _____ Date: _____

Witness Signature: _____ Date: _____

Fig. 8.4 (continued)

has proper expectations. Documenting preexisting defects with photography is imperative, as many patients do not appreciate asymmetry or recall defects until after their surgery. During the consent process it is important to emphasize the risk of scar formation. Patients rarely seem to understand that the removal of their skin cancer will result in a scar that is likely to be much larger than the primary lesion. A simple explanation of the reasons behind the need for longer or distant excision lines, as well as outlining the excision with a marking pen on the patient prior to surgery, will allow patients to visualize the procedure and prepare for the outcome.

> Often an outcome that the patient perceives as unexpected may have been fully anticipated by the surgeon. Thorough explanations may minimize misunderstandings and prepare patients for the postoperative course.

Intraoperative Considerations

Once potential pitfalls have been addressed preoperatively, it is very important to continue the same diligence while working in the operating suite.

Operating Suite

The organization of the operating suite may play a role in optimizing the surgical outcome. In offices with multiple procedure rooms, the setup will ideally be identical from room to room. This standardization prevents unnecessary wasted time searching for materials or equipment, particularly while a procedure is ongoing. The most common design of our procedure rooms is depicted in Fig. 8.5. There is certainly significant variation and personal preference associated with room design. There are several good resources available to individuals interested in planning their own office space [40, 41].

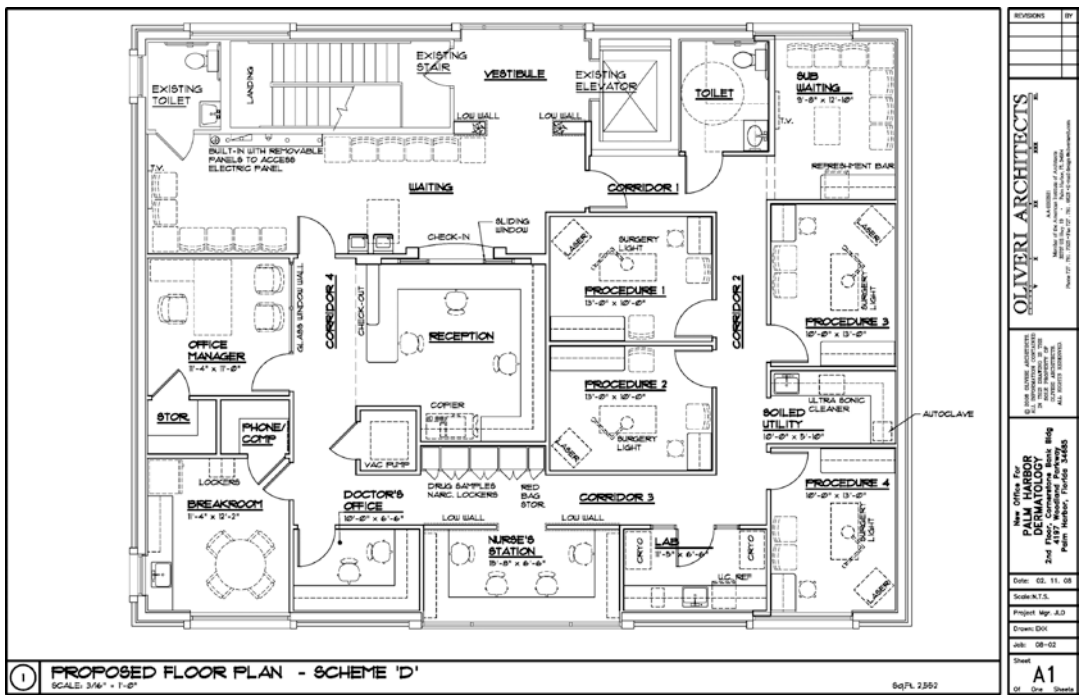


Fig. 8.5 Example of an office design

Specific equipment details are beyond the scope of this chapter; however, easy access to supplies, clearly marked surgical trays, reliable patient positioning, and excellent lighting are key in optimizing surgical outcomes and ensuring patient safety.

Surgical Site Preparation

Skin Marking

Prior to any intervention, the surgical site is marked with a surgical marking pen. There are numerous pens available, but most are filled with gentian violet. This ink is nontoxic to the skin and can easily be reinforced intraoperatively. Pens are available in sterile form when needed. It is essential to confirm the location of the skin cancer to be removed *with the patient* prior to marking the surgical site. At our institution, prior to the surgeon marking the skin, the patient is asked to point to the location without direction from the physician. Biopsy sites may heal completely while the patient is awaiting definitive surgery and the patient and the surgeon may have difficulty pinpointing the correct site. There have been several publications suggesting ways to reproducibly document the site of a lesion [42, 43]. Digital photographs are an excellent method of documentation. Problems most often arise in patients referred in for a procedure at a time remote from the biopsy.

> If there is any doubt as to the location of the surgical site, the procedure should be delayed until proper identification can be made and all parties are in agreement.

Choice of Antiseptic Solution

Depending on the location of the surgical site, the area is cleansed with either chlorhexidine or iodophor. In most patients, chlorhexidine will be used if the site is not within 2 cm of the orbit or in the ear.

One of the possibly preventable complications in skin cancer surgery is wound infection. Although the overall infection rate for dermatologic surgery in an outpatient setting is low, at reportedly 0.7–2.45% in several published case series [44–46], surgeons should employ basic standard techniques to ensure minimal risk of infection. These techniques are discussed below; however, the administration of antibiotics should not be considered standard therapy.

Anesthesia

The specifics of anesthesia are covered in Chap. 9; however, a few points are worth emphasizing. The vasoconstrictive effect of epinephrine may take up to 15 minutes to work. In patients with an increased risk of bleeding, allowing the full 15 minutes between injection and incision will usually decrease bleeding. The epinephrine in vials of lidocaine is usually at a 1:100,000 dilution. Dilutions as low as 1:500,000 have been shown to provide adequate hemostasis.

Reduction of the amount of epinephrine may be advisable if large quantities of anesthesia are anticipated or will be used in the frail and elderly. To avoid excessive exposure to epinephrine, we routinely use lidocaine with epinephrine 1:300,000.

Another important factor to consider is the use of regional nerve blocks. Although nerve blocks require more time for effect, there are instances in which the use of a nerve block may be beneficial to the patient and the surgeon and help optimize the outcome. For instance, the infiltration of local anesthesia can greatly distort the anatomy of the lip. In this circumstance an infraorbital block for the upper lip, or a mental block for the lower lip, may be beneficial.

There are some instances where tumescent anesthesia may be advantageous. The use of tumescent anesthesia may allow the treatment under local anesthesia of larger tumors or larger surface areas. In these circumstances conventional anesthesia might be limited over concerns about lidocaine toxicity. In addition, tumescent anesthesia may provide benefits of prolonged duration and decreased bleeding (see Chap. 9).

Staff Preparation

Hand Washing/Surgical Scrubbing

To reduce the risk of postsurgical infections, use of an antimicrobial preparation for hand washing is necessary. There are now numerous waterless surgical scrub products in the market for use as an alternative to traditional cleansers that require rinsing with water after use. We use a solution of chlorhexidine gluconate 1% with 61% by weight ethyl alcohol. This product has been shown to be effective for microbial reduction [47]. There are several other waterless products that have also been found to be effective as antiseptics prior to putting on sterile gloves [48]. These products are strictly alcohol based and are less costly than the products containing chlorhexidine gluconate. When using products with a significant ethyl alcohol component, care must be taken to assure the preparation has thoroughly dried before there is any exposure to the spark of an electrosurgical instrument or the heat of electrocautery.

Surgical Site Draping

Although most surgeons complete the reconstruction phase of MMS utilizing sterile technique, there is a difference in sterile technique among surgeons during the taking of Mohs layers. There is evidence indicating that there is no difference in infection rates when stages are taken clean compared to sterile [49, 50]. Utilizing clean technique to take stages can be more cost-effective and efficient compared to the utilization of sterile technique. Nonsterile gloves have also been shown to be generally safe for the practitioner in dermatologic surgery. The rate of perforation of nonsterile examination gloves is published to be 2.3% for routine dermatologic procedures [51] but may increase up to 11.7% for procedures such as MMS [52]. An effective alternative to more costly but less easily perforated sterile gloves may be to double glove with nonsterile gloves. This has been shown to be an effective method of protection against blood exposure in dermatologic surgery [53].

Intraoperative Monitoring

While intraoperative vital sign monitoring is not routine practice in MMS [54], the recording of basic vital signs including blood pressure and heart rate is useful and prudent. Surgery is generally deferred in patients with systolic blood pressures greater than 180 or diastolic blood pressures greater than 100. Except in patients in an exceptionally fragile state or with a high risk of cardiac arrhythmia, intraoperative monitoring is not warranted in low-risk procedures under local anesthesia. All procedure room personnel should have current training in basic life support and physicians should be familiar with more advanced techniques, such as advanced cardiac life support. Every medical office should have a comprehensive emergency plan including immediate access to basic resuscitation equipment such as breathing devices, oxygen, and an automatic external defibrillator, as well as a protocol for activating the local emergency medical response system. Facilities that provide higher-risk procedures such as conscious sedation should have more extensive resources and appropriate personnel training.

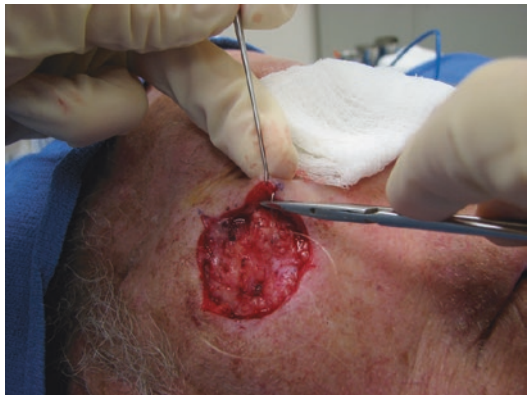


Fig. 8.6 Proper use of the skin hook to allow atraumatic positioning of a subcutaneous suture. Note the careful positioning of the finger behind the hook to stabilize the tissue

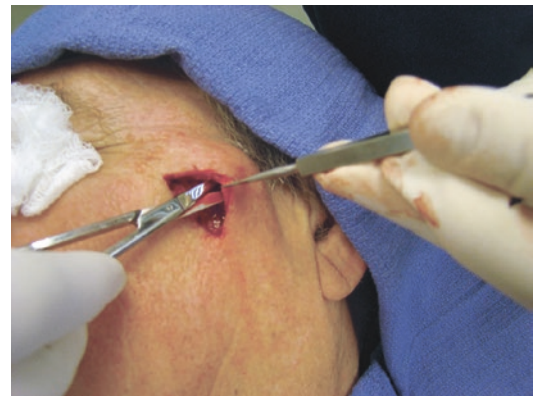


Fig. 8.7 Undermining utilizing scissors and skin hook

Tissue Manipulation

After the skin has been incised, it is important to minimize trauma to any tissue that will become part of the closure. A properly utilized skin hook is an excellent way to avoid crush injury to the epidermis, which may result from handling tissue edges with forceps. Figure 8.6 demonstrates the proper handling of skin edges with skin hooks. These instruments, when handled properly by the physician and assistants, are safe and the most effective way to manipulate tissue without significant injury. Crushed skin margins will lead to localized tissue necrosis and detract from the operative result.

> The most effective surgeon is gentle with the patient and the wound.

Optimal closure can often be obtained by undermining the wound edges aggressively with blunt scissors or semi-sharp scissors. Extensive undermining in the proper plane will result in less tension on the sutured wound edges and ultimately a better cosmetic outcome. Figure 8.7 demonstrates an appropriate degree and level of undermining for a wound following MMS removal of a nonmelanoma skin cancer. Inadequate undermining may lead to increased tension across the surface of a wound and suboptimal outcomes.

Hemostasis

Hemostasis must be assured at every stage of the procedure. The approach for obtaining hemostasis should be adjusted to account for the patient's risk factors for bleeding and the operative procedure. In some circumstances, simple prolonged external intraoperative pressure may provide adequate hemostasis. This approach has the benefit of limiting the tissue damage caused by chemical or electrical cauterization.

For wounds that are to be sutured, hemostasis may often be obtained with electrocoagulation or electrodesiccation. It is important to remember that these methods are only effective in a relatively dry surgical field, so attempting to blindly stop bleeding in a pool of blood is futile. Good visualization of the source of bleeding is key in obtaining hemostasis. Although efforts should be employed to minimize postoperative bleeding, the surgeon should resist the temptation to use the electrosurgical device excessively and indiscriminately. Too much char from electrocoagulation or cautery will impede wound healing, especially if applied near the skin edges. Larger vessels may require ligation with suture ties to stop the immediate bleeding and assure continued hemostasis.

If this is necessary, an absorbable suture of sufficient gauge such as 4-0 polyglactin 910 suture may be utilized. Ties must be placed securely and encompass as little extra tissue as possible to prevent rebleeding during the immediate postoperative period.

On rare occasions, diffuse bleeding continues despite these measures. This most often occurs in patients on blood thinners or with coagulopathies. Renewed intraoperative manual pressure for 15–20 minutes often makes a significant difference in patient bleeding. An open wound may be packed with oxidized cellulose to help control bleeding. If this material is placed in a closed wound, healing may be impaired by the foreign body reaction it induces. A commercially available sponge made of purified porcine skin gelatin (Gelfoam®) may be used in a similar manner with less risk of foreign body reaction. Thrombin is available in several forms to place within the wound bed to control bleeding. Of particular use is thrombin in a gelatin matrix (FloSeal™). Almost any repair can be performed with the material in place. Although expensive, this product is simple to use and can effectively stop bleeding and prevent potential postoperative complications in patients with a bleeding diathesis.

Alternative, more aggressive approaches in patients with known bleeding disorders, including the use of prophylactic therapy, such as 1-desamino-8-arginine vasopressin (DDAVP) or plasma concentrates, may prevent postoperative bleeding complications. Decisions regarding these prophylactic measures should be made in consultation with a hematologist.

Designing the Closure

There are several fundamental principals to consider in designing an optimal closure. Figure 8.8 demonstrates the relaxed skin tension lines on the face of a photoaged individual. These lines tend to run perpendicular to the underlying muscle, and if possible, the skin closure should be oriented parallel to the relaxed skin tension lines. In some locations, the direction of closure is not clear. In these instances, removing the skin cancer and undermining around the entire defect may facilitate determining the optimal direction of closure.

> It is important to note that following relaxed skin tension lines on the face should not be done at the expense of crossing cosmetic subunits or placing traction on free margins.

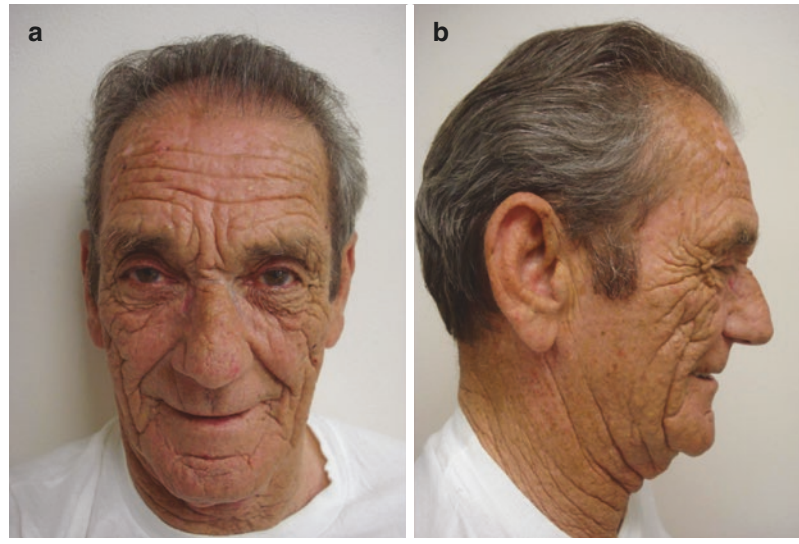


Fig. 8.8 Relaxed skin tension lines on the face of a photoaged individual: (**a**) front and (**b**) profile

The face is divided into distinct regions (Fig. 8.9). These boundaries represent the cosmetic subunits of the face, and if possible, closures should be designed to be completed within the unit. This will usually result in the least visible and most cosmetically acceptable scar.

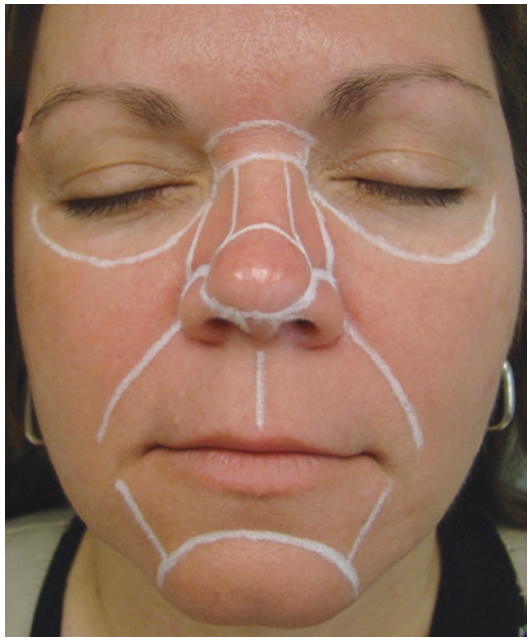


Fig. 8.9 Outline of the cosmetic subunits of the central face

Specific techniques regarding excision, flaps, and grafts are covered in other chapters (Chaps. 10, 12, and 13); however, it is worth mentioning an important principle:

> The surgeon should always measure twice and cut once.

The importance of planning the closure prior to making any additional incisions in the skin should not be underestimated.

Suturing the Wound

Excessive tension on wounds hinders the blood supply and may result in suboptimal surgical outcomes. As discussed previously, extensive undermining may minimize tension across the entire wound, and precise epidermal apposition with subcutaneous sutures is key to minimizing tension on the epidermis. As scars tend to spread over time, the placement of appropriate deep dermal or subcutaneous sutures and an emphasis on eversion (Fig. 8.10) of the tissue will result in a more cosmetically acceptable scar in the long term.

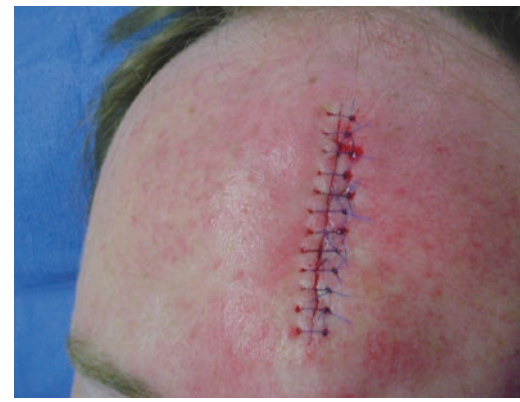


Fig. 8.10 Eversion of a wound under significant tension

Tension in the wound bed has also been found to influence keloid formation [55]. Extraordinary attention to minimization of wound tension may reduce the risk of postoperative keloid formation.

Postoperative Considerations

After the surgical procedure is complete, the surgical site is cleansed with normal saline, a postoperative photo is obtained, and a dressing is applied.

There are many variations of dressings; however, a key feature of the postoperative dressing is to provide even firm pressure. Figure 8.11 details a typical postoperative dressing. When the vasoconstrictive effect of epinephrine wears off, patients have a tendency to bleed. A pressure dressing left on for the first 24 hours will aid in maintaining hemostasis. Studies have demonstrated a lack of effectiveness in topical antibiotics preventing wound infection [56]. Applying white petrolatum ointment to the wound followed by a nonstick pad, appropriate dry gauze to pro-

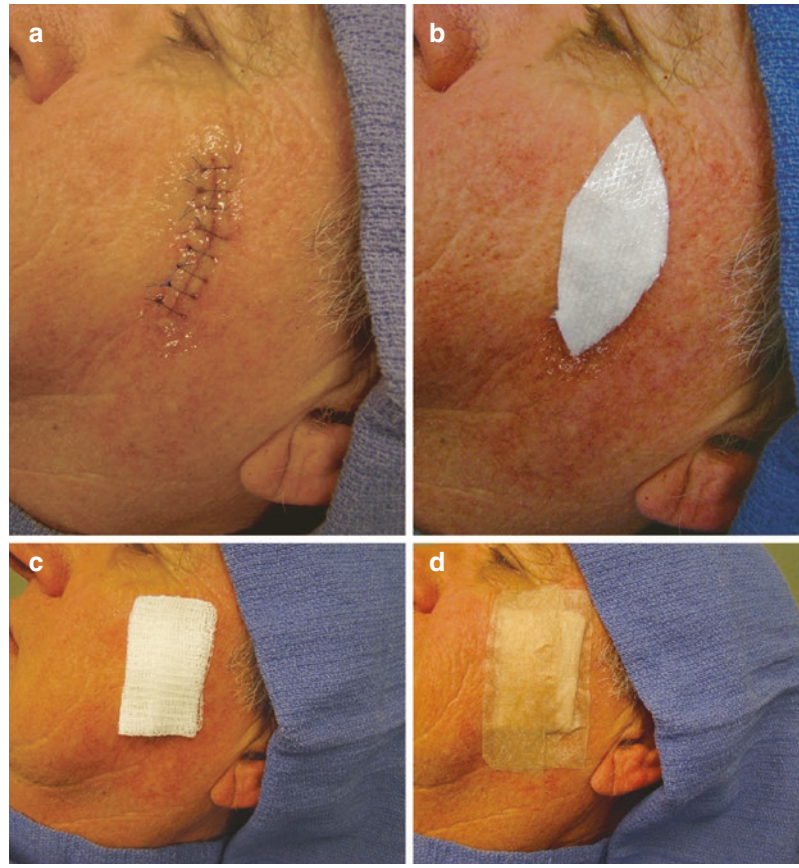


Fig. 8.11 (**a**) Wound prior to placement of dressing. (**b**) Wound coated with petrolatum and covered with a nonadherent dressing layer. (**c**) Placement of a layer of dry absorbent gauze. (**d**) Dressing firmly held in place by tape

vide pressure, and tape is sufficient. Patients are instructed to keep the wound covered with ointment and dressing until the time of suture removal. Patients are also advised to avoid heavy lifting, vigorous exercise, or activity that might traumatize the wound until the sutures are removed. Activity should be discussed explicitly with each patient as daily routines vary dramatically. One patient's definition of vigorous activity may be quite different from another's. Postoperative wound care instructions (Fig. 8.12a, b) should be provided in writing as retention of oral instructions after a procedure is quite limited.

Pain Control

All patients should be questioned on their use of, and possible need for, pain medication. It is important to address this issue with patients individually instead of having a standard set of prescriptions for patients postoperatively. Some patients are on pain medication preoperatively for an unrelated ailment, while others are completely resistant to taking any narcotic medications. For simple procedures, the patient is advised that acetaminophen will provide adequate pain relief. The patient is always provided with access to a physician if the need for stronger medication develops. This allows evaluation of the patient when necessary in addition to assuring patient comfort. The rest of our patients are told to begin with acetaminophen but are given a prescription for either hydrocodone/acetaminophen or propoxyphene/acetaminophen to take if needed. Except in exceptional circumstances, we always dispense twelve tablets so if there is ever any question from a pharmacy about the legitimacy of the prescription, the staff may be easily alerted to problems.

a

INSTRUCTIONS FOR "CLOSED" (SUTURED) WOUND CARE

MATERIALS

Q-tips, cotton tip applicators
Vaseline
Telfa dressing pads (Non-adherent dressing)
½" or 1" paper tape

PROCEDURE

1. Allow the pressure bandage to remain in place for 24 to 48 hours.
2. Using liquid antibacterial soap and water, gently cleanse the sutures and surgical wound using a Q-tip.
3. Apply a small amount of Vaseline ointment to sutures.

NOTE

1. Keep wound dry for 24 hours
2. Avoid strenuous activity for at least two weeks following surgery.
3. Dressing can be changed as often as necessary; however, dressing change once daily is usually sufficient.

WHAT TO EXPECT FOLLOWING SURGERY

1. Swelling, bruising, and redness around the wound are common. These symptoms typically resolve within several days.
2. Drainage from wound will occur. The drainage may have a yellowish color or foul odor. The drainage and odor will resolve after several days.
3. Significant bleeding is unlikely but may occur. Should you experience significant bleeding it is recommended that you lie down and apply firm, constant pressure to the surgical site for a minimum of 20 minutes. If bleeding continues, repeat the pressure on the surgical wound for an additional 20 minutes. In the event that bleeding persists, please contact our office as early as possible during the day so that we may make arrangements for your evaluation. If you are unable to reach our office or your doctor, please proceed to the nearest emergency room for evaluation and assistance.
4. Discomfort at the surgical site may be experienced for several days following your surgery. One or two **NON-ASPIRIN** pain relievers taken every four hours may be used as needed. **CAUTION**: **Bufferin, Anacin, Goody Powders, Excedrin, and B.C. Powders all contain aspirin products**.
5. Icepacks may be placed over the wound dressing during the first 24 hours. The icepack is placed over the wound for 15 minutes and may be repeated four times per day. You may also use a bag of frozen peas in substitution for an icepack.
6. Please contact our office or your local physician should you experience excessive bleeding, swelling, redness, fever, or pain.

Further questions can be addressed through our office at 727-786-3810.

Our normal business hours are Monday through Friday 7:30am – 4:30pm.

Fig. 8.12 (**a**) Postoperative wound care instructions for sutured wounds. (**b**) Postoperative wound care instructions for open wounds (see next page)

b

Palm Harbor Dermatology
CANCER AND LASER SURGERY CENTER

INSTRUCTIONS FOR WOUND CARE (SECOND INTENTION)

MATERIALS

Cotton tip applicator or Q-tips
Vaseline
Telfa surgical dressing pads (non-adherent dressing)
½" or 1" paper tape
Scissors

PROCEDURE

1. Remove bandage in 24 hours.
2. Gently cleanse any drainage on or around wound using mild soap and water applied with a Q-tip.
3. With clean applicator, dry wound.
4. With clean applicator, spread a thin layer of Vaseline ointment over the wound.
5. Cut Telfa pad to cover the wound. This is held in place with paper tape. If the Telfa pad adheres to the wound when you remove it at the time of the next dressing change, use more ointment to prevent further sticking. If excessive drainage occurs, cut gauze pad to size and place over Telfa pad.

NOTE

1. Change the dressing 1-2 times daily for 1-2 weeks and then once daily until the wound is completely healed (some wounds may require 4-6 weeks for complete healing).
2. Before changing bandages, you may take a shower, wash your hair, shave, etc., then follow the above procedure (the dressing will more than likely get wet, but will act as protection during shower, etc.).
3. Avoid alcohol, smoking, aspirin, aspirin containing products, and blood thinners as they thin the blood and cause bleeding.

WHAT TO EXPECT

1. Some swelling, redness and/or bruising around the wound. This usually resolves within a few days.
2. Some drainage from the wound which may have a foul odor and be yellowish in color. This will resolve in a few days.
3. Significant bleeding is unlikely, but may occur. Should you experience significant bleeding, it is recommended that you lie down and apply firm, constant pressure to the surgical site for a minimum of twenty minutes. If bleeding continues, repeat the pressure on the surgical wound for an additional twenty minutes. In the event that bleeding persists, please contact our office as early as possible during the day so that we may make arrangements for your evaluation. If you are unable to reach our office or your doctor, please proceed to the nearest emergency room for evaluation and assistance.
4. Discomfort at the surgical site may be experienced for several days following your surgery. One or two **NON-ASPIRIN** pain relievers taken every 4 hours may be used as needed. **CAUTION: Bufferin, Anacin, Goody Powders, Excedrin, and B.C. Powders all contain aspirin products.**
5. Icepacks may be placed over the wound dressing during the first 24 hours. The icepack is placed over the wound for 15 minutes and may be repeated 4 times per day. You may also use a bag of frozen peas in substitution for an icepack.
6. Please contact our office or your local physician should you experience excessive bleeding, swelling, redness, fever, or pain.

Further questions can be addressed through our office at 727-786-3810.

Our normal business hours are Monday through Friday 7:30am – 4:30pm.

Fig. 8.12 (continued)

Table 8.4 Timing for suture removal

Location	Number of days postoperative	Other considerations
Face	5–7 days	May use fast absorbing gut, or polyglactin 910 Rapide if wound under no tension
Scalp	10–14 days	
Neck	7–10 days	
Trunk and extremities	14 days	If on acral surface, silk sutures for epidermal closure may minimize tissue tearing

Antibiotics

As discussed previously, oral antibiotics following surgery are prescribed very judiciously. In such cases these patients are most often given cephalexin 500 mg po bid for 7 days or levofloxacin 750 mg po qd for 7 days if they are allergic to cephalosporins.

Timing of Suture Removal

The final consideration prior to sending the patient home is establishing the proper follow-up time. The timing of suture removal is key in optimizing surgical outcomes. "Track marks" may result if sutures are allowed to remain in place for too long. Table 8.4 identifies timing suggestions for suture removal. Timing is dependent upon the location of the wound. Many patients drive for considerable distances to have their skin cancer removed. If a local physician can remove the sutures at the proper time, it may save the patient considerable time and travel expense. If that is not possible, consideration may be given to using absorbable suture such as fast-absorbing surgical gut, fast-absorbing polyglactin 910, or poliglecaprone 25. Patients should be instructed to call with any problems and be provided with easy access numbers. In general, patients are very appreciative of the effort to minimize the inconvenience associated with a noncomplicated suture removal visit.

Summary

In order to optimize outcomes associated with cutaneous surgery, there are many factors to consider in the perioperative period. Many of the most important factors are addressed preoperatively with careful preparation and planning. With appropriate attention to detail, dermatologic surgery can be performed on a wide range of patient populations, safely, and with excellent results.

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Chapter 9
Anxiolysis, Anesthesia, and Analgesia

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Preoperative Considerations

A thorough preoperative evaluation should include asking the patient about anxiety, vasovagal syncope to previous anesthetic reactions, allergies, medications, and underlying medical conditions that may affect the means utilized to administer anxiolysis, anesthesia, and analgesia. Knowing these facts prior to commencing with surgery will allow the physician to anticipate potential problems and tailor pain control to a patient's specific set of needs and conditions. Furthermore, the inability to control intraoperative pain has been associated with aborted dermatologic procedures [1].

Easing anxiety is an important part of anesthesia. Though this seems obvious, it has the potential to be overlooked in a busy surgical setting. Patients exhibiting high levels of anxiety prior to or during a procedure have been shown to have an increased perception of postoperative pain [2]. Anxiety in patients undergoing dermatologic surgery is principally related to concerns about oncologic cure, cosmesis, and anticipated pain during the procedure [2, 3]. Research is not needed, however, to acknowledge that reducing patient anxiety pre- and intraoperatively is inherently valuable, and to this end, many approaches exist to ease patient angst during this timeframe. These can grossly be divided into nonpharmacologic and pharmacologic interventions.

Nonpharmacologic interventions begin prior to surgery, where the surgical staff should explain the procedure to the patient and highlight the steps that will be taken to reduce or eliminate their pain. Clear communication has been shown to be associated with improved patient experience [4], and reassurance from the physician that one of the expectations during the procedure is that the patient will not experience pain can quell a significant amount of anxiety in the patient. Other simple steps include ensuring patients are comfortable and warm. Preoperative phone calls have not been shown to reduce anxiety [5], so providing reassurance about the procedure on the day of surgery may be preferable. A nonpharmacologic intervention that has been shown to reduce anxiety is playing patient-selected music during the procedure [6]. Physician-selected music and recorded guided imagery [7], hand holding, and stress ball use [8] have not been shown to be effective in decreasing patient anxiety prior to or during skin surgery.

If the patient requires pharmacologic anxiolysis, several options are available (Table 9.1). Often, these medications are prescribed in advance and brought by the patient to the clinic. Following informed consent, the anxiolytic can be administered, and once this is effective, the procedure can commence. With these agents, it is advisable to start with the lowest dose and gradually increase until the desired anxiolytic effect is obtained. Some providers utilize conscious sedation or an inhaled nitrous oxide/oxygen mixture

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Table 9.1 Common oral anxiolytic agents

Drug	Dose	Onset time	Duration	Notes
Midazolam [11]	>45–77 kg, 10 mg >77–100 kg, 15 mg ≥100 kg, 20 mg	60 minutes	2 hours	Elimination reduced in the elderly, not tested in pregnancy
Lorazepam [12]	0.5–4 mg	60 minutes	8 hours	
Alprazolam [13]	0.5–0.75 mg	60 minutes	5 hours	
Diazepam [12]	2–10 mg	20–40 minutes	6–8 hours	Prolonged action in elderly, liver dysfunction
Zolpidem [12]	5–10 mg	30 minutes	0.5–4.5 hours	Amnestic effect, not contraindicated in pregnancy

to achieve both anxiolysis and analgesia. These techniques are certainly available to the dermatologic surgeon but come with additional requirements for staffing and patient monitoring to maintain safety [9, 10].

Local Anesthetic Agents

Local anesthetics work on nerve fibers by blocking sodium channels which prevents depolarization and the propagation of a pain signal along the nerve [14]. The small, unmyelinated C-fibers, which conduct pain, are blocked quickly. Local anesthetics are also able to affect larger unmyelinated fibers that conduct heat and cold, myelinated A-fibers that conduct pressure, and motor neurons. These latter nerve types are harder to block due to their size and myelination, if present. Therefore, the effect of local anesthetics on these nerves is delayed and often requires a larger dose of local anesthetic to be affected. This explains why patients will often sense "pulling and tugging" during a procedure but feel no pain. Further, this explains why patients may show signs of a motor neuron palsy following large procedures, such as eyebrow droop, that spontaneously resolves once the effect of the anesthetic has waned.

The two basic classes of local anesthetics, amides and esters, have clinically significant differences with respect to their metabolism as well as their likelihood to elicit allergic reactions (Table 9.2).

Table 9.2 Esters vs. amides [15]

	Ester anesthetics	Amide anesthetics
How to recognize	Generic name contains one "i"	Generic name contains two "i"s
Examples	Procaine (Novocain) Chloroprocaine (Nesacaine) Tetracaine (Pontocaine) Benzocaine (Hurricaine, Americaine) Cocaine	Lidocaine (Xylocaine, LMX) Bupivacaine (Marcaine) Prilocaine (in EMLA)[a]
Metabolized and inactivated by	Plasma pseudocholinesterases	Liver
Metabolite	Para-aminobenzoic acid (PABA)	Prilocaine's metabolite oxidizes hemoglobin to methemoglobin
Metabolite excreted by	Kidney	N/A
Caution in patients with	Pseudocholinesterase deficiency, allergy to PABA, severe renal dysfunction	Severe liver dysfunction, risk of methemoglobinemia[a]

[a]Do not use in infants less than 4 months of age or those with G6PD deficiency. Use with caution in those patients less than 12 months of age and in those who are taking sulfa drugs

Table 9.3 Allergens in local anesthesia [16–18]

Allergen	Where found	How to avoid
The anesthetic itself	In the anesthetic solution	1. Use an anesthetic of another class 2. Use Benadryl or normal saline for small procedures 3. Consider general anesthesia
PABA[a]	The metabolite of ester anesthetics	Use a preservative-free amide
Sodium Metabisulfite	Preservative in epinephrine	Avoid epinephrine
Methylparaben[a]	Preservative found in multidose vials of anesthetics	Use a preservative-free amide

[a]PABA and methylparaben are chemically related. Both should be avoided if an allergy to one is suspected

Indications and Contraindications

The primary indication for local anesthesia in outpatient skin cancer surgery is pain management. Contraindications for local anesthesia include an allergy to the anesthetic or a preservative in the anesthetic (Table 9.3) and those with specific underlying medical conditions (Table 9.4).

Topical Anesthesia

Topical anesthetics can be useful either as primary anesthesia to reduce the discomfort of minor procedures, such as with many cosmetic procedures or minor pediatric procedures involving needle sticks, or as an adjunct to injectable anesthetics for skin surgery.

Table 9.4 Common anesthetics [15, 18–20]

Common anesthetics	Class	Onset of action	Duration (without epinephrine)	Duration (with epinephrine)	Cautions[a]
Bupivacaine hydrochloride (Marcaine)	Amide	5–8 minutes	2–4 hours	3–7 hours	Stings on injection Use with caution in patients with severe CAD or arrhythmias as circulatory arrest due to bupivacaine may be refractory to treatment
Lidocaine (Xylocaine, LMX, Topicaine)	Amide	<1 minute	0.5–2 hours	2–6 hours	Stings on injection
Prilocaine hydrochloride (in EMLA, Citanest)	Amide	5–6 minutes	0.5–2 hours		Methemoglobinemia risk[b] and risk for corneal abrasions if used near the eye
Mepivacaine (Carbocaine)	Amide	1–2 minutes	1–2 hours	2–6 hours	Slow neonatal clearance
Procaine (Novocain)	Ester	5 minutes	1–1.5 hours		
Tetracaine (Pontocaine)	Ester	7 minutes (<1 minute for conjunctiva)	2–3 hours (<1 hour for conjunctiva)		
Benzocaine (Hurricaine, Topex, Cetacaine)	Ester	<1 minute for mucosa	<1 hour for mucosa		Frequently causes contact dermatitis Methemoglobinemia risk[b] if sprays are used in the mouth or throat

[a]Also refer to esters vs. amides table for class-specific precautions
[b]Do not use in infants less than 4 months of age or those with G6PD deficiency. Use with caution in those patients less than 12 months of age and in those who are taking sulfa drugs

There are several varieties of topical anesthetics that can be used safely on intact skin. A common prescription preparation is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, which is marketed under the trade name EMLA® (AstraZeneca, London, UK). This is applied in a thick layer to intact skin 1 hour prior to a planned procedure and occluded, typically with over-the-counter plastic wrap or a thin occlusive adhesive dressing [19]. Lidocaine is also available in 4% OTC and 5% prescription creams under the trade name L.M.X.4® or L.M.X.5® (Ferndale Laboratories, Ferndale, MI) from most pharmacies. For best results, it should be applied in a manner similar to EMLA®. Other agents frequently used are compounded combinations of varying concentrations of any or all of the following: benzocaine, lidocaine, tetracaine, and prilocaine in a variety of vehicles. These combinations are FDA off-label uses, and care should be taken to avoid toxicity with these agents as they typically contain much higher concentrations of local anesthetic than the commercially available preparations.

For the conjunctiva, two common anesthetic drops are proparacaine and tetracaine. Both are ester anesthetics and should not be used in patients who are allergic to esters. Both eye drops cause some stinging upon instillation, tetracaine more so than proparacaine [21]. For each, the conjunctival anesthesia lasts approximately 10 minutes and can be re-instilled as needed. Neither should be used in a patient with narrow angle glaucoma.

The oral mucosa can be anesthetized quickly and easily, making subsequent injections relatively painless. The oral mucosa should first be dried with a piece of gauze. A topical anesthetic such as lidocaine jelly, viscous lidocaine, or 20% benzocaine gel can then be applied with a cotton-tipped applicator or a second gauze pad. This is held in place for 1–2 minutes. Care should be taken to limit the degree to which the patient swallows any of the topical anesthetic as this will cause uncomfortable anesthesia of the pharynx.

Topical cocaine has historically been used for intranasal procedures though its use has fallen out of favor due to a poorer risk-benefit ratio relative to other agents currently available [22]. Cocaine achieves very effective anesthesia of the nasal mucosa with excellent hemostasis due to its vasoconstrictive properties. As cocaine is a controlled substance, additional record-keeping rules must be followed. For a discussion of complications of topical anesthetic agents, please refer to the end of the chapter.

Infiltrative Anesthesia

Infiltrative anesthesia is the most common approach for anesthesia in skin cancer surgery. Though there are many types of anesthetics to choose from (Table 9.4), lidocaine is the most commonly used in skin surgery due to its rapid onset of action and excellent safety profile. Bupivacaine is often used as a secondary agent to extend the length of anesthesia but is infrequently used alone due to its greater pain on injection and its slow onset of action.

The injection of local anesthetics is associated with discomfort due to both the needle stick and a burning sensation that occurs upon instillation of the agent into the tissue. By utilizing some simple techniques, the pain associated with injection of the anesthetic can be minimized. One of the simplest early interventions used to calm patients prior to injecting local anesthetic is to talk to them about the injection and prepare them for what to expect. Simply having knowledge that the injection is about to begin and that it will cause discomfort during the injection can allow patients to psychologically prepare for and better tolerate the injection. This need for communication applies to both initial instillation of the anesthetic and instances where the anesthetic needs to be readministered during a procedure because the initial anesthesia has lost effect.

Several physical factors can also affect the pain of an anesthetic injection. The size of the needle, the diameter of the syringe, the direction of the needle bevel, the laxity of the skin, the rate of injection, and the placement of multiple needle sticks are all important.

> The smaller the needle and the smaller the diameter of the syringe, the less pain there is on injection.

A 30-gauge needle on a 1-ml or 3-ml syringe should be used whenever possible. The bevel of the needle should be up, and the injection should be made through taut skin. If the skin is loose, one can apply traction to the skin during injection. The rate of injection should be as slow as possible. Though it seems time-consuming for a busy office, injecting local anesthetic slowly will take a little additional time and will result in a more positive experience for the patient. Finally, one should use a single needle stick whenever possible, but if multiple injections are required, one should attempt to reenter the skin through an area that is already numb from prior injections [14].

Buffering acidic anesthetic solutions with sodium bicarbonate has also been shown to reduce the pain associated with anesthetic infiltration as described below [23].

Nerve distraction techniques have been shown to be helpful in this setting as well. Rubbing or vibration of the skin can be effective in reducing the discomfort associated with local anesthetic injections (the gate theory of pain) [24].

> A simple vibrating apparatus placed near, and especially proximal to, the injection site just prior to and during the injection has been shown to reduce discomfort while injecting the anesthetic [24].

Having the patient hold the device can help involve the patient in the procedure and gives them a sense of control. Many surgeons will simply pinch the skin at or near the injection site just prior to the needle stick, while others will apply ice to the injection site for a minute or so prior to injection [25]. Using a cold air blower on the skin prior to injection reduces pain of injection. The cold air needs to be kept away from the injection needle as it will freeze the anesthetic in the needle and prevent further injection.

Certain areas of the body are more sensitive to pain than others. These places include the nose, the lips, and the digits. Thorough anesthesia is especially important in procedures such as melanoma excisions which extend deeply to muscle fascia. In these situations, it can be helpful to administer anesthetic in a bi-level fashion: one plane in the superficial dermis and another in the subcutaneous tissue. Since injection in the deeper plane is less painful, one should start in the deep plane first, and longer needles are helpful in more readily reaching this plane.

Additives to Local Anesthetics

Epinephrine

The most common additive used with injected local anesthetic agents is epinephrine. The addition of epinephrine prolongs the duration of action of the local anesthetic and provides improved short-term hemostasis through its local vasoconstrictive effect. Although rare, the addition of epinephrine carries some risk to a subset of patients with certain underlying medical problems (Table 9.5) [26]. Providers should therefore consider using the lowest effective dose of epinephrine needed for the planned procedure. Vasoconstrictive effects of epinephrine have been shown to be equally effective at doses ranging from 1:100,000 to 1:200,000, while prolongation of anesthetic effect without hemostatic benefit has been demonstrated at doses as dilute as 1:3,200,000 [26].

A triple-blind randomized controlled trial showed that peak epinephrine-mediated vasoconstrictive effect occurs 25 minutes following injection of a 1% lidocaine, 1:100,000 solution into the skin [32]. Therefore, surgeons should consider waiting to begin a procedure for approximately this long if maximal vasoconstriction is desired.

Table 9.5 Epinephrine precautions [27–31]

Avoid epinephrine or use dilute with caution in patients	Due to
Taking tricyclic antidepressants	Risk of hypertensive crisis
Taking MAO inhibitors	Risk of hypertensive crisis
Taking beta-adrenergic blockers	Risk of hypertensive crisis
Taking nonselective beta-blockers	Risk of hypertensive crisis and reflex bradycardia
With narrow angle glaucoma (avoid use periorbitally)	Increased intraocular pressure
With severe peripheral vascular disease (avoid use on digits)	Risk of digital ischemia
Who are pregnant	Pregnancy class C
Allergic to sulfites	Risk of allergic reaction
With severe coronary artery disease	Risk of coronary artery vasospasm
With hyperthyroidism	Risk of hypertensive crisis
With a pheochromocytoma	Risk of hypertensive crisis
With unstable angina or uncontrolled hypertension	Risk of hypertensive crisis and/or myocardial infarction

Many physicians continue to be trained to avoid the use of epinephrine in local anesthetic injections in anatomic areas such as the digits, nose, ears, and penis out of concern for causing vasoconstriction-mediated necrosis; however, research has refuted this [26].

Epinephrine is supplied at a concentration of 1:1000 or premixed with local anesthetics at concentrations of either 1:100,000 or 1:200,000. Because epinephrine is only stable in an acidic environment, when it is premixed with local anesthetics, the pH of the mixture is lowered. This acidity is a major reason why the injection of local anesthetics stings and burns [33, 34]. Two ways to avoid this problem include avoiding using premixed solutions and mixing the epinephrine with the local anesthetic in office (Table 9.6) or adding sodium bicarbonate to the anesthetic at a ratio of 1:10 to neutralize the pH of the anesthetic [33, 34] (Table 9.7).

Table 9.6 Lidocaine and epinephrine dilutions

Epinephrine concentrations desired	Plain 1% lidocaine	Epinephrine (1:1000)[a]
1:100,000	50 ml	0.5 ml
1:200,000	50 ml	0.25 ml
1:500,000	50 ml	0.1 ml

[a]1:1000 dilution means 1 mg of epinephrine per ml

Table 9.7 Buffered lidocaine with epinephrine [38]

Lidocaine and epinephrine 1:100,000	Sodium bicarbonate 8.4%
50 ml	5 ml

Sodium Bicarbonate

The addition of sodium bicarbonate to local anesthetic at a ratio of 1:10 will neutralize the pH of the anesthetic and reduce the pain of infiltration. Buffering a lidocaine-epinephrine mixture with sodium bicarbonate at this ratio has been shown to significantly reduce the pain associated with anesthetic injection [26, 35].

Buffered solutions of lidocaine-epinephrine have been shown to be efficacious even after 1 week of storage [26, 35]. It is a common and safe practice to buffer local anesthetic from multidose vials with sodium bicarbonate into syringes in batches before a planned procedural clinic. If syringes are filled in advance, it is good practice to label them with the contents and the date and time they were filled. This practice has been safely utilized in dermatology practices for decades [36]. However, the current regulatory environment may apply guidelines proposed by the United States Pharmacopeia (USP) chapter 797 for sterile, in office, compounding of medications or drawing of sterile solutions for later use [37], and dermatologists are therefore encouraged to be aware of this.

It should be noted that if deeper procedures are planned, such as Mohs surgery with tumor infiltrating skeletal muscle, epinephrine has a vasodilatory effect in muscle and therefore is counterproduc-

tive in hemostasis in that setting [39]. For a discussion of the complications of infiltrative anesthesia, please refer to the end of this chapter.

Field Blocks

A field block involves injecting a ring of local anesthetic around the surgical site. Advantages to this technique include lack of distortion of the surgical site and less volume of anesthetic required to anesthetize a large area. The anesthetic should be injected into both the superficial and deep planes to be maximally effective. Sites conducive to this include the scalp, the nose, the ear, the trunk, and the extremities. The only disadvantage is the lack of hemostasis at the central surgical site; therefore, if this is a concern, additional anesthetic mixed with epinephrine could be injected centrally once the ring block has been placed [38].

Regional Nerve Blocks

Peripheral nerve blocks are a great way to anesthetize large areas with few injections and are achieved by anesthetizing around a nerve root to produce anesthesia in the distribution of that nerve. Benefits of nerve blocks include the possible use of a reduced volume of anesthesia, reduced distortion of the operative site by injected anesthetic, and improved patient comfort.

> Nerve blocks should be performed at least 10–20 minutes prior to surgery, as it may take that long for the block to take effect due to the larger diameter of nerves at the nerve root.

If local hemostasis or additional anesthesia is desired, a local anesthetic containing epinephrine may be used at the operative site in addition to the nerve block. With the nerve block in place, the local anesthetic can be injected quickly and painlessly.

Facial Nerve Blocks

Facial sensory nerve blocks can be performed at several points on the face. Each point lies above a sensory nerve: the supraorbital nerve and supratrochlear nerves superiorly; the infraorbital nerve, external nasal nerve, and infratrochlear nerves centrally; and the mental nerve inferiorly. The locations of these injection points and the regions of the face they supply can be seen in Fig. 9.1.

> When placing any nerve block, the surgeon should ensure that a needle of sufficient length is being used to reach the vicinity of the nerve root, and prior to injecting, the surgeon may aspirate first to ensure the needle is not within a blood vessel in order to avoid an intravascular injection of anesthetic though aspiration may prove difficult with small-gauge needles.

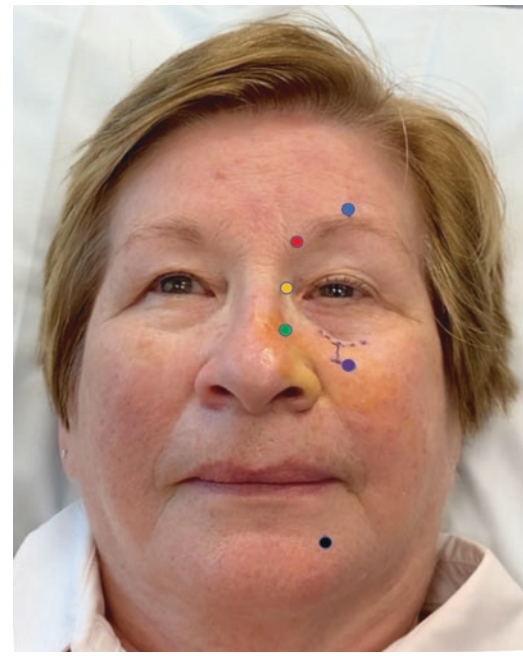

Fig. 9.1 Injection points for facial nerve blocks: supraorbital (blue), supratrochlear (red), infratrochlear (yellow), external branch of the anterior ethmoidal (green), infraorbital (purple), and mental (black)

Additionally, massage of the injected area immediately following placement of the nerve block can facilitate diffusion of the anesthetic into and around the nerve.

The supraorbital nerve block can be administered by inserting a needle into the skin over the supraorbital foramen/notch and advancing deep enough to be just superficial to the periosteum where 2 ml of anesthetic is injected. The needle should not enter the foramen or touch the nerve. If the patient complains of paresthesias during injection, the needle should be withdrawn, as it is likely to be touching the nerve. The supratrochlear nerve can be blocked by inserting a needle angled toward the junction of the nasal bone and the orbit near the glabellar line. The needle is advanced to a submuscular plane where 0.5–1 cc of anesthetic is injected.

Alternatively, a single-needle insertion can be utilized to accomplish both the supraorbital nerve block and the supratrochlear nerve block. With this technique, the supraorbital nerve is blocked as described above. Next, the needle is slightly withdrawn and subsequently advanced along the eyebrow toward the glabellar line. At this point, an additional 2–3 ml of anesthetic is injected as the needle is slowly withdrawn [38, 40].

To accomplish a nerve block on the nose, the infratrochlear, external nasal, and infraorbital nerves may need to be blocked. The infratrochlear nerve can be blocked by inserting the needle at the point where the nasal bone meets the orbit and injecting 1 ml of anesthetic at the level just above the periosteum in this region. To block the external nasal nerve, the needle is placed at the palpable junction of the nasal bone with the nasal cartilage slightly lateral to the midline (0.5–1 cm), and 1–1.5 ml of anesthetic is injected in the submuscular plane in this region immediately at the level of the bone/cartilage [40]. The infraorbital nerve can be blocked by injecting 2 ml of anesthetic into a point 1 cm below the orbital rim in the midpupillary line at the level just superficial to the periosteum [40].

The mental nerve can be blocked by placing a needle into the skin over the mental foramen, which can be located in the midpupillary line approximately 5 mm inferior to the labial sulcus of the lower lip.

An alternative approach to the infraorbital and mental nerves is intra-orally. Though it may seem counterintuitive, this approach may be less painful for the patient. The needle is inserted at the midpupillary line, the landmark for which is the space between the first and second premolars (bicuspids), at the labial sulcus (Fig. 9.2). The needle should be kept just superficial to the periosteum with the bevel facing the bone [38]. The prior application of topical anesthesia to the mucosa will decrease the initial pain of the needle stick.

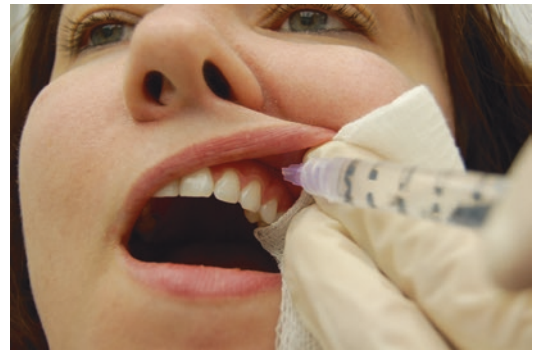

Fig. 9.2 The intraoral injection site for an infraoral nerve block: the needle is inserted between the first and second premolars at the labial sulcus

Digital Nerve Block

Digital nerve blocks are helpful when working on or around the nail. Each digit is innervated by four nerve branches: a ventral pair and a dorsal pair. A simple way to perform the block is with two injections, on either side of the digit (Fig. 9.3). The needle is inserted on the dorsal aspect of the digit, lateral and just distal to the metacarpophalangeal

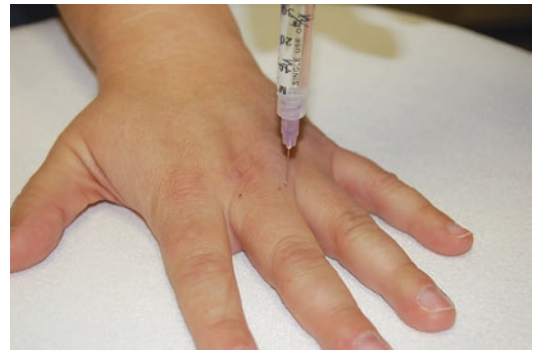

Fig. 9.3 The injection sites for a digital nerve block

(MCP) joint. The needle is inserted perpendicular to the digit and just lateral to the bone. The needle, once inserted into the skin, can be advanced superiorly to a point near the bone where 0.5 mL of anesthetic should be injected slowly. Next, the needle is withdrawn a few millimeters and then advanced inferiorly to a point near the inferior part of the proximal phalange where another 0.5 mL of anesthetic is injected. Repeat these steps on the other side of the digit. If, at any point, the patient complains of paresthesias, the needle should be withdrawn, as it is likely touching a nerve. For further details of digital blocks, see Chap. 14.

Hand Nerve Blocks

The hand is innervated by the radial, median, and ulnar nerves (Fig. 9.4). Depending on where the skin cancer is located, one, two, or all three of the nerves can be blocked.

To block the radial nerve, locate the injection site at the dorsal wrist by measuring three finger breadths proximal to the distal wrist crease or anatomic snuff box, just beside the cephalic vein (Fig. 9.5). Inject 2–5 ml of local anesthetic in a "bleb" just above the tough superficial fascia. Then, massage the bleb across the path of the nerve first one way and then the other.

The median nerve enters the carpal tunnel at the distal wrist crease where it should not be blocked (neuritis may result). The ideal injection site is just under the tendon of the palmaris longus (PL), three finger breadths from the distal wrist crease [23]. The PL can be easily seen by apposing the thumb and fifth finger with the wrist slightly flexed [18] (Fig. 9.6). The needle should enter the skin in the groove between the PL and the flexor carpi radialis (Fig. 9.7). Advance the

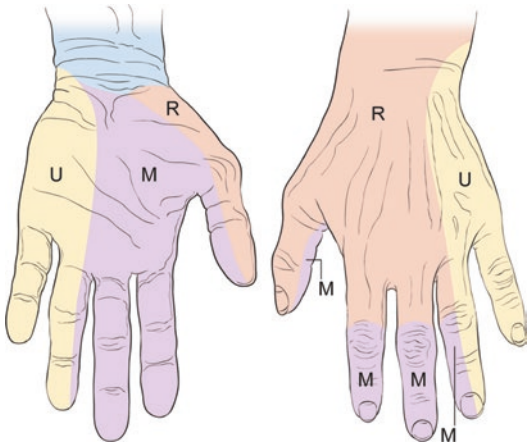

Fig. 9.4 Nerves in the hand. R radial nerve, U ulnar nerve, M median nerve. (Illustration by Alice Y. Chen)

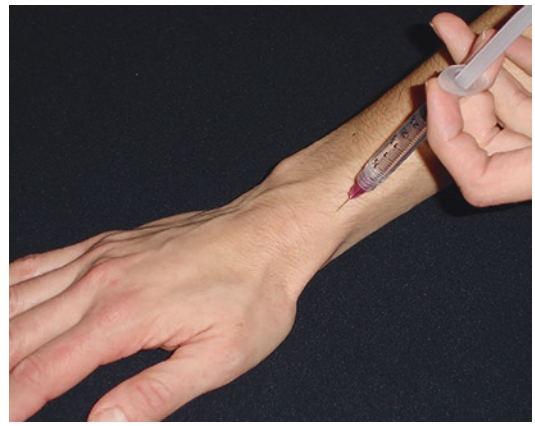

Fig. 9.5 The injection site for the radial nerve block

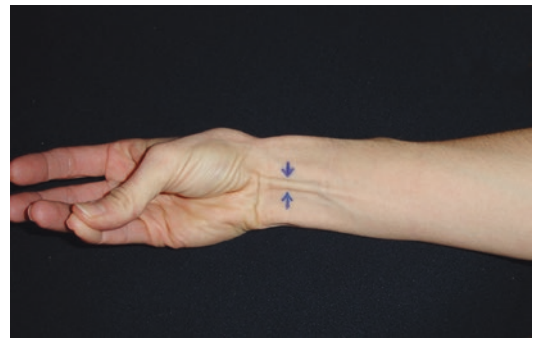

Fig. 9.6 The palmaris longus tendon is easily seen by apposing the thumb and fifth finger with the wrist slightly flexed

Fig. 9.7 The injection site for blocking the median nerve

needle slowly to avoid the tendon sheath, and inject 3–5 ml of anesthetic.

The ulnar nerve is most easily blocked at the elbow where it travels between the olecranon process and the epicondyle of the humerus. With the patient's arm flexed, the needle is inserted between the bones, and 3–5 ml of anesthesia is injected [38].

Foot Nerve Blocks

The five sensory nerves of the foot are the posterior tibial, the sural, the superficial peroneal, the saphenous, and the deep peroneal nerves (Fig. 9.8).

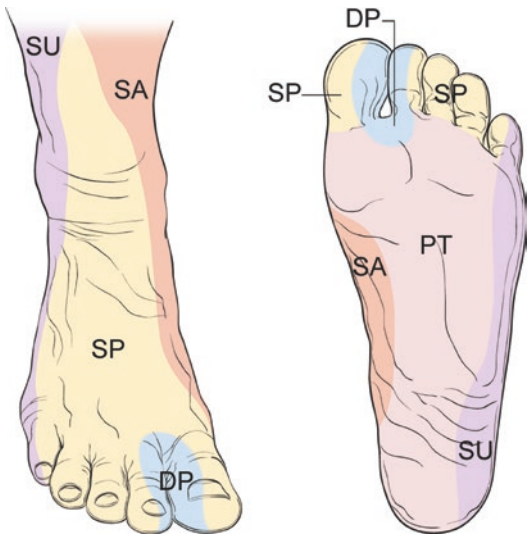

Fig. 9.8 Nerves of the foot. SP superficial peroneal, DP deep peroneal, SU sural, SA saphenous, PT posterior tibial. (Illustration by Alice Y. Chen)

The posterior tibial and sural nerves are easiest to block with the patient in the prone position. The posterior tibial artery is palpated between the medial malleolus and the Achilles tendon. A 1.5-inch needle is directed anterior and lateral to the arterial pulse until the bone is touched. The needle is withdrawn slightly, and 3–5 ml of anesthetic is injected. The sural nerve is blocked by injecting into the groove between the lateral malleolus and the Achilles tendon in an identical fashion to the tibial nerve injection [38].

The saphenous and superficial peroneal nerves are easiest to block with the patient supine. Here, anesthetic is infiltrated subcutaneously from malleolus to malleolus on the dorsal surface of the foot [38].

The deep peroneal nerve is easiest to block, locally, between the first and second toes.

Penile Nerve Block

The easiest way to anesthetize the penis is to do a ring block of the shaft. By injecting a ring of anesthetic in the subcutaneous plane around the base of the penis, most of the penis will be anesthetized. If the surgery is to involve the periurethral region of the glans or the frenulum, additional local anesthetic will be required [38].

Tumescent Anesthesia

Tumescent anesthesia is the infiltration of large amounts of dilute lidocaine (0.05–0.1%) and epinephrine (1:1000,000) into the subcutaneous fat (Table 9.8). It is used most commonly for liposuction, ambulatory phlebectomy, and hair transplantation, but it can also be used for skin cancer surgery. It produces swelling and firmness (tumescence) of the targeted area [41] and can be used to aid in dissection by separating tissue planes and leaving vital structures out of

Table 9.8 Tumescent anesthesia formula[a] [38]

Ingredient	Quantity (ml)
Lidocaine 1%	50–100
Epinephrine 1:1000	1
Sodium bicarbonate 8.4%[b]	10
Normal saline 0.9%	900–950

[a]Final concentration: 0.05–0.1% lidocaine and 1:1,000,000 epinephrine

[b]If solution is freshly prepared, do not include sodium bicarbonate

harm's way. Other advantages include prolonged anesthesia and decreased intraoperative bleeding [42]. Because dilute lidocaine is absorbed slower in the subcutaneous fat, doses as high as 35–50 mg/kg have been found to be safe [38].

The tumescent solution is infiltrated with the help of one of several pumps or large 30-ml syringes, with the injection carried out through long 18–20-gauge 3.5-inch spinal needles or specially designed multiport cannulas. The infiltration rate is started slowly with small needles and gradually increased by the use of spinal needles and, finally, infiltration cannulas. The deep subcutaneous plane is infiltrated first, followed by the superficial fat compartment. The solution is injected until firm tumescence of the tissue has been achieved. Anesthesia- and epinephrine-induced hemostases develop within 20 minutes and last for several hours [38].

Postoperative Analgesia

Most surgery involving the skin tends not to cause a great deal of postoperative discomfort. Mild pain, usually resulting from swelling, can be relieved with acetaminophen, ibuprofen, or a combination of these in most cases. Therefore, first-line therapy for postoperative pain following skin surgery is acetaminophen 1000 mg orally as frequently as every 6 hours in patients with no known hepatic impairment. Alternatively, ibuprofen 400 mg orally as frequently as every 6 hours can be used in patients with no known renal impairment and has not been associated with an increased risk of bleeding complications [43]. For those requiring additional analgesia, the acetaminophen and ibuprofen can be used simultaneously or taken at alternating three-hour intervals with one another. This approach will work for the majority of skin surgery patients.

There are a few exceptions where a more potent pain control agent may be needed. A large defect on a tight scalp or forehead that is closed primarily can predictably give the patient a headache for a few days. Also, surgery involving the cartilage of the ear or the nail can result in more significant postoperative pain. Further, large flap reconstructions may result in more pain than more straightforward primary closures. In these instances, patients may benefit from a prescription for a narcotic analgesic such as tramadol, codeine, hydrocodone, or oxycodone. It is imperative that the patient be warned not to drive or operate heavy machinery while taking these agents, and only a small number of tablets should be needed to control pain in these cases as pain is typically short-lived, and longer courses of narcotic analgesia may mask the painful symptoms of a complication such as an infection.

> Exposed ear cartilage may develop a chondritis that is best managed with oral anti-inflammatory drugs taken around the clock for 1–3 weeks.

Adverse Effects and Complications

In addition to the aforementioned risks of allergic reactions to anesthetic agents or their additives and vehicles, there are other potential risks associated with the use of these agents–either topically or by injected means–that are important to acknowledge.

With respect to topical anesthetics, one should be mindful to use the agent on a limited surface area of intact skin to avoid toxicity due to transdermal absorption of the drug into the bloodstream. This is of particular concern in infants or in adults where large body surface areas are being treated or where epidermal integrity will be modified by the planned treatment as instances of toxicity and death attributable to the topical anesthetic have occurred [44, 45]. All topical local anesthetic preparations meant for cutaneous use, and EMLA specifically, may cause a caustic burn if it contacts the conjunctiva [19]. Prilocaine can cause methemoglobinemia in susceptible patients (Table 9.1). Symptoms of methemoglobinemia can range from cyanosis to dyspnea and headache to coma [44].

Common side effects of injected local anesthesia include local bruising and edema (especially periorbitally), vasovagal response, and temporary motor paralysis.

Edema from local anesthesia can be significant. When working on the lower half of the forehead, the nose, or near the eyelids, patients should be forewarned about the risk of periorbital swelling. Having someone drive the patient home is recommended, as the swelling can interfere with vision. To minimize swelling, the patient should ice the periorbital area for 24–48 hours and keep the head elevated above the level of the heart by sleeping on a few pillows or in a recliner for the first few postoperative nights.

Vasovagal reactions present with diaphoresis and dizziness and can lead to syncope (Table 9.9). Calming the patient prior to injection can help, but is not always successful. For this reason, it is important to always anesthetize patients while they are lying down. If the patient complains of these symptoms, placing them in the Trendelenburg position with a cool, moist cloth over their forehead can ease the symptoms associated with a vasovagal response.

Patients expect to feel "numb" after surgery, but once the anesthesia wears off, they expect to feel normal. Occasionally, there is a temporary paralysis of the local muscle group that may last beyond when the "skin numbness" resolves and should resolve in a matter of hours. Warning patients that this is a possible occurrence while they are still in the office can alleviate patient anxiety.

More serious complications of local anesthetics, though rare, can happen. These include allergy, epinephrine effect, overdose, and necrosis.

Allergy to anesthetics is rare. True hypersensitivity accounts for less than one percent of adverse reactions seen with injectable local anesthetics [46]. Nonetheless, a true allergic reaction could be life-threatening. For this reason, it is important to take a detailed history of previous reactions and then try to determine the cause.

Table 9.9 Differential diagnosis of local anesthetic systemic reactions [38]

Diagnosis	Pulse rate	Blood pressure	Signs and symptoms	Emergency management
Vasovagal reaction	Low	Low	Excess parasympathetic tone; diaphoresis, hyperventilation, nausea	Trendelenburg, cold compress, reassurance, oxygen
Epinephrine reaction	High	High	Excess α(alpha)- and β(beta)-adrenergic receptor stimulation; palpitations	Reassurance (usually resolves within minutes), phentolamine, propranolol
Anaphylactic reaction	High	Low	Peripheral vasodilation with reactive tachycardia; stridor, bronchospasm, urticaria, angioedema	Epinephrine 1:1000 0.3 ml sc, antihistamines, fluids, oxygen, airway maintenance
Lidocaine overdose: 1–6 μg (micrograms)/ml	Normal	Normal	Circumoral and digital paresthesias, restlessness, drowsiness, euphoria, lightheadedness	Observation
Lidocaine overdose: 6–9 μg/ml	Normal	Normal	Nausea, vomiting, muscle twitching, tremors, blurred vision, tinnitus, confusion, excitement, psychosis	Diazepam, airway maintenance
Lidocaine overdose: 9–12 μg/ml	Low	Low	Seizures, cardiopulmonary depression	Respiratory support
Lidocaine overdose: >12 μg/ml	None	None	Coma, cardiopulmonary arrest	Cardiopulmonary resuscitation and life support

Symptoms of hypersensitivity include urticaria/hives or other generalized rash, bronchospasm, angioedema, or anaphylaxis (Table 9.9). If any of these symptoms are elicited in the history, one should try to identify exactly to what the patient is allergic. Patients can be allergic to the anesthetic itself, a metabolite of the anesthetic, or a preservative used in either the anesthetic or the epinephrine.

Anesthetics in the ester class are the most problematic due to the para-aminobenzoic acid (PABA) metabolite. Using a preservative-free anesthetic from the amide class is the solution. It should be preservative-free because preservatives used in these agents can be chemically similar to PABA (methylparaben).

Finally, epinephrine contains sodium metabisulfite as a preservative. Patients with sulfite allergies (different from "sulfa" allergies) may need epinephrine-free anesthesia or freshly mixed lidocaine and epinephrine.

In the rare case that a patient is allergic to both classes of anesthetics, one could use injectable diphenhydramine (Benadryl) or normal saline with benzyl alcohol preservative for small procedures. For larger procedures, general anesthesia in a hospital setting is the most suitable option.

If there is any question regarding the source of allergy, a referral to an allergist is beneficial. If the allergy occurs in your office, and is limited, it can be safely managed with antihistamines and prednisone. However, if the allergy is more severe (i.e., bronchospasm or anaphylaxis), immediate emergency management is required. It is good practice to have antihistamines, injectable 1:1000 epinephrine, oxygen, and an automatic external defibrillator in the office so that quick action can be taken.

Common side effects of epinephrine include palpitations, anxiety, tremor, tachycardia, and hypertension. These side effects are usually transient. Patients will often recall these symptoms and relate them to future providers as an "allergy" to the local anesthetic. For this reason, it is wise to obtain a detailed history if a patient claims to be allergic to a local anesthetic. Potentially life-threatening side effects of epinephrine—such as cardiac arrhythmias, digital ischemia, and cerebral hemorrhage—are rarely encountered at the doses used for skin surgery (Table 9.9). However, patients who are especially susceptible to these side effects, due to underlying medical conditions or certain medications, should be given dilute epinephrine or none at all (Table 9.10). Necrosis of the skin related to epinephrine use with local anesthesia is rare, but it may be prudent to limit or eliminate the use of epinephrine in the digits of patients with peripheral vascular disease.

Table 9.10 Dilute epinephrine

Epinephrine concentrations desired	Plain lidocaine	Lidocaine with epinephrine 1:100,000[a]
1:200,000	5 ml	5 ml
1:500,000	4 ml	1 ml

[a]50 ml contains 500 mg of lidocaine and 0.5 mg of epinephrine

Overdose from local anesthetics is rarely encountered in uncomplicated skin surgery. If a high volume of anesthetic is needed, or if the patient is of an especially low weight, one should be aware of the recommended weight-based limits (Table 9.11). When lidocaine toxicity occurs, it affects the central nervous system first and is heralded by perioral tingling, numbness of the tongue, metallic taste, or lightheadedness (Table 9.9). If these symptoms occur, an emergency response team should be notified, as the treatment requires oxygen, fluids, inotropes, and close cardiovascular monitoring. If unrecognized, this could progress to seizures (central nervous system [CNS] stimulation) followed then by respiratory arrest (CNS depression). Local anesthetic overdose can also depress the cardiovascular system. Usually, this happens after the CNS symptoms appear but can present earlier if the anesthetic is inadvertently injected intravascularly. Initially, bradycardia occurs and can quickly progress to a fatal arrhythmia leading to cardiovascular collapse. A risk to consider when using bupivacaine in particular is its depressive effect on the conduction system of the heart, which can lead to arrhythmias, and while bupivacaine is in the patient's system, these arrhythmias may be unresponsive to cardioversion [15].

Table 9.11 Maximum doses of anesthetics [14, 47]

Anesthetic	Maximum total adult dose per procedure[a]	Volume of maximum adult dose if wt >145 lb/65 kg	Volume of max dose if wt is 120 lb/54 kg	Volume of max dose if wt is 100 lb/45 kg	Volume of max dose if wt is 80 lb/36 kg
Lidocaine 1%: 10 mg/ml 2%: 20 mg/ml	4.5 mg/kg Max:300 mg	30 ml (1%) 15 ml (2%)	24 ml (1%) 12 ml (2%)	20 ml (1%) 10 ml (2%)	16 ml (1%) 8 ml (2%)
Lidocaine with epinephrine 1:100,000 or 1:200,000	7 mg/kg Max: 500 mg	50 ml (1%) 25 ml (2%)	38 ml (1%) 19 ml (2%)	31 ml (1%) 15 ml (2%)	25 ml (1%) 12 ml (2%)
Bupivacaine (Marcaine) 0.25%: 2.5 mg/ml	2.5 mg/kg Max: 175 mg	70 ml	61 ml	45 ml	36 ml
Bupivacaine with epinephrine[b]	Max: 225 mg	90 ml			
Mepivacaine 1%: 10 mg/ml	Max: 400 mg	40 ml			

[a]Maximum doses should be decreased in patients with severe liver disease or severe congestive heart failure due to decreased metabolism by the liver

[b]Buffering bupivacaine with sodium bicarbonate is not advisable as the anesthetic may precipitate out of solution

Summary

Local anesthesia is a critical part of skin cancer surgery. It is often the fear of pain that makes the patient most concerned. When local anesthesia is done well, it will provide the patient with a safe, painless, and anxiety-free experience. This, in turn, will allow the surgeon to concentrate on the bigger job at hand. The authors recommend that interested readers review the references cited for additional detail.

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Chapter 10
Excision Techniques and Materials

Mollie MacCormack

Excisions are one of the most commonly performed dermatologic procedures and are carried out for a variety of reasons including diagnosis, the therapeutic removal of malignant and benign growths, and simply for improved appearance. While the vast majority of excisions are straightforward in nature, close attention to a few basic tenets will enhance both the efficiency of the procedure and overall final aesthetic result. This chapter will review the basic materials required for a successful excision as well as the most commonly utilized excision and wound closure techniques.

Patient Preparation

Patient preparation is of great importance in assuring a successful outcome to any surgical procedure. Early identification of any potential complicating factors can greatly reduce the incidence of adverse events (Table 10.1). Preoperative evaluation should begin with assessment of patient comorbidities that may prevent the patient from providing informed consent, decrease the patient's ability to tolerate the procedure, place them at increased risk of complications such as bleeding or infection, or interfere with appropriate wound healing. All women of childbearing age should be asked about potential pregnancy. While pregnancy is not an absolute contraindication to cutaneous surgery, for medicolegal reasons, one may choose to defer elective procedures until after delivery. Medically necessary care, however, should not be delayed regardless of trimester, a position supported by a 2019 committee opinion from the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the American Society of Anesthesiologists [1]. A complete list of medications is required, with close attention paid to those medications and herbal supplements that may affect the ability to obtain hemostasis (Table 10.2) or potentially complicate wound healing such as systemic corticosteroids or immunosuppressants [2–5]. It is important to note that while in the past it was common practice to discontinue those medications that may increase the risk of bleeding, a number of studies have shown that the actual negative impact of such medications is quite small, while the potential ramifications of discontinuation on overall health (stroke, myocardial infarction, pulmonary embolus, etc.) are devastating [6–9]. For this reason, while patients may be advised to discontinue herbal supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), or aspirin taken for primary prevention, it is strongly recommended that patients be maintained on all necessary medications such as prescription anticoagulant/

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Table 10.1 Preoperative patient evaluation

Medical comorbidities	Anxiety Arthritis/severe musculoskeletal disease (Positioning/ Post-procedure care) Artificial heart valves Cardiovascular disease/cardiac anomalies Clotting disorders Dementia Diabetes History of endocarditis History of poor wound healing/ keloid formation History of radiation Hypertension Malnutrition Obesity Peripheral vascular disease Pregnancy Prosthetic joints Smoking
Medications/herbal supplements	Anticoagulants Antiplatelet agents Accutane use within the past 6–12 months Chemotherapy Corticosteroids Herbal supplements Immunosuppressants
Allergies	Drug Adhesive Latex Other
Electrical devices	Pacemaker Implantable cardiac defibrillator Brain/bladder stimulator Cochlear implant Other
Social environment	Patient ability to care for wound/obtain assistance in wound care Travel plans Work restrictions

Table 10.2 Agents affecting coagulation cascade [3–5]

Anticoagulants	Antiplatelet agents	Dietary/herbal supplements (partial list)
Direct thrombin inhibitor	COX inhibitors	Black cohosh
Argatroban	Aspirin	Chamomile
Bivalirudin	NSAIDS	Feverfew
Dabigatran	GPIIb/IIIa inhibitors	Fish oil
Desirudin	Abciximab	Flaxseed
Hirudin	Eptifibatide	Garlic
Indirect thrombin inhibitors	Tirofiban	Ginger
Dalteparin	P2Y12 inhibitors	Ginkgo biloba
Enoxaparin	Cangrelor	Ginseng
Fondaparinux	Clopidogrel	Green tea
Heparin	Prasugrel	Magnesium
Direct Xa inhibitors	Ticagrelor	Saw palmetto
Apixaban	Ticlopidine	St. John's wort
Betrixaban	Phosphodiesterase inhibitors	Turmeric
Edoxaban	Cilostazol	Vitamin E
Rivaroxaban	Dipyridamole	
Vitamin K antagonist	Bruton's tyrosine kinase inhibitor	
Warfarin	Ibrutinib	

antiplatelet agents. One exception to this rule is ibrutnib, a therapeuatic agent used in the treatment of B-cell lymphoproliferative disorders that carries a significant risk of bleeding. Pre-operative consulation with hematology is advisable. Risk of bleeding is more profoundly increased for patients on combination therapy [10, 11]. In a similar vein, while previously it was commonly taught that recent isotretinoin use could have a negative impact on wound healing, this is not supported by the literature pertaining to cutaneous excisions and should not be considered prohibitive [12].

Any existing drug allergies should be recorded and avoided as should allergies to disinfectants, suture material, and dressing supplies (latex and adhesive). Patients should be evaluated for any implanted electrical devices such as pacemakers, cardiac defibrillators, and nerve stimulators that may receive interference from electrosurgery. In addition, needle/surgical phobias or simply patient anxiety is not uncommon in the surgical setting and should be addressed. Frequently, a complete explanation of the procedure is all that is required to allay patient concerns.

Simple nonpharmacologic interventions such as a peaceful office setting, soothing music, the use of drapes to minimize visualization of surgical instruments and the surgical field, and distracting conversation are often quite beneficial in placing a patient at ease.

In more severe cases, premedication with low-dose anxiolytics such as lorazepam given orally prior to the procedure can be helpful (after first ensuring that the patient has a companion available to drive them home).

Antibiotic Prophylaxis

> The vast majority of dermatologic excisions do not require pre- or postoperative antibiotics.

Guidelines for endocarditis prophylaxis were published by the American Heart Association in 2007 [13] followed by a more focused update in 2017 [14]. Based upon these recommendations, routine prophylaxis is rarely required and is deemed appropriate only for procedures involving perforation of the respiratory tract/oral mucosa or performed in actively infected tissue in a small subgroup of patients at highest risk of adverse outcome from infective endocarditis (Table 10.3).

For those patients who require prophylaxis, antibiotic choice should be directed toward the eradication of viridans group streptococci for procedures involving perforation of oral/respiratory mucosa and staphylococci and beta-hemolytic streptococci if the procedure involves infected skin. Should methicillin-resistant *Staphylococcus aureus* (MRSA) be suspected, clindamycin or vancomycin would be the drug of choice (Table 10.4).

While no official guidelines exist addressing the issue of cutaneous surgery and prophylaxis of artificial joints, in 2015, the American Dental Association Council on Scientific Affairs published clinical practice guidelines stating that routine antibiotic prophylaxis was not indicated

Table 10.3 Cardiac conditions associated with endocarditis and high risk of adverse outcome [13]

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Some congenital heart disease (CHD) Unrepaired cyanotic CHD, including palliative shunts and conduits Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

Adapted from AHA guidelines on Prevention of Infective Endocarditis. Wilson W, Taubert KA, Gewitz M, et al., Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group, Circulation, Vol. 116/Issue 15, pages 1736–175, © 2007, https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.106.183095?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed, with permission from Wolters Kluwer Health, Inc.

Table 10.4 Regimens for endocarditis/prosthetic joint prophylaxis for high-risk patients undergoing procedure involving oral/respiratory mucosa or infected surgical site [20]

Regimen: Single dose 30 to 60 min before procedure			
Skin		Respiratory/oral mucosa	
No penicillin or cephalosporin allergy	Penicillin or cephalosporin allergy	No penicillin or cephalosporin allergy	Penicillin or cephalosporin allergy
Cephalexin 2 g PO Dicloxacillin 2 g PO Cefazolin/ceftriaxone 1 g IM/IV	Clindamycin 600 mg PO Azithromycin/clarithromycin 500 mg PO Clindamycin 600 mg IM/IV	Amoxicillin 2 g PO Cefazolin/ceftriaxone 1 g IM/IV Ampicillin 2 g IM/IV	Clindamycin 600 mg PO Azithromycin/clarithromycin 500 mg PO Clindamycin 600 mg IM/IV

Adapted from Journal of the American Academy of Dermatology, Vol. 59/Issue 3, Wright TI, Baddour LM, Berbari EF, et al., Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008, pages 464–473, © 2008, with permission from Elsevier

Table 10.5 Patients with potential increased risk of prosthetic joint infection [16]

First 2 years after procedure
Prior prosthetic joint infection
Hemophilia
Insulin-dependent diabetes
Immunocompromised/immunosuppressed
Malignancy
Malnourished

Adapted from The Journal of the American Dental Association, Vol. 134/Issue 7, American Dental Association, American Academy of Orthopedic Surgeons, Antibiotic prophylaxis for dental patients with total joint replacements, pages 895–899, ©2003, with permission from Elsevier/American Dental Association

for patients with a history of prosthetic joints [15]. Previous consensus recommendations from the American Dental Association and the American Academy of Orthopedic Surgeons had suggested treating a subset of patients who may be at higher risk of developing bacteremia-induced prosthetic joint infection, including all patients within the first 2 years following their procedure (Table 10.5) [16]; however, a 2010 study indicated that neither dental procedures nor antibiotic prophylaxis prior to dental procedures was associated with risk of prosthetic hip or knee infections [17]. Increasingly narrowed joint prophylaxis has been reflected in appropriate use criteria developed by the American Academy of Orthopedic Surgeons [18]. Given that the incidence of bacteremia is far lower for cutaneous surgery than dental work, at the current time, there is no evidence to suggest that prophylaxis is required for the vast majority of prosthetic joint recipients undergoing clean cutaneous procedures. As bacteremia associated with skin infections can seed prosthetic joints, prophylaxis should be considered for procedures involving a clean-contaminated site, and any active infection should be aggressively treated [19, 20].

Site Preparation and Anesthesia

Preoperative Antisepsis

The ideal cutaneous antiseptic would provide complete, long-lasting sterilization of the operative field with no tissue toxicity. A number of choices are available for antiseptic preparation of the cutaneous surface (Table 10.6). The most commonly used are 10% povidone-iodine, 4% chlorhexidine gluconate, 70% isopropyl alcohol, and 2% chlorhexidine gluconate combined with 70% isopropyl alcohol. Povidone-iodine has broad-spectrum activity against bacteria and some viruses; however, it is easily inactivated as it is only effective when dry. Chlorhexidine is slower in onset; however, its overall effect is of longer duration, and it has been demonstrated to be superior to povidone-iodine in decreasing bacterial load [21]. Prolonged, direct contact with chlorhexidine can lead to irreversible keratitis and ototoxicity; thus, care must be taken with use close

Table 10.6 Antiseptic solutions

Antiseptic agent	Advantages	Disadvantages
Povidone-iodine	Broad spectrum, including fungi	Quickly neutralized by blood, serum proteins, or sputum; irritant; potential systemic toxicity with large body surface area
Chlorhexidine gluconate	Prolonged effect	Keratitis and otitis
Hexachlorophene		Neurotoxicity in infants
Hypochlorous acid	Minimal cytotoxic effect	Not yet studied on corneal cells
Isopropyl alcohol	Inexpensive	Flammable, must allow it to dry, toxic to the cornea

to the ears and eyes [22]. 0.01% hypochlorous acid has been shown to have antibacterial properties with minimal cytotoxic effect, yet no studies have looked directly at effect on corneal cells [23]. Comparative studies suggest that a combination of 70% isopropyl alcohol and 2% chlorhexidine gluconate, as well as a combined isopropyl alcohol/povidone-iodine scrub, provides the best immediate and persistent antimicrobial effect [24, 25].

Anesthesia

Most cutaneous excisions can be performed under local anesthesia. The most commonly used anesthetic for dermatologic procedures is 0.5–1% lidocaine due to its rapid onset of action and intermediate duration of effect. The addition of epinephrine not only provides increased hemostasis but also extends efficacy. Maximum recommended dose is 4.5 mg/kg for the plain formulation and 7 mg/kg for lidocaine plus epinephrine [26]. While it was once thought that only plain lidocaine could be used in anatomic areas such as the nose, ear, or penis, this is not the case, and there are no absolute anatomic contraindications to epinephrine use [27–29]. The use of epinephrine should be avoided in patients taking propanolol, a nonselective beta-blocker, as it could potentially lead to malignant hypertension [30]. True allergy to anesthetics is rare. It is important to obtain a complete history of reported allergic reactions as what many patients interpret as an allergic response is actually a vasovagal episode or symptoms due to epinephrine effect (palpitations, shaking, sweating, light-headedness). In the uncommon case of actual allergy, the offending agent is often the preservative present in multidose vials or a sodium metabolite found in epinephrine-containing products [31]. Should a true lidocaine allergy exists, an ester anesthetic such as procaine can be substituted.

The discomfort associated with anesthesia injection is multifactorial, in part due to tissue distension and the acidity of the anesthetic (especially in epinephrine-containing formulations). Simply buffering the anesthetic with sodium bicarbonate in a 9:1 formulation, initiating the injection in the more distensible subcutaneous tissue, and decreasing the speed of infiltration can increase patient comfort substantially [32]. An in-depth review of cutaneous anesthesia is provided in Chap. 9.

Excision Margins

Surgical margins vary based on factors such as tumor type, intent of procedure (diagnostic versus therapeutic), and tumor size/depth. For basal cell carcinomas less than 2 cm in diameter located in low-risk anatomic areas (the trunk, extremities), a margin of 4 mm provides a 98% initial cure rate [33]. Larger basal cell carcinomas, as well as tumors with more aggressive histologic growth patterns—such as morpheaform and micronodular tumors—have been shown to potentially have a greater degree of subclinical extension and thus should be either excised with wider margins or treated with Mohs micrographic surgery [33–36]. Recurrence rates for primarily excised basal cell carcinomas range from approximately 5% to 10% at 5 years [37, 38]. Well-differentiated squamous cell carcinomas less than 2 cm in diameter and located in low-risk anatomic areas excised with a 4-mm margin have a 95% initial clearance rate; however, moderately/poorly differentiated tumors or tumors greater than 2 cm in diameter require a 6-mm margin [39]. Recurrence is about 8% at 5 years [40]. For tumors in high-risk locations (H-zone of the face, genitalia, hand/feet, ears) or very large tumors, Mohs micrographic surgery may be a better treatment option due to its higher cure rate [41].

Table 10.7 Principles of surgical margins for wide excision of primary melanoma [42]

Melanoma Tumor Thickness	Recommended Clinical Margins Excision recommendations are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1)
In situ	0.5–1.0 cm (category 2A) For large and/or poorly defined MIS, lentigo maligna type, surgical margins >0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered, particularly prior to complex surgical repair. For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with MIS) or RT (category 2B)
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2.0 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)
Margins may be modified to accommodate individual anatomic or functional considerations Consider histologic margin assessment prior to reconstruction and closure	
NCCN categories of evidence *Category 1:* Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate *Category 2A:* Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate *Category 2B:* Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate	

Recommendations for the surgical margins to use during wide excision of primary melanoma have been made by the National Comprehensive Cancer Network as outlined in Table 10.7 [42] and further discussed in Chap. 15.

Specimen Handling

Proper handling of tissue specimens is essential. Specimen containers should be prepared and labeled prior to the start of the procedure. All specimens should be transported directly from patient to container with immediate confirmation that the specimen is indeed in the container before continuing.

Hemostasis

Obtaining hemostasis is essential for appropriate field visualization as well as prevention of adverse postoperative events such as excessive bruising and/or hematoma formation. For very small procedures, simple pressure and suturing may be all that is needed. However, most excisions proceed more smoothly with the use of an external device such as a heat cautery unit, hyfrecator, or electrocoagulation device. Heat cautery can be provided either via disposable handheld units or by a freestanding unit with single-use or sterilizable tips and is a good choice for patients with pacemakers, implantable cardiac defibrillators, brain stimulators, or other internal electronic devices as there is no current transmitted that could cause potential interference; low-voltage, high-amperage current is used to create heat. Hyfrecators work via the emission of monoterminal, high-voltage, low-amperage current, while full electrosurgery units use high-amperage, lower-voltage AC electricity to achieve effect (Table 10.8). Most electrosurgery units have "cut" and "coagulation" settings. The "cut" current is a continuous, lower-voltage, high-amperage current producing high levels of heat that rapidly vaporizes tissue, while the "coagulation" current is a pulsed, lower-voltage, higher-amperage current that produces heat more slowly, leading to blood coagulation and more diffuse tissue damage [43]. Monopolar electrocautery units require the use of a return (dispersive) electrode and entail passage of electrical current through the patient, whereas in bipolar electrocautery units, the current should

Table 10.8 Electrosurgical devices

Device	Current	Terminal	Voltage	Amperage	Tissue contact	Tissue destruction
Electrocautery	Direct	N/A	(Low)	(High)	Yes (heat only)	Very high
Electrocoagulation	Alternating	Mono	Low	High	Yes	Very high
Electrodesiccation	Alternating	Mono	High	Low	Yes	High
Electrofulguration	Alternating	Bi	Very high	Low	No	Moderate
Electrosection	Alternating	Bi	Low	High	Yes	Low

pass only through the tissue placed between the forceps probe, making it a safer choice for patients with internal electrical devices [40, 43–45].

To obtain hemostasis, the wound should first be blotted with gauze or similar material so that active sites of bleeding can be identified. The offending blood vessels can then be treated directly or grasped with forceps to which the electrosurgery tip is then placed. The desired endpoint is a bloodless field, yet it is important to remember that excessive cautery can delay wound healing and increase risk of infection. On occasion, some vessels are too large to be treated with electrosurgery and need to be tied off with suture. As cautery is by its very nature a destructive process, unnecessary cautery and treatment of the skin edge should be avoided.

Suture Materials

Sutures are classified by their physical characteristics: whether they are composed of natural or synthetic materials, their ability to be broken down by the body (absorbable versus nonabsorbable), whether they consist of one or more filaments (mono- versus multifilament), size, and tensile strength (the force the suture can stand before breaking).

Natural Versus Synthetic

Natural suture materials include silk and surgical gut suture, the latter of which is composed of purified connective tissue derived from the sheep or bovine intestine [46]. Natural sutures tend to cause greater tissue inflammation and may be more prone to point variabilities in strength than their synthetic counterparts.

Absorbable Versus Nonabsorbable

Traditionally, absorbable sutures are used for deep closure, and nonabsorbable sutures are used for epidermal repair; however, there are many exceptions to this rule. Absorbable sutures are defined as those that maintain tensile strength for less than 60 days. Natural absorbable sutures are digested by body enzymes (proteolysis), while synthetic absorbable sutures are hydrolyzed as they absorb water (hydrolysis), a process which is felt to be less inflammatory than enzymatic breakdown. Nonabsorbable sutures maintain tensile strength for more than 60 days; if used internally, it should be anticipated that such suture will maintain indefinitely.

Monofilament Versus Multifilament Versus Barbed

Multifilament sutures are composed of two or more strands twisted together, increasing tensile strength and flexibility. Such sutures are sometimes coated with various materials to reduce friction [46]. Monofilament sutures are composed of a single strand which is felt to not only minimize trauma while passing through tissue but also decrease the risk of bacterial colonization and growth. Monofilament sutures typically display a greater degree of memory and may require greater care to ensure knot security. In addition, care must be taken when handling monofilament suture as weak spots can be cre-

ated by crushing or crimpling. Newer suture materials include self-anchoring barbed sutures which eliminate the need to knot as well as sutures coated or laced with antimicrobial and other pharmacologic agents to facilitate wound healing [47, 48].

Size and Tensile Strength

Suture size is classified numerically; the higher the number of "0s," the finer the suture. Suture sizes currently range from 11-0 (smallest) to 7 (largest). For a particular suture type, the finer the suture, the lower the tensile strength. In general, the tensile strength (defined as the force required in newtons to break a knot) of a suture needs not exceed that of the tissue in which it will be placed. The very act of knotting can have a dramatic impact on tensile strength, decreasing it by as much as 19–62% [49]. This differs from knot strength which is the ability of a knot to avoid opening [50]. Nylon suture has been shown to have a higher tensile strength than polypropylene, yet the reverse is true when knotted, which is more representative of clinical use. For absorbable sutures, poliglecaprone has been shown to have a 57% drop in failure load when knotted making it a less ideal option for high-tension repairs [49]. Loss of tensile strength and suture absorption do not go hand in hand. A suture may lose tensile strength quickly yet be absorbed slowly or may maintain tensile strength throughout wound healing until the suture is absorbed.

Choice of suture material is largely a matter of physician and patient preference. The major characteristics of the most commonly used suture materials are outlined in Table 10.9 [49].

As a general rule, the smallest suture providing adequate tensile strength is preferred. Superficial placement of dermal suture and knots may result in "spitting sutures" or suture granulomas. Overly tight epidermal sutures, as well as failure to remove epidermal sutures in a timely fashion, may lead to the formation of suture marks resulting from epidermal ingrowth/scarring along the suture line. In most cases, facial sutures should come out within 5–7 days, while sutures on the trunk and extremities should be removed between days 10 and 14.

Table 10.9 Suture characteristics

Suture	Filament type	Tensile strength/ retention	Inflammatory response	Absorption	Notes
Absorbable					
Surgical gut (plain)	Mono	Low 7–10 days	++	70 days	Collagen from the sheep/beef intestine
Surgical gut (fast absorbing)	Mono	Low 5–7 days	++		Treated with heat to speed absorption Good for low-tension facial closures, full-thickness skin grafts
Surgical gut (Chromic)	Mono	Low 10–14 days	++	90 days	Chromium salts slow absorption and decrease reactivity
Polyglactin 910 (coated Vicryl Rapide)	Mono and braided	Good 50% at 5 days, 0% at 14 days	+	40 days	Copolymer of lactide and glycolide with 370 and calcium stearate coating

Table 10.9 (continued)

Suture	Filament type	Tensile strength/ retention	Inflammatory response	Absorption	Notes
Polyglactin 910 (Vicryl)	Braided	High 65–75% at 14 days 20–50% at 21 days 10% at 35 days	+	Minimal for 45 days, complete by 70 days	Rapid absorption once tensile strength is lost
Poliglecaprone 25 (Monocryl)	Mono	High 50–60% at 7 days 20–30% at 14 days 0% at 21 days	–	120 days	Very pliable, good for subcuticular closure, potentially lower rate of suture extrusion compared to polyglactin-910
Polydioxanone (PDS II)	Mono	High 70% at 14 days 50% at 28 days 25% at 42 days	+	6 months	Lower initial tensile strength but longer retention providing extended wound support
Polydioxanone barbed (Quill)	Mono	High 80% at 2 weeks, 60% at 4 weeks, 40% at 6 weeks	+	180 days	Available in sizes of 2 to 3-0, upsize by one USP
Polyglycolic acid/ polycaprolactone (Monoderm, Quill)	Mono	High 42–76% at 7 days, 36–52% at 14 days	+	90–120 days	Available in sizes of 3-0 to 5-0, upsize by one USP
Polyglyconate (Maxon)	Mono	Very high 59% at 28 days	–	180 days	Expands to accommodate swelling
Nonabsorbable					
Silk	Braided	0% by 1 year	+++	+/– 2 years	Handles well, high reactivity
Nylon (Ethilon)	Mono	81% at 1 year	–	Slowly hydrolyzed	Good elasticity, high memory
Nylon (Nurolon)	Braided	High	–	Slowly hydrolyzed	Inexpensive
Polyester (Ethibond Excel, Mersilene)	Mono (Excel) Mono and braided (Mersilene)	High	–	+	
Polypropylene (Prolene)	Mono	2 years	–	–	Does not stick to tissue, good for subcuticular or other "pullout" closures

Needles

Surgical needles are made from stainless steel. They need to be strong enough to pass through tissue with minimal alteration of shape (needle strength) yet flexible enough to bend without breaking if tissue resistance is met (needle ductility). Needles should be selected to be as slim as possible to pass though tissue and sharp enough to minimize tissue trauma. Silicone coatings can enhance needle glide.

There are three main components to every needle: the point, the body, and the eye (the swaged end attached to the suture) (Fig. 10.1). Needle length refers to the distance from the point to the end along the needle. Chord length refers to the distance measured by drawing a straight line connecting the point of the needle to the swag. The thickness of the needle is called the needle diameter, and needle radius is calculated by measuring the distance from circle center to needle body if the needle curvature was continued to create a full ring. Needles come in a variety of shapes; those most often used in dermatologic surgery are either 3/8 or 1/2 circles.

> To avoid weakening the needle, it should always be grasped by the needle holder at 1/3 to 1/2 the distance from the swaged end to the needle point.

The needle point extends from the tip to the widest cross section of the body. Cutting needles have sharpened tips with at least two opposing cutting edges to enable passage through dense tissue. Conventional cutting needles have a third cutting edge on the inner needle curvature, while reverse cutting needles have a third cutting edge located on the outer convex curve.

> Reverse cutting needles have many advantages for dermatologic surgery: the needles tend to be stronger; by positioning the cutting edge on the outer arc, the suture placed pulls against a flat edge decreasing the risk of suture pull through; and the needle itself is less likely to result in unwanted cut through of the tissue edge.

Needles are manufactured with varying degrees of sharpness. In general, the more a needle is honed, the more expensive it becomes. Needles designated as "P,""PS," or "PC" (plastic, plastic skin, and precision cosmetic—Ethicon US, LLC, Bridgewater, NJ) are excellent choices for facial reconstruction, while a lower-quality needle such as "FS" (for skin, Ethicon US, LLC, Bridgewater, NJ) may be adequate for work on the trunk and extremities.

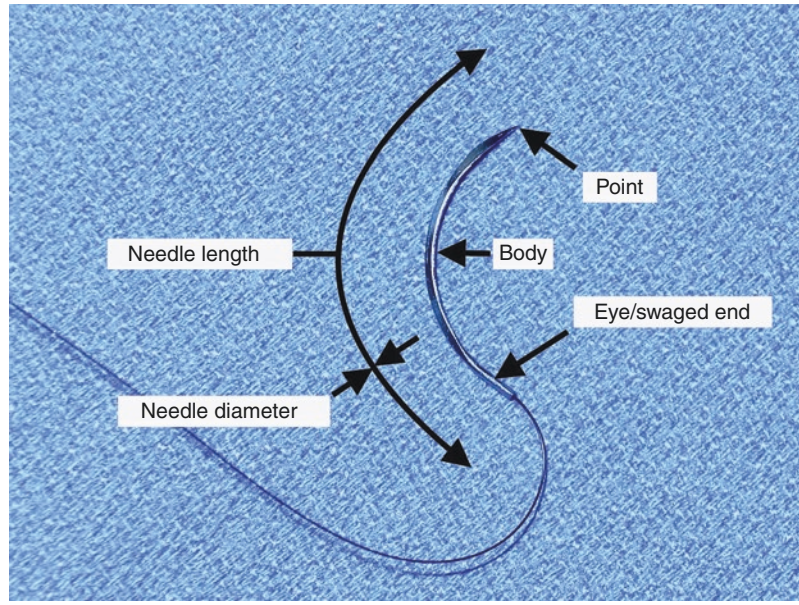

Fig. 10.1 Surgical needle anatomy

Staples

Composed of stainless steel, staples provide a rapid, secure means of wound closure. While sutures typically allow for more precise alignment of wound edges, in certain areas such as the scalp, staples can provide an equivalent or even slightly improved overall cosmetic outcome [51, 52]. Staple placement can be four to ten times faster than suturing and thus be of use when time is a pressing concern [53, 54].

A variety of disposable stapler sizes and designs are available. To place a staple, the stapler tip is firmly placed perpendicular to the wound edge and the handle depressed. Staplers typically provide excellent wound edge eversion; however, if additional eversion is required, an assistant can manually evert the wound edge using a pair of toothed Adson forceps prior to staple discharge. Specialized staple removers enable easy extraction.

Skin Adhesive

Skin adhesives composed of cyanoacrylates can be an acceptable choice for closure in appropriately selected wounds. When used in conjunction with carefully placed dermal sutures, cosmetic outcome has been shown to be excellent in low-tension repairs [55–57]. However, as tensile strength is low, in areas of high mobility or tension, epidermal sutures may be a better choice [58, 59]. For proper application of skin adhesive, the wound should first be completely reapproximated with deep sutures. The skin surface is cleaned and dried, the wound edges manually are everted and apposed with forceps, and the adhesive is applied extending at least 1/2 cm beyond the wound edge, gradually building up to three or four layers.

As skin adhesive forms its own dressing, minimal postoperative care is required. Patients should be instructed to avoid over-washing or application of topical antibiotics and other petrolatum-based products as this can result in rapid breakdown of the adhesive.

Skin Tape

Various types of skin tapes are available, typically composed of nonocclusive, microporous material. While simple tapes such as Steri-Strip® closures (3M, St. Paul, MN) are more often used to provide additional support to an already closed wound, in certain cases with appropriately placed dermal sutures, adhesive skin strips may be an acceptable replacement for epidermal alignment [60]. In addition, more complex products such as Clozex® tape (Clozex Medical LLC, Wellesley, MA), an adhesive film with multiple interlocking filaments that allow for wound edge approximation, have been shown to have good effect [61]. To obtain best adhesive results, the skin should be degreased with alcohol or acetone and Mastisol® (Ferndale Laboratories, Ferndale, MI) or tincture of benzoin applied prior to application (after first verifying that the patient does not have an adhesive allergy).

Closure Techniques

Second Intention

After an excision has been performed, the surgical site can be left to heal on its own (second intention healing), which, while often slow, can be a suitable choice for defects in areas where primary closure is prohibited due to lack of tissue mobility or other issues such as a contaminated wound site or concerns regarding graft take. In certain instances such as a patient who does not wish to limit physical activity during wound healing, with wounds located in concavities such as the conchal bowl, medial canthus, and alar groove, as well as in many mucosal surfaces, second intention healing can be the closure of choice providing excellent cosmesis. In certain situations; a patient who does not wish to limit physical activity during wound healing, wounds located in concavities such as the conchal bowl, medial canthus and alar groove, and mucosal wounds, second intention

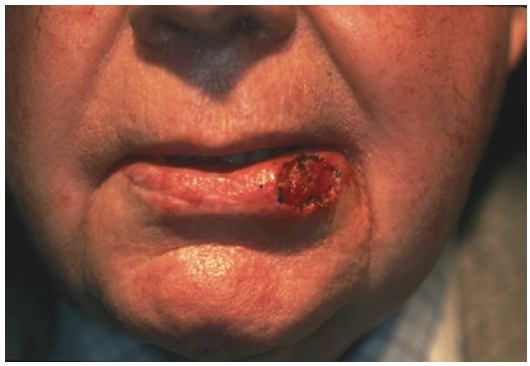

Fig. 10.2 Wound resulting from surgical removal of squamous cell carcinoma. (Photograph courtesy of Suzanne Olbricht, M.D.)

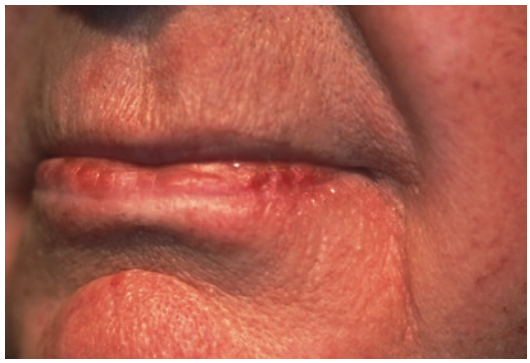

Fig. 10.3 Healed wound by second intention, 4 weeks after initial surgery. (Photograph courtesy of Suzanne Olbricht, M.D.)

healing can be the closure of choice providing excellent cosmesis [62–64] (Figs. 10.2 and 10.3). As second intention wounds contract as they heal, this type of healing should be undertaken with caution in areas adjacent to free margins such as the eyelid, nasal alar rim, and lip, as unwanted tissue distortion may result.

Layered Closures: Suture Techniques

The vast majority of excisions are closed primarily, and there are a number of techniques available to achieve closure. The simplest closure consists of purely epidermal sutures, a type of repair suitable only for areas with negligible tension. Should wound tension be present, a layered closure is a more appropriate choice. Deep dermal sutures function to close dead space, approximate wound edges, minimize epidermal tension, and provide wound eversion, while epidermal sutures act to further refine edge alignment. The unique characteristics of each wound, location, tension of repair, and skin quality, should influence the chosen suture technique.

Deep Sutures

Deep sutures refer to sutures placed entirely underneath the epidermal layer. While the benefits of wound eversion may be debated by some [65–67], all wounds benefit from appropriately placed dermal sutures resulting in a tight wound seal and decreased tension on the epidermis.

Buried Vertical Mattress/Set-Back Suture

When placing dermal sutures, use of the "buried vertical mattress technique" provides an excellent result due to prolonged dermal support and edge eversion [68, 69]. While similar to a traditional dermal suture, this technique is characterized by a few key differences. To begin, the needle should enter the base of the undermined skin edge through the subcutaneous fat, head up toward the superficial dermis, and then dive back down to exit the ipsilateral skin edge at the level of the deep dermis; the opposite pattern is repeated on the contralateral side, and a buried knot is placed. When drawn together, the central portion of the wound is elevated forming a tightly opposed, well-everted repair line (Fig. 10.20a).

Some practitioners have found this technique so effective that they forgo additional epidermal sutures [67, 69, 70]. In the rare situation where significant eversion is not desired, the dermal suture can be placed in the dermis

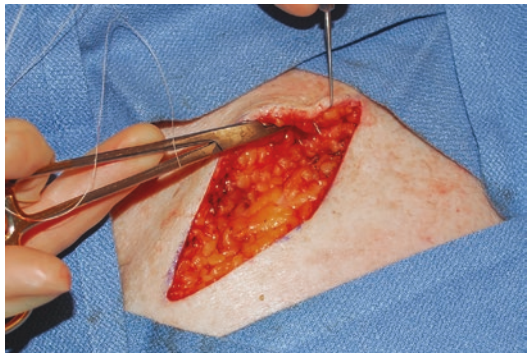

Fig. 10.4 In a set-back suture, the needle both enters and exits in a plane parallel to the skin surface, not along the incised skin edge. Once undermined, the wound edge is everted, and the needle enters roughly 5–10 mm from the wound edge; following the arc of the needle, the stitch exits along the subcutaneous plane approximately 2–4 mm from the wound edge. The movement is repeated on the contralateral side

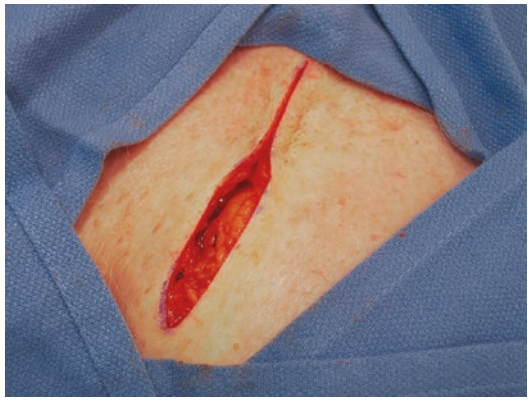

Fig. 10.5 Set-back sutures result in a highly everted wound with diminished dead space

without the exaggerated upward arch. An even more extreme form of this suture technique, referred to as the "set-back suture," has the dermal suture both entering and exiting from the undermined surface of the superficial subcutis (Figs. 10.4 and 10.5) [70]. High-tension wounds may benefit from additional techniques employed to decrease pressure along the wound edge, including deep plication sutures

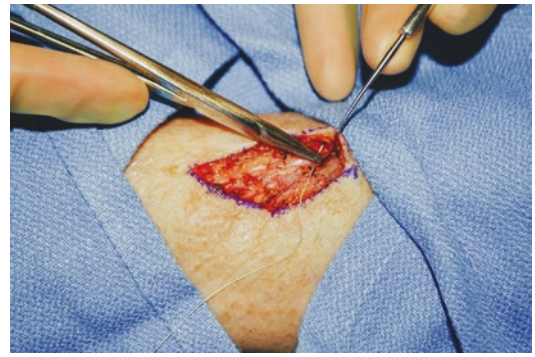

Fig. 10.6 The subcutaneous inverted cross mattress stitch is initiated as a buried vertical mattress suture. The needle enters from the undermined subcutaneous surface 3–5 mm from the wound edge, extending up to grasp a hearty bite of the upper dermis

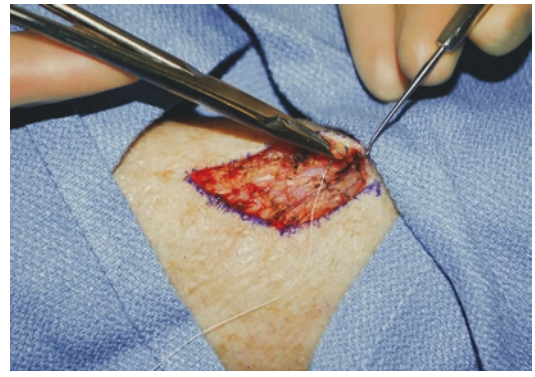

Fig. 10.7 The needle then descends to exit at the level of the deep reticular dermis

placed in the underlying tissue, suspension sutures where the deep tissue is tacked to an immobile entity such as periosteum, or pulley sutures where suture is placed with a double cycle of near-far or two identical sutures are placed in series before being tied off decreasing tension on each individual stitch. The subcutaneous inverted cross mattress stitch nicely illustrates this principle, placing two buried vertical mattress sutures in series before knotting [71] (Figs. 10.6, 10.7, 10.8, 10.9, 10.10, and 10.11).

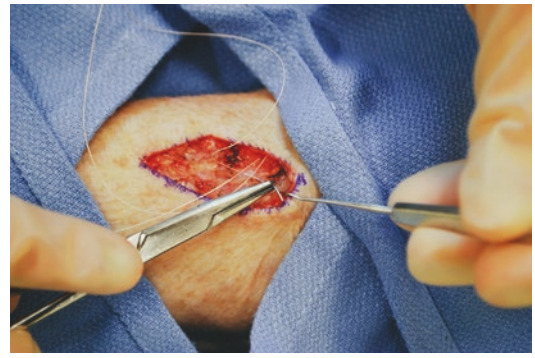

Fig. 10.8 The opposite is performed on the contralateral side as the needle enters at the level of the deep dermis, projects upward to the reticular dermis, and then exits in the undermined plane

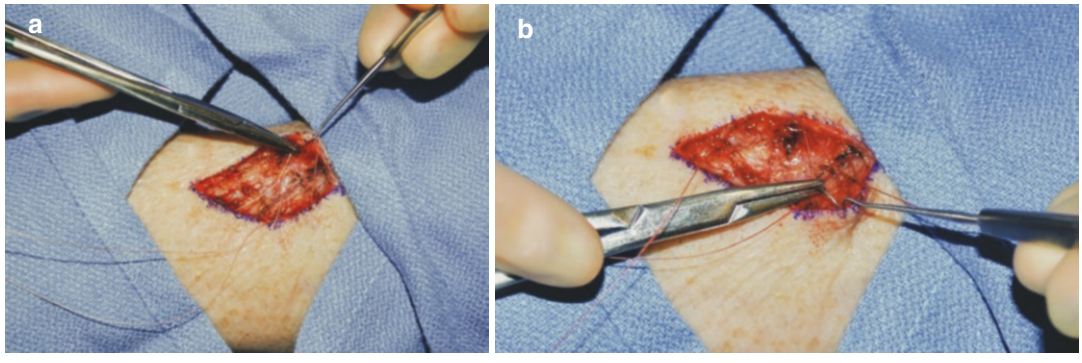

Fig. 10.9 To perform the SICM stitch, the needle is then advanced a few mm along the wound (**a**), and the same steps are repeated (**b**) the same

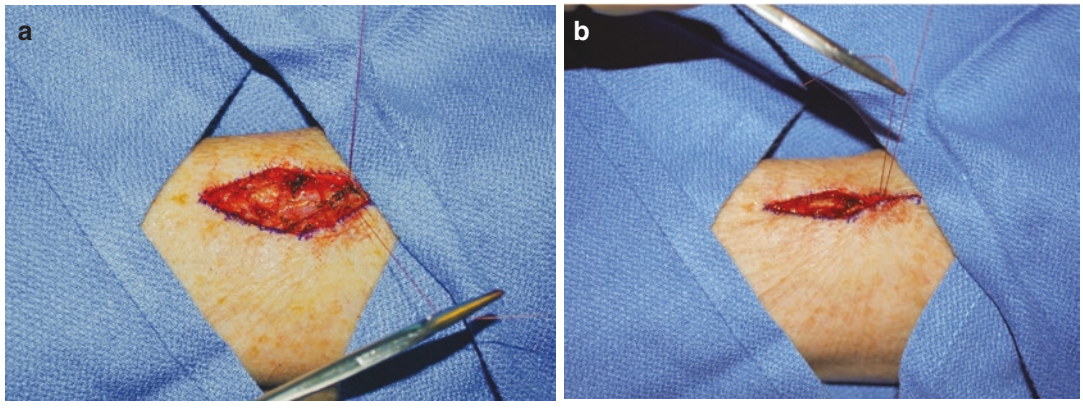

Fig. 10.10 The tail ends of the suture can then be tied lateral to the double stitch (**a**) or can be brought up between the two stitches and tied as shown (**b**) here

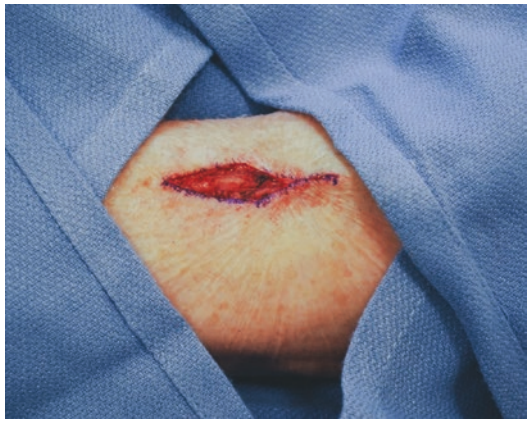

Fig. 10.11 The subcutaneous vertical mattress stitch results in a nicely everted wound with tension borne between two adjacent sutures and increased speed of placement compared to a traditional vertical mattress suture closure

Running Subcuticular Closure

Running subcuticular suturing can be an excellent choice for wounds with minimal tension or wounds where the tension has been relieved via deeper dermal sutures. If performed with nonabsorbable suture, selection of monofilament suture material will ease suture extraction due to decreased friction. If absorbable suture is selected, monofilament suture is again an excellent choice as it may lessen inflammation in the superficial dermis as the suture is hydrolyzed. Suture placement begins at one tip of the wound, passing the suture parallel to the skin surface taking relatively small bites just below the epidermis. As the suture exits the dermis, it should enter the contralateral side either directly across from or just slightly behind the point of exit. The technique is repeated, with care taken to maintain a uniform depth. Once the end of the wound is reached, the two suture tails can be tied to each other (nonabsorbable suture), or the suture can be tied back upon itself in a half-buried fashion (absorbable suture) [72, 73]. A variant referred to as a "zipper suture" essentially links a series of running buried vertical mattress sutures placed once wound tension has been alleviated by deeper dermal sutures [74].

Purse-String Repair

On occasion, it is beneficial to excise lesions in a disc design instead of the more traditional elliptical technique. Such wounds are often best repaired utilizing a "purse-string" closure. Various techniques exist for placing a purse-string suture. The original publication in the dermatologic literature described using a nonabsorbable 3-0 or 4-0 polypropylene subcuticular suture with an epidermal knot at 12 o'clock and escape loops placed at 3, 6, and 9 o'clock [75]. An alternative option is to use an absorbable suture weaving in and out horizontally in the mid to deep dermis as if one was placing a deep subcuticular running stitch without any escape loops. A third variant is to utilize a nonabsorbable suture, such as polypropylene, using vertically oriented bites placed approximately 5–10 mm from the wound edge. As the purse-string suture is drawn together and tied, the wound becomes puckered, much like the top of a draw-string purse. Once the wound has been maximally reapproximated, simple interrupted epidermal sutures can be placed to increase edge approximation and further speed healing [76, 77]. At the time of suture removal, the wound will continue to display moderate pleating; however, as long as the wound is in an area of moderate tension, these skin-folds almost always resolve. On occasion, it is impossible to close the wound completely, and the central area is closed with a skin graft or is left to heal by second intention (Figs. 10.12, 10.13, 10.14, 10.15, 10.16, 10.17, 10.18, and 10.19).

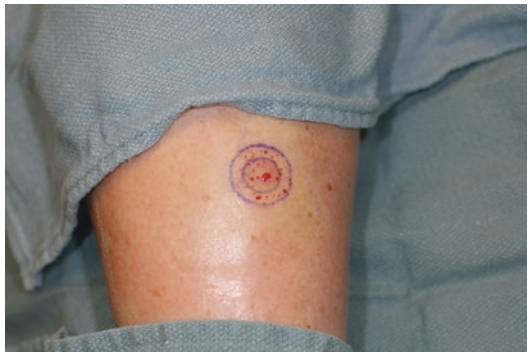

Fig. 10.12 Purse-string closure, margin marked

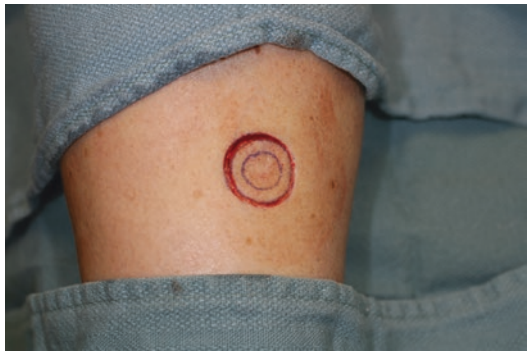

Fig. 10.13 Purse-string closure, margin incised

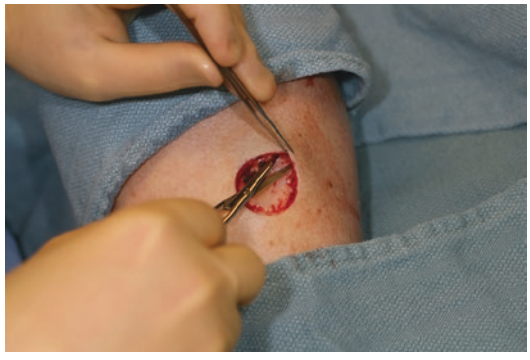

Fig. 10.14 Purse-string closure, undermining

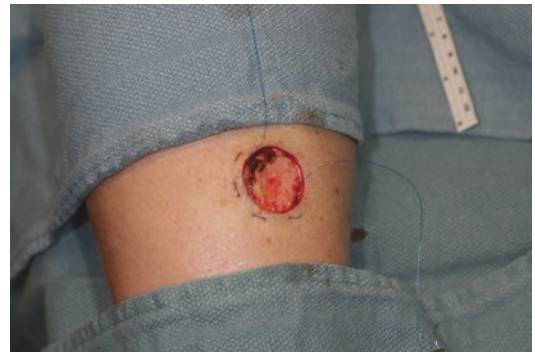

Fig. 10.15 Purse-string closure, purse-string suture of 4.0 Prolene placed

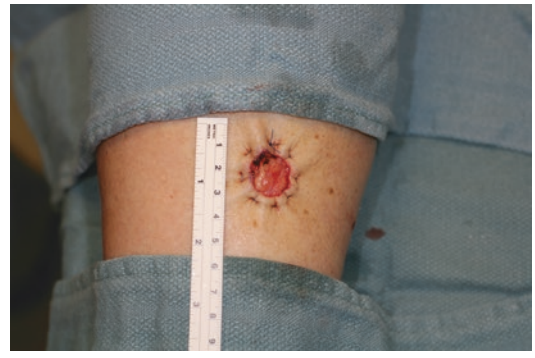

Fig. 10.16 Purse-string closure, purse-string suture tied

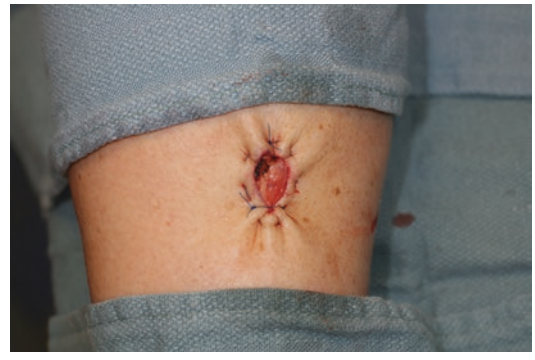

Fig. 10.17 Purse-string closure, further edge approximation

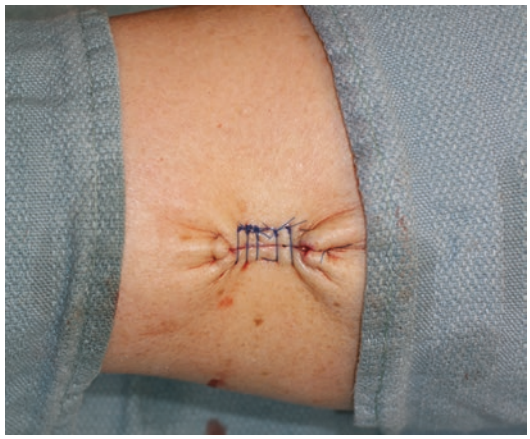

Fig. 10.18 Purse-string closure, final repair

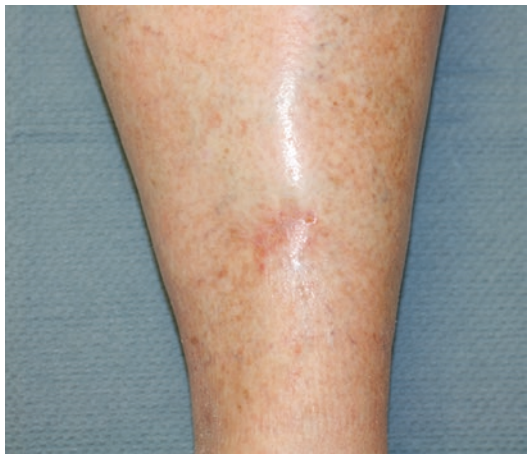

Fig. 10.19 Purse-string closure, 4-month outcome

Epidermal Suture Techniques

A myriad of techniques can be used for epidermal closure (Fig. 10.20).

Buried vertical mattress suture: When drawn together, the central portion of the wound is elevated forming a tightly opposed, well-everted wound (Fig. 10.20a).

Simple interrupted sutures provide good strength and allow for excellent wound edge alignment but are considered time-consuming by some (Fig. 10.20b). To be properly placed, the needle should enter the skin at 90 degrees within 1–2 mm of the wound edge; the needle should move smoothly through the dermis and subcutaneous fat to the contralateral side following the curve of the needle and exiting the skin in a similar manner. The two ends of suture are typically tied using an instrument tie in which a double loop (to help prevent knot slippage) is made around the needle driver tip utilizing the needle end of the suture. The needle driver then grasps the short (free) end of the suture and the two sides are pulled tight. The procedure is then repeated from the opposite direction to create the next knot; however, after the first knot is placed, only a single loop around the needle driver is required. Depending on the type of suture used, between three and six knots should be placed to avoid untying (more for monofilament as opposed to braided suture). Knots should be tight, but care must be taken to avoid strangulating the skin. One trick is to leave some laxity in the first one or two knots to accommodate potential swelling. If the wound is under tension and the first knot wants to slip, simply have an assistant firmly pinch with thumb and index finger the suture strands directly above the skin after the first knot is thrown. The second knot is placed in the usual fashion, sliding between the assistant's thumb and finger until it meets the first knot. Once the second knot is locked in place, the assistant may release the suture without fear of knot movement (Figs. 10.21, 10.22, and 10.23).

Running epidermal sutures are faster to place but may sacrifice some precision, run a greater risk of being pulled too tight leading to tissue strangulation, and are more vulnerable should the suture break (Fig. 10.20c). Locked running sutures in which the suture is passed underneath the epidermal loop just placed before proceeding to the next stitch are similar, may allow for more even tension, but carry a higher risk of vascular compromise (Fig. 10.20d).

Previously described running subcuticular sutures are faster to place than simple interrupted sutures and with good technique can provide

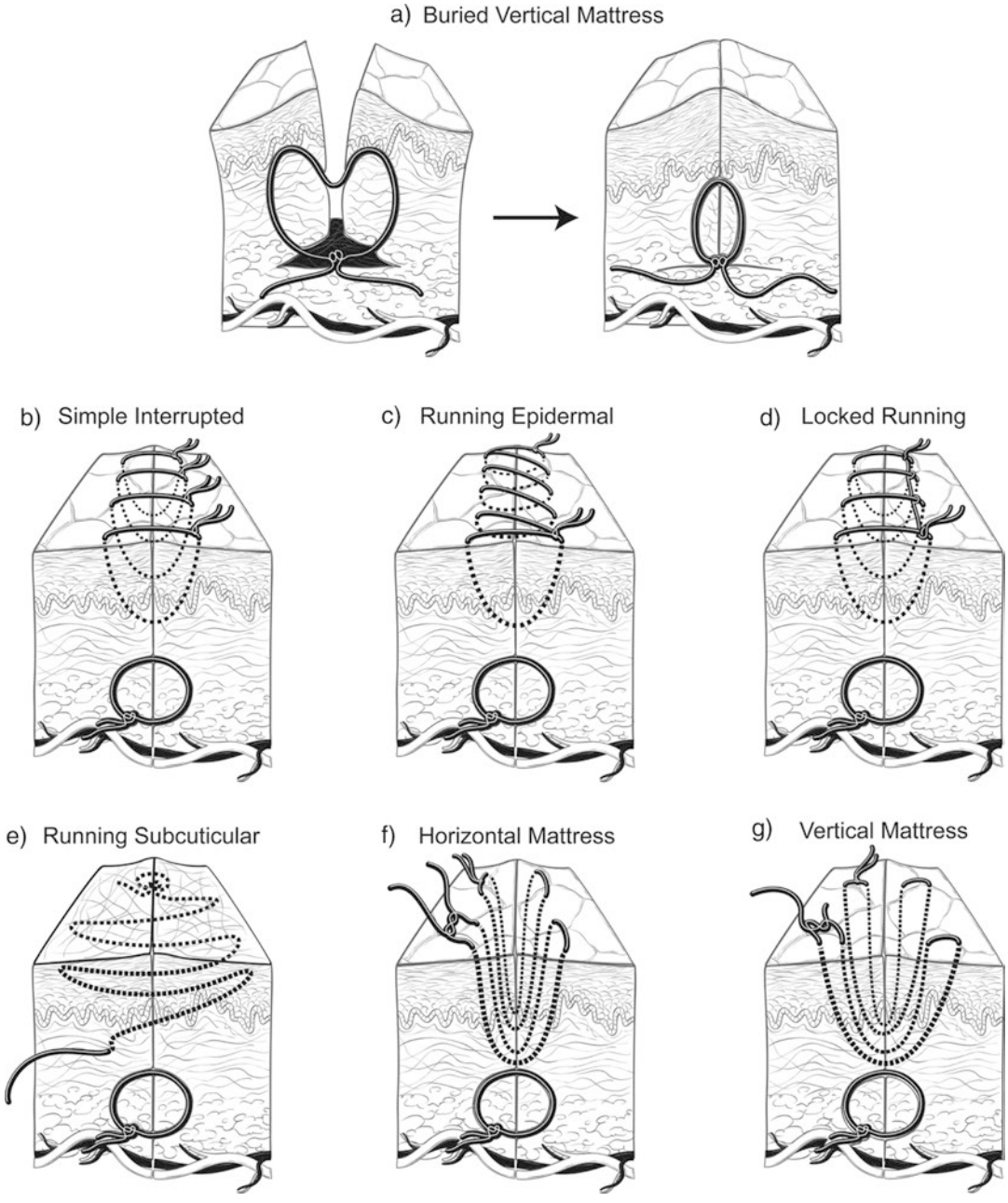

Fig. 10.20 Various suture techniques for dermal and epidermal closure. (Illustration by Alice Y. Chen)

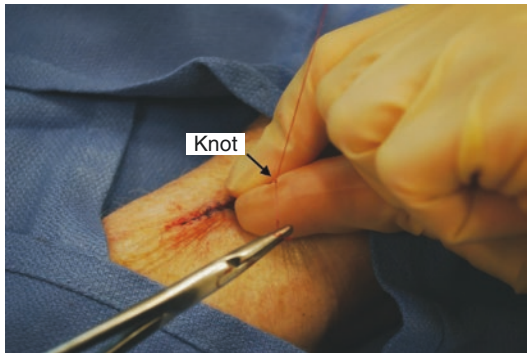

Fig. 10.21 After initial knot is thrown, the assistant pinches the free ends of suture tightly to prevent knot slippage. Second knot can then be easily created and advanced

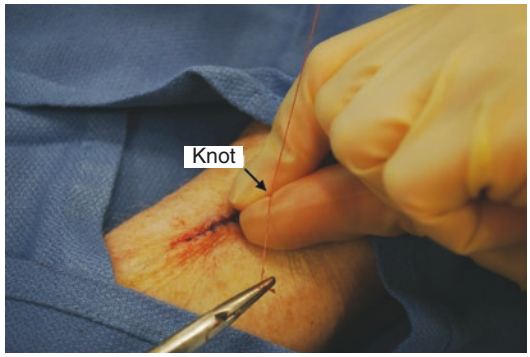

Fig. 10.22 Second knot is tightened while the assistant continues to pinch firmly

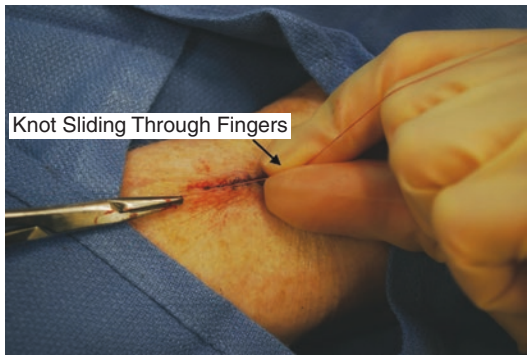

Fig. 10.23 Knot is passed through the pinch until it meets the first knot at which point the assistant releases suture

excellent wound edge alignment (Fig. 10.20e). Such sutures eliminate the risk of suture marks across the incision line, and if placed with buried knots and absorbable suture, the need for suture removal is eliminated.

Vertical mattress sutures where suture is placed utilizing a near-near-far-far design provide excellent wound edge eversion and are useful in areas such as the helical rim, where a depressed scar would be quite visible; however, if not removed promptly, they carry a high risk of leaving suture scar (Fig. 10.20g). Horizontal mattress sutures, either individual or running, are useful for closing areas under high tension, although if there is difficulty in edge approximation or concerns about tissue strangulation an alternative repair may be a better choice (Fig. 10.20f). High wound tension not only increases risk of vascular compromise, tissue injury, infection, and overall poor healing but also significantly increases risk of scar spread. Even for low-tension wounds, when tying off suture, it is important to use the minimal amount of force necessary to obtain edge approximation.

Description of Procedure

Elliptical Excision

The majority of excisions are elliptical or fusiform in design. By designing an excision with a length/width ratio of approximately 3:1 or 4:1 or with apical angles approximating 30° (on a flat plane), the likelihood of standing cone deformities or "dog ears" is markedly reduced, resulting in a cosmetically elegant flat scar.

> When performing excisions on convex areas, the desired apical angle is often less than 30°, while on a concave surface, apical angles greater than 30° are often well tolerated.

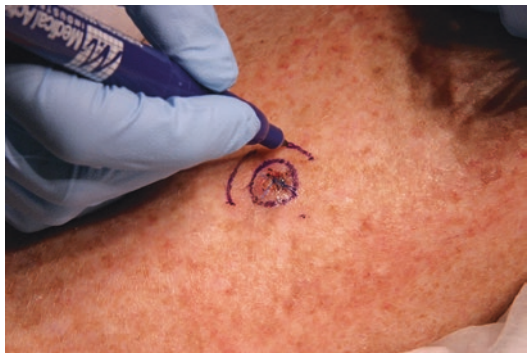

Fig. 10.24 Elliptical excision, marking margins

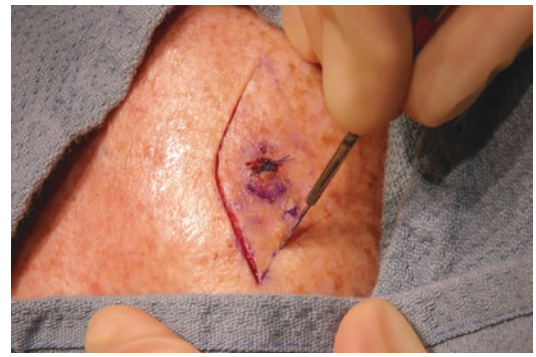

Fig. 10.26 Elliptical excision, initial incision

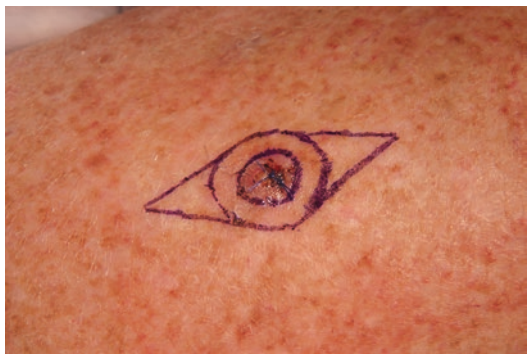

Fig. 10.25 Elliptical excision, planned incision line

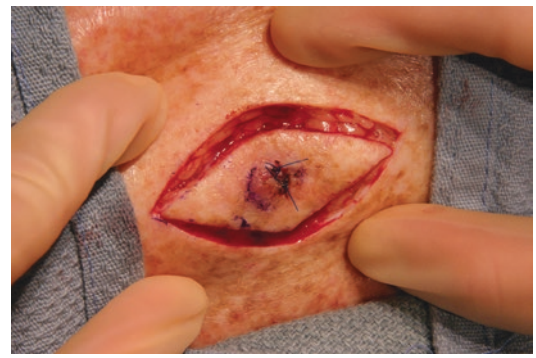

Fig. 10.27 Elliptical excision, incision completed

As maintaining an even arc of curvature while incising skin can be difficult, altering the surgical plan slightly to a rhombic design often eases execution [78].

Aesthetic outcome can be further enhanced by orienting the long axis of the excision parallel to existing skin tension lines and/or the intersection of two cosmetic units. When planning an excision, the borders of the tumor should be marked, the appropriate margins delineated, and the incision line drawn, taking care to place the long axis in the most desirable orientation, as described previously (Figs. 10.24 and 10.25).

Once anesthesia has been obtained, the procedure may begin. The scalpel handle should be held firmly between the first and second fingers, similar to a pencil, with the opposing hand used to provide skin traction. While a no. 15 blade is a reasonable choice for many anatomic areas, in regions of very thick skin, such as the back, a no. 10 blade may be more effective.

Starting at one end of the excision site, the skin should be scored in a single pass utilizing the belly of the blade. This is repeated on the opposing side, with care being taken to cleanly free the specimen tips. Utilizing firm pressure, the skin should then be incised completely down to subcutaneous tissue using the minimal number of passes possible (one to two strokes) (Figs. 10.26 and 10.27).

At all times, it is important to hold the blade perpendicular to the skin surface to allow for good edge approximation later during closure. After the excision edges are freed to the appropriate depth, the specimen is grasped with forceps and separated from the wound base by scalpel blade, scissors, or electrosection. To help maintain an even base, it is helpful to draw the specimen over the blade or scissors while cutting (Fig. 10.28). Once freed (Fig. 10.29), the specimen should immediately be placed in a correctly labeled container.

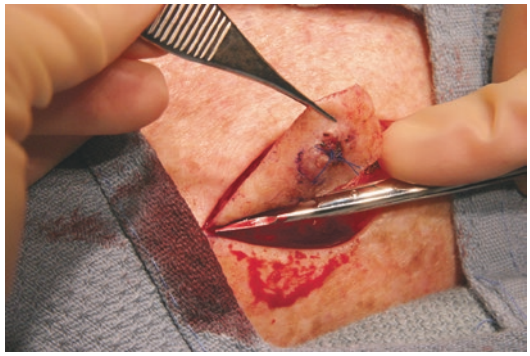

Fig. 10.28 Elliptical excision, separation from subcutaneous tissue

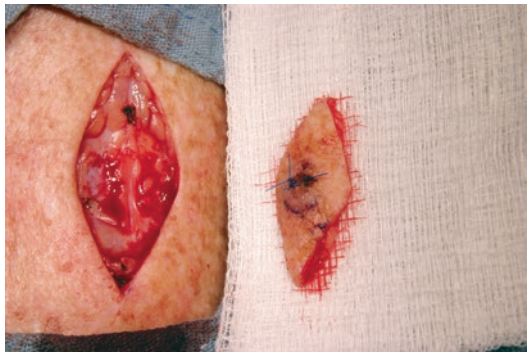

Fig. 10.29 Elliptical excision, specimen removed

Hemostasis should be obtained, if needed, utilizing the techniques described previously to provide a clear operative field (Fig. 10.30). If the wound is very small, one can then progress immediately to closure. However, in most cases, wounds will benefit from lateral tissue undermining as it increases tissue mobility, decreases tension, and facilitates edge eversion. The large platelike scar resulting from wide undermining may even help in the resolution of tissue redundancies/dog ear deformities [79]. It is important while undermining to always be aware of the surrounding anatomy in order to avoid unwanted injury to adjacent nerves, vessels, or other structures.

Undermining can be performed via either blunt dissection or sharp dissection. In blunt dissection, the wound edge is stabilized in a nontraumatic manner, such as with a skin hook. A pair of surgical scissors is inserted with closed blade into the wound, parallel to the skin surface. The blades are then opened, gently separating the subcutaneous tissue. Blunt dissection is a good option for areas where nerve or vessel injury is a concern as these structures are often pushed aside rather than severed. However, blunt dissection can also lead to an uneven dissection plane and is frequently slower than sharp dissection. In sharp dissection, either the scalpel blade or one blade of an open pair of scissors is inserted into the wound—again parallel to the skin surface—and the tissue separated either by cutting, pushing the scissors through the skin in a planing motion, or blade closure (Fig. 10.31). Sharp undermining tends to be faster and allows for more control over the dissection plane. The depth of undermining varies by anatomic site. In general, undermining should be performed at the level of the wound base in the mid to deep subcutaneous fat or just above the fascial layer; however, exceptions apply (Table 10.10) [80]. There are no hard and fast rules governing the extent of undermining; each wound must be considered individually with the goal of creating a tension-free repair.

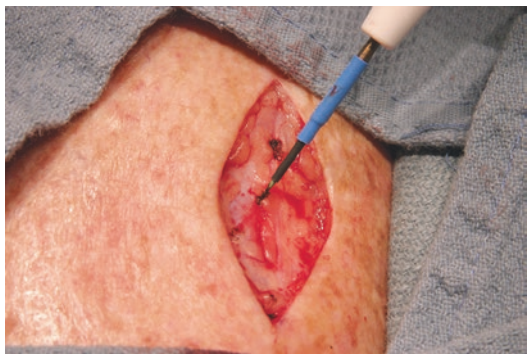

Fig. 10.30 Elliptical excision, obtaining hemostasis

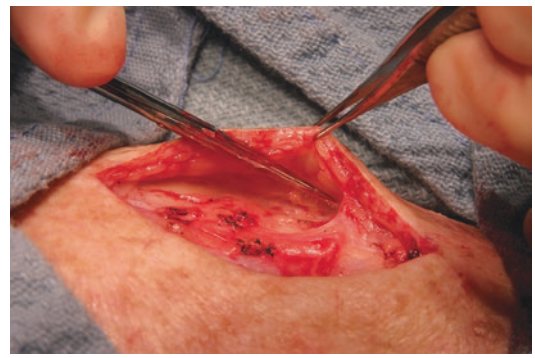

Fig. 10.31 Elliptical excision, tissue undermining

Table 10.10 Recommended undermining planes

Scalp	Subgaleal
Forehead: small	Subcutaneous fat
: large	Subgaleal
Nose	Subnasalis
Temple	Subcutaneous fat (need to stay above superficial temporal fascia to avoid temporal branch CN VII)
Cheek	Subcutaneous fat
Jaw/neck	Superficial subcutaneous fat (above marginal mandibular nerve, CN XI)
Trunk/extremities	Deep subcutaneous fat/fascia
Dorsal hands/feet	Subdermal

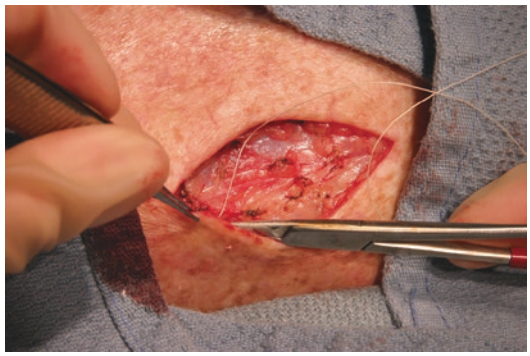

Fig. 10.32 Elliptical excision, initial dermal suture

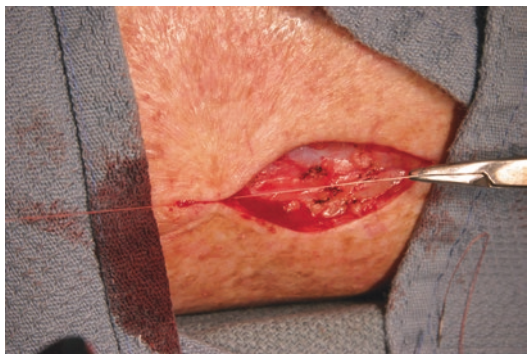

Fig. 10.33 Elliptical excision, initial dermal suture tied

Once the wound has been completely undermined, it should be reassessed for hemostasis. When all active bleeding has been controlled, the wound is ready for sutures. Dermal sutures are placed first. It is often helpful to start at the tips (areas of lower tension), gradually moving in toward the center (area of highest tension).

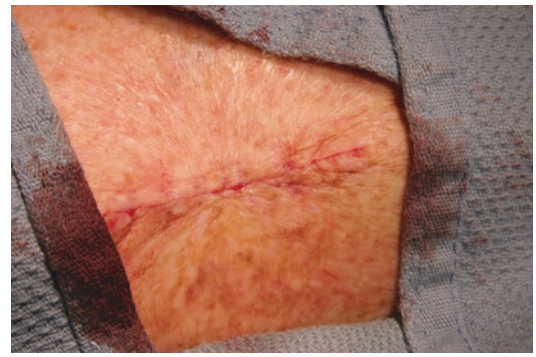

Fig. 10.34 Elliptical excision, dermal sutures completed

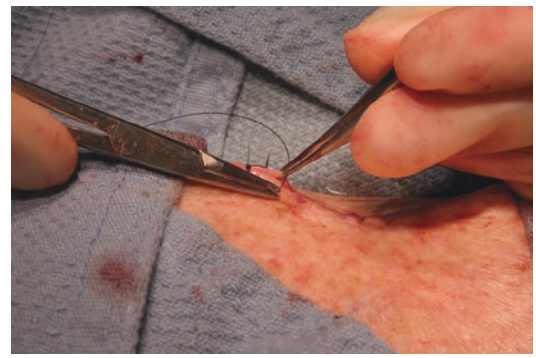

Fig. 10.35 Elliptical excision, epidermal sutures

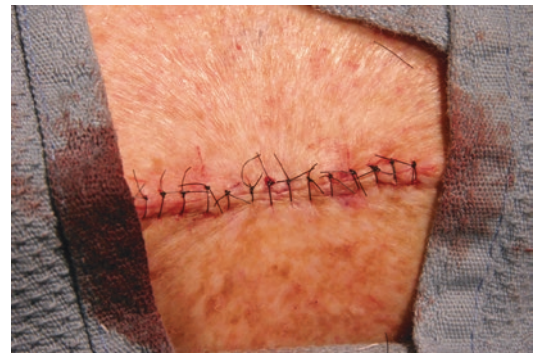

Fig. 10.36 Elliptical excision, final wound

Once the dermal sutures are completed, the wound should appear as a slightly raised ridge with the skin edges nicely apposed. The dermal sutures are followed by epidermal sutures, again utilizing one of the aforementioned techniques (Figs. 10.32, 10.33, 10.34, 10.35, and 10.36).

A common variation of the classic elliptical excision gently curves the ends of the incision resulting in an S-shaped repair. S-plasty closure has the advantage of decreasing wound tension and may often result in a more aesthetically pleasing scar; however, the resulting scar is often longer than that created by a traditional ellipse.

Standing Cones (Dog Ears)

On occasion, after elliptical excision, the wound continues to exhibit vertical cutaneous elevations at the tips or "dog ears." Many factors can contribute to the formation of tissue redundancies including initial apical angles greater than 30°, inadequate undermining, failure to maintain a 90-degree incision angle, or unequal side lengths. When an excision borders a free margin, such as the lip or ala, such tissue redundancy presents not as a vertical elevation, but rather as a pushing distortion of that margin. Small dog ears, especially in areas of high tension/tissue mobility, such as the dorsal hand, will often resolve on their own. Larger redundancies, however, are often best rectified at the time of the initial procedure. One of the easiest means of resolution is simply by wound extension. While holding the redundancy steady, an incision can be made through the center of the standing cone to its base. After careful undermining, the two resulting triangular halves can be laid across the initial incision line and neatly trimmed (Figs. 10.37, 10.38, 10.39, 10.40, 10.41, and 10.42). As one becomes more proficient in dog ear management, it becomes clear that by utilizing the same principles, the tissue redundancy can be removed from almost any direction. The same technique can be applied when performing immediate linear closure

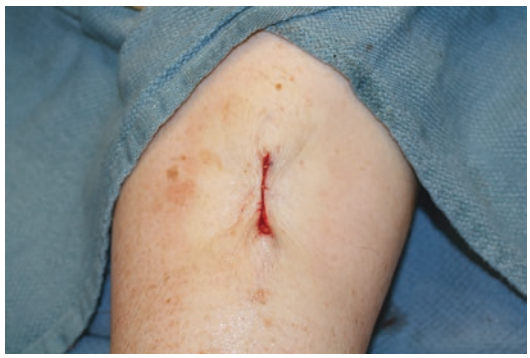

Fig. 10.37 Cutaneous redundancy

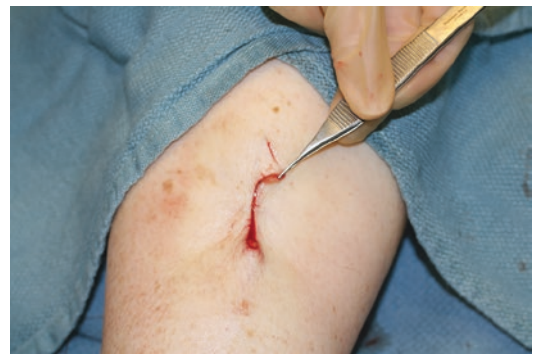

Fig. 10.39 Cutaneous redundancy, tissue overlap

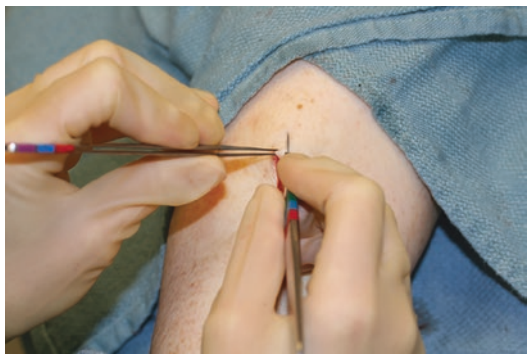

Fig. 10.38 Cutaneous redundancy, initial incision

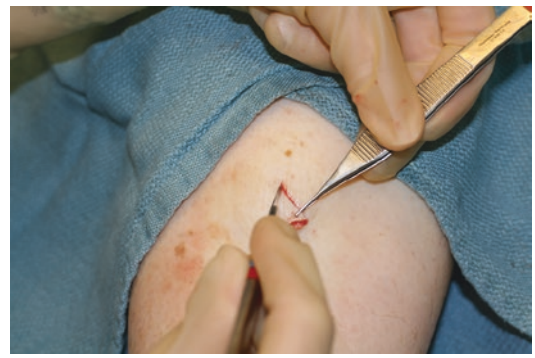

Fig. 10.40 Cutaneous redundancy, second incision

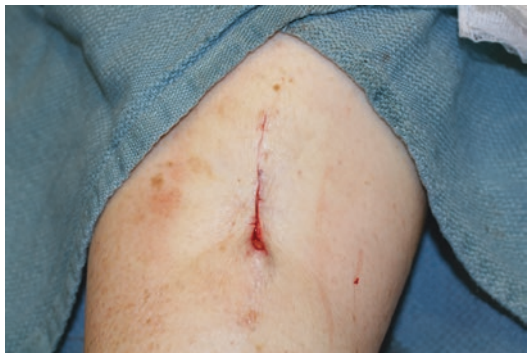

Fig. 10.41 Cutaneous redundancy, dog ear removed

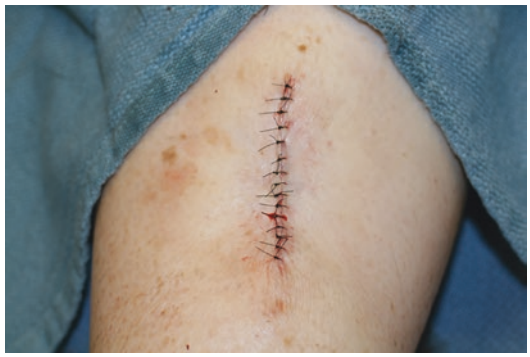

Fig. 10.42 Cutaneous redundancy, final wound

following disc excision. In fact, this method of surgical removal has been demonstrated to result in overall shorter scar lengths than those seen with preplanned ellipses [81].

If a difference in wound edge lengths is appreciated prior to closure, it can often be dealt with via "the rule of halves." The first suture is placed in the midportion of each side and the wound bisected. The process is repeated—continuing to divide the un-sutured areas in half until the wound is closed—ultimately resulting in a curvilinear repair.

An excellent review of dog ear management has been published by Weisburg, Nehal, and Zide [82].

Post-Procedure Care

Wound dressings serve a number of functions. Not only do they act to keep the wound clean and protected from unwanted exposure, they also act to provide pressure, limit postoperative bleeding complications, and can help support and stabilize the wound. While small procedures require little more than daily cleansing followed by application of ointment (such as petrolatum) covered by gauze, larger procedures often benefit from a more substantial dressing. Many patients prefer a "leave-on" bandage that requires no wound care on the part of the patient. One such example is to begin by applying a thin layer of ointment over the wound edge. Steri-Strips held in place with liquid adhesive are then placed perpendicular across the incision line to further enhance edge support. The next layer is an absorptive material such as a hydrocolloid (i.e., Cutinova Hydro®, Smith & Nephew, London, UK) trimmed to fit the wound, which is in turn covered by a breathable, waterproof film (i.e., Tegaderm®, 3M) allowing the patient to shower. On top of all of this is a pressure dressing composed of gauze and tape, which is removed by the patient at 24–48 h.

Complications

When properly performed, surgical excisions have a very low complication rate.

> All patients should be informed pre-procedure that some sort of scarring is inevitable and localized cutaneous numbness is not uncommon due to transaction of sensory nerves.

With time, typically within 1 year, sensation often returns to normal, and scar cosmesis can be enhanced via proper planning, orientation, and execution. Appropriate knowledge of surgical anatomy can prevent inadvertent injury to surrounding vessels and nerves as well as tissue distortion. Allergic reactions to topical antibiotics, dressing materials, or adhesive tape are not uncommon and can be easily addressed by removal of the offending agent and application of a mild topical steroid (Fig. 10.43).Wound infection occurs in less than 2% of cases and is

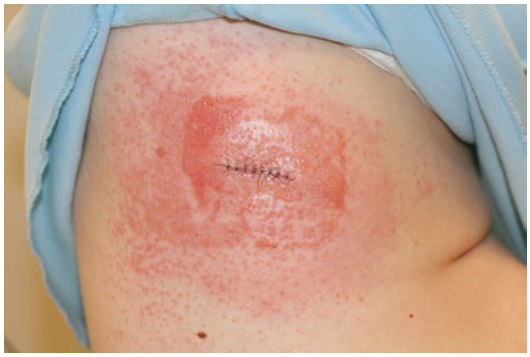

Fig. 10.43 Allergic contact dermatitis to adhesive

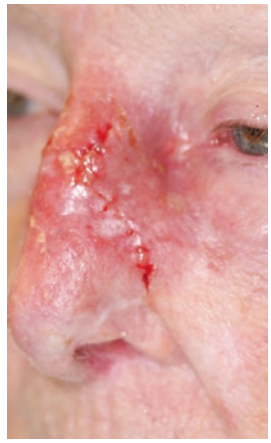

Fig. 10.44 Postoperative wound infection

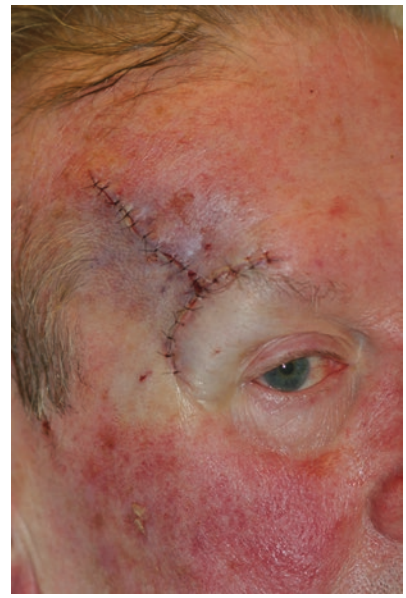

Fig. 10.45 Postoperative hematoma

often heralded by an increase in pain [83, 84] (Fig. 10.44). Risk can be minimized by use of good sterile technique and appropriate wound care. Should infection occur, the wound should be cultured and drained if necessary, and the patient started on a suitable antibiotic. Bleeding complications occur in about 3% of cases, but careful attention to intraoperative hemostasis as well as use of a good pressure dressing for the first 24–48 h following the procedure can help to decrease this risk [84] (Fig. 10.45). Wound dehiscence can occur as a result of excessive wound tension, hematoma formation, or infection. In such cases, the underlying issue should be addressed and the wound either re-sutured or allowed to heal by second intention. Once healed, the scar can be revised, if necessary. For further discussion on surgical complications, see Chap. 12.

Summary

Correctly performed, excisions represent an efficient, effective, and low-cost intervention that can be beneficial in many situations. Technological advances on the horizon may increase patient comfort, procedure speed, and treatment efficacy via improved local anesthetics, suture materials, and in vivo imaging, yet at least for the foreseeable future, the basics will remain unchanged, and cutaneous excisions will remain one of the mainstays of surgical dermatology.

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Chapter 11
Mohs Surgery

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Mohs surgery is named after Dr. Frederic Mohs, who pioneered a technique for removing skin cancers termed "chemosurgery" and first published his technique in 1941 [1]. Dr. Mohs' initial method involved applying a zinc chloride paste directly to the patient's tumor to chemically fix the tissue, after which the patient was allowed to return home. On the following day, the patient came back to the office. The tumor was then removed in precise, serial layers that were horizontally oriented and systematically mapped. This allowed all peripheral and deep margins of the specimen – essentially the interface between the patient and his or her tumor – to be examined under the microscope. If any part of the tumor remained, these steps were repeated until all peripheral and deep margins were clear. The goal of "chemosurgery" was to remove the tumor in its entirety while preserving the surrounding normal skin. After using this original technique, necrotic wounds created by zinc chloride paste were allowed to heal by second intention, as they were unsuitable for surgical reconstruction.

The Mohs surgery technique has been refined to allow microscopic evaluation of fresh tumor without prior fixation, mapping of this fresh tissue, and examination of horizontally oriented frozen sections by the surgeon. The fresh-frozen tissue technique allows for serial tissue layers to be removed from those specific areas that have residual tumor on microscopic examination, without otherwise enlarging the defect. When margins are deemed clear microscopically, the defect may be repaired in the office under local anesthesia or by another surgical specialist. At times, secondary intention healing is still employed and may produce a good cosmetic result in certain anatomic locations. Zinc chloride paste, which causes tissue necrosis, is no longer used, so that the wound edges are fresh and optimal for healing either by primary reconstruction or by secondary wound contraction. Today, the Mohs micrographic surgical procedure is recognized as the most precise method of removing skin cancers and is performed by dermatologists who have completed additional fellowship training in micrographic surgery and dermatologic oncology. This training includes comprehensive experience in all aspects of cutaneous oncology, the Mohs technique of tumor removal with precise tissue mapping and orientation, laboratory processing with horizontally oriented frozen sections, pathologic examination of the tissue, and surgical reconstruction of the resulting defects. Figure 11.1 compares tumor removal and tissue orientation in standard excision versus excision with Mohs surgery.

Indications for Mohs Surgery

Standard modalities for removing skin cancers such as basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) include excisional

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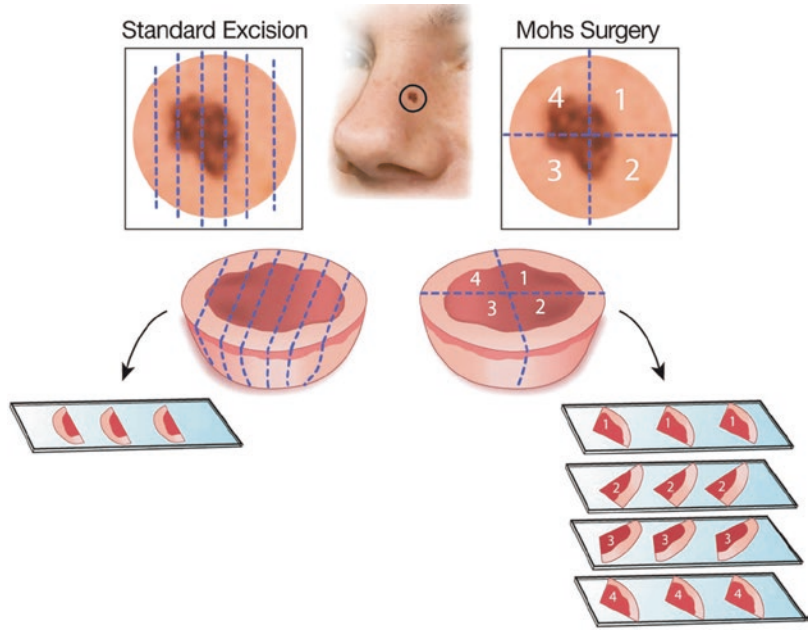

Fig. 11.1 Comparison of techniques: A standard excision specimen is fixed and sectioned vertically to assess a representative sampling of the tissue margin. This technique is also termed "breadloafing." The Mohs technique orients the entire margin in a horizontal fashion so that 100% of the peripheral and deep tissue margins can be examined microscopically by the surgeon

surgery, electrodesiccation and curettage, topical chemotherapy, cryosurgery, and radiation. These techniques are appropriate for the majority of nonmelanoma skin cancers. The Mohs technique is more time-consuming and requires specialized training and expertise. It is therefore reserved for the removal of certain types of skin cancers in sensitive locations or those at high risk for recurrence or metastasis [2].

The specific indications for Mohs micrographic surgery are listed in Table 11.1. The Mohs surgical technique is most commonly used to treat BCC and SCC on high-risk areas of the head and neck, locations where tissue conservation is essential and subclinical extension beyond the visible margins of the tumor is common. If the tumor border is poorly defined or if the tumor is recurrent after previous surgery, Mohs surgery can identify and remove infiltrating cancer cells with a high degree of accuracy. Tumors with aggressive histologic subtypes are also treated with Mohs surgery. Finally, patients who are immunosuppressed or who have received cutaneous irradiation develop aggressive tumors that tend to recur and/or metastasize with greater frequency; their tumors should also be treated with Mohs surgery. Mohs surgeons also treat other types of skin tumors characterized by locally infiltrative or aggressive growth patterns, including sebaceous carcinoma, microcystic adnexal carcinoma (MAC), dermatofibrosarcoma protuberans (DFSP), atypical fibroxanthoma, and lentigo maligna melanoma (LMM). A more

Table 11.1 Indications for Mohs surgery: nonmelanoma skin cancer (BCC and SCC) [3–5]

High-risk nonmelanoma skin cancer (BCC and SCC)
Large size (>2 cm) Aggressive histologic subtypes ≥0.6 cm Immunocompromised patients with tumors ≥1.1 cm
Ill-defined clinical borders
Rapid growth or aggressive clinical behavior
Aggressive or mixed histology: BCC – morpheaform, micronodular, infiltrating SCC – high-grade, deeply penetrating, perineural invasion
High-risk location Periorbital, perinasal, auricular or preauricular, perioral
Areas where tissue preservation is important Hands, feet, eyelids, lips, nose, genitalia
Recurrent
History of incomplete removal
Tumor arising in irradiated skin
Tumor arising in prior scar, burn, or other dermatoses (discoid lupus erythematosis, lichen sclerosis et atrophicus, dystrophic epidermolysis bullosa, etc.)
Patient factors
Immunosuppression
Certain genodermatoses (xeroderma pigmentosum, nevoid BCC syndrome, others)

Table 11.2 Types of tumors treated with Mohs surgery [2]

Types of tumors treated with Mohs surgery
Basal cell carcinoma (BCC)
Squamous cell carcinoma (SCC)
Verrucous carcinoma
Erythroplasia of Queyrat
Extramammary Paget's disease
Keratoacanthomas (aggressive, recurrent, deep, or mutilating)
Lentigo maligna and lentigo maligna melanoma*
Dermatofibrosarcoma protuberans (DFSP)
Atypical fibroxanthoma
Malignant fibrous histiocytoma
Leiomyosarcoma
Adenocystic carcinoma of the skin
Sebaceous carcinoma
Oral and central facial paranasal sinus neoplasms
Merkel cell carcinoma
Microcystic adnexal carcinoma
Apocrine carcinoma of the skin
Aggressive locally recurrent benign tumors

comprehensive list of the tumors managed with Mohs surgery is included in Table 11.2.

Cure Rates Following Mohs Surgery

Standard excision or superficial ablative techniques are appropriate treatments for most nonmelanoma skin cancers; however, for high-risk tumors such as those outlined in Table 11.1, Mohs surgery offers superior cure rates. Table 11.3 summarizes the estimated long-term recurrence rates following Mohs surgery for both primary and recurrent BCC and SCC.

Table 11.3 Recurrence rates following Mohs surgery (5–10 years follow-up)

	Mohs (%)	Excision (%)
Basal cell carcinoma [6–8]		
Primary tumor	1.0–4.4	10.1–17.4
Recurrent tumor	3.9–5.0	10.9–23.2
Squamous cell carcinoma [7–15]		
Primary tumor	2.6–6.7	8.0–10.9
Recurrent tumor	5.9–10.0	23.3

Basal Cell Carcinoma

Recurrence rates following standard excision of BCC have been best documented by van Loo et al. who reported a 10-year recurrence rate of 12.2% after excision of primary BCC versus 13.5% after Mohs surgery [8]. When the Mohs surgical technique was used, recurrence rates decreased to 4.4% for primary and 3.9% for recurrent BCC. Recurrence rates may be higher in patients with large tumors (>2 cm), tumors with infiltrative histology, or a midfacial location (e.g., nose). Interestingly, in an Australian database of 3370 patients [16] and a similar study of 620 patients in the Netherlands [17] treated with Mohs surgery for BCC, comparable 5-year recurrence rates were found. In the Australian study, however, no significant differences relating to tumor size, histology, or location were noted [16].

Squamous Cell Carcinoma

Traditionally, cutaneous SCC was treated with standard excision, with a 5-year recurrence rate of 8–10.9% for primary tumors and 23.3% for recurrent tumors [8]. Reports of recurrence rates following Mohs for high-risk SCC on the head/neck [7–14], however, range from 2.6% to 10.0%, with the greatest number of recurrences occurring in tumors with a high-risk location (e.g., lip or ear), prior recurrence, or perineural invasion [12]. It is likely that immunosuppressed patients or those with hematologic malignancies are at even greater risk for recurrence. Mehrany et al. reported that patients with chronic lymphocytic leukemia were seven times more likely to develop recurrent SCC following Mohs surgery than controls [18]. Further studies are also needed to assess recurrence rates for SCC following Mohs surgery in the growing population of organ transplant recipients.

Preoperative Considerations

Prior to surgery, patients should have a full-skin examination, including a biopsy of suspected skin cancers, to confirm the diagnosis. A previous

history of cutaneous malignancies and their treatments should be reviewed. In addition, a full medical and surgical history should be taken with particular attention to cardiac, pulmonary, renal, hepatic, and infectious diseases. A complete medication list, including supplements and alcohol/drug/smoking hist**o**ry, is essential. Decisions regarding the management of blood thinners and the need for antibiotic prophylaxis should be made in consultation with the primary care physician and/or cardiologist. Patients with implanted cardiac devices, such as pacemakers or defibrillators, can usually undergo Mohs micrographic surgery safely with the use of bipolar cautery.

There is no current standard of care regarding the management of anticoagulant and antiplatelet therapy for Mohs surgery, and practices differ between physicians [19]. The risks of discontinuing medically necessary blood thinners is now considered to outweigh the risk of postoperative bleeding [19, 20]. Warfarin and antiplatelet agents are generally continued during Mohs surgery if they have been prescribed to treat or prevent cerebral, cardiovascular, and vascular thrombosis in high-risk patients. The international normalized ratio (INR) value should be checked prior to the procedure and determined to be within the therapeutic range (2–3.5). Patients with levels above this range are at the greater risk for excessive bleeding, and their medications should be adjusted by their primary physician as appropriate. Few data exist regarding the management of clopidogrel for cutaneous surgery. Aspirin or nonsteroidal inflammatory medications taken as primary prevention can be discontinued 10 days prior to the procedure, although the continuation of treatment should not adversely affect the surgical outcome if adequate hemostasis is achieved intraoperatively [19, 21]. Newer oral anticoagulants including rivaroxaban (Xarelto), dabigatran (Pradaxa), and apixaban (Eliquis) were associated with a sevenfold higher likelihood of perioperative hemorrhagic complications compared to traditional oral agents including warfarin, clopidogrel, and aspirin ($p = .004$) [21].

Decisions regarding antibiotic prophylaxis for the prevention of endocarditis and prosthesis infection in high-risk patients are usually individualized, and consultation with the patient's general, cardiac, or orthopedic physician prior to Mohs surgery may be required. According to the latest American Heart Association (AHA) recommendations regarding antibiotic prophylaxis for the prevention of endocarditis in the highest risk individuals, prophylaxis is reasonable for procedures involving oral sites, respiratory tract, or infected skin structures [22]. Procedures involving intact surgically scrubbed skin do not require antibiotics for the purpose of preventing endocarditis in high-risk individuals. For patients with joint prostheses, the American Academy of Orthopaedic Surgeons (AAOS) recommends antibiotic prophylaxis for high-risk patients undergoing procedures involving oral sites [23]. In concordance with this, the most recent advisory statement for antibiotic prophylaxis in dermatologic surgery recommends such prophylaxis for Mohs surgery in patients at risk for infective endocarditis or total joint prosthesis infections when the surgery involves perforation of oral mucosa, an infected site, or a noninfected site that is at high risk of surgical site infection. Since Mohs surgical cases are heterogeneous – some, for instance, may breach the nasal mucosa or may extend over many hours – each patient's clinical scenario should be considered individually, and decisions regarding antibiotic prophylaxis should be made after taking into account all relevant factors [24].

Prior to surgery, patients should be educated about the procedure necessary to treat their particular type of tumor, the reconstruction that will follow, and potential risks of surgery, including acute complications, as well as later aesthetic or functional problems, which may vary depending upon the size and location of the tumor. Occasionally, additional laboratory testing or imaging will be required. For large or complex tumors invading deeper facial structures – particularly around the eyes, ears, or central face – ophthalmology, otolaryngology, plastic surgery, and/or neurosurgery may also be called upon to evaluate the patient. If multidisciplinary care is required, the procedure may be coordinated with the Mohs surgeon resecting the tumor until margins are microscopically confirmed to be clear, after which another specialist repairs the defect. Patient instructions regarding the possible need for limited activity in the postoperative period, recommendations regarding smoking cessation

and alcohol avoidance, and the list of supplies required for wound care should be given. Written instructions are often provided to patients to minimize later confusion of preoperative recommendations with postoperative care.

Guide to the Mohs Surgery Procedure

Mohs surgery is usually performed in an outpatient surgical facility under local anesthesia. On the day of surgery, the site should be confirmed with the patient and the original biopsy report reviewed to confirm location and diagnosis. The tumor is measured, photographed, and marked, and the site is infiltrated with local anesthetic. If necessary, hair may be removed from the surgical site prior to prepping and draping the area in standard, sterile fashion.

The sequence of events performed in a typical Mohs surgical procedure is outlined below and depicted in Fig. 11.2. The actual surgical procedure used to remove a skin cancer may vary somewhat depending on the surgeon's preferences, the tumor type, and the anatomic location. The tumor is usually removed and reconstructed on the same day, with suture removal 1–2 weeks thereafter (Fig. 11.3a–c).

The visible lesion depicted in Fig. 11.2, Step 1, may be debulked preoperatively to remove obvious tumor. Since tumors are more friable than healthy tissue and are easily scraped away, preoperative curettage may help to define tumor margins and reduce the number of stages required for tumor clearance [25–28].

Figure 11.2, Step 2: The remaining defect is excised with a narrow margin around and under it using a scalpel to remove a saucer-shaped disk of tissue (first stage or layer 1). Hatch marks are made (usually at 12, 3, and 9 o'clock) to orient the specimen with respect to the tissue map. Blood vessels are cauterized, and the patient receives a temporary bandage. The tissue is mapped, frozen, and sectioned for microscopic examination. The Mohs surgeon examines the tissue to determine whether microscopic tumor is present at any of the surgical margins (Fig. 11.4).

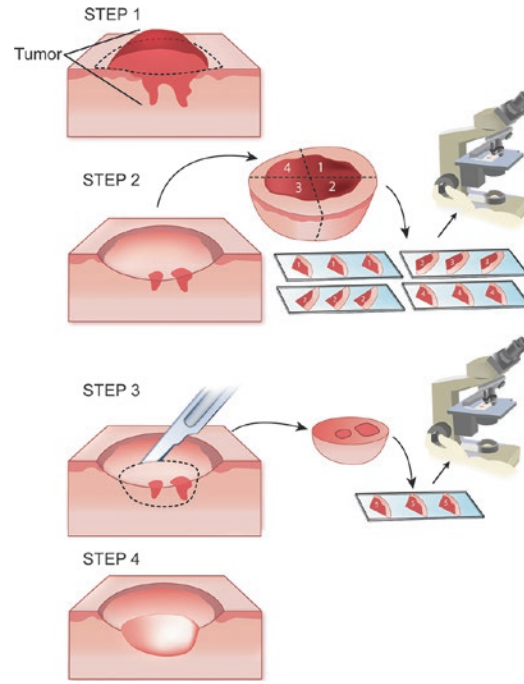

Fig. 11.2 Guide to the Mohs surgery procedure: Step (1) Preoperative lesion. The dotted line depicts the portion of the tumor that is debulked prior to surgery. Step (2) After the visible lesion has been debulked to remove obvious tumor, the remaining defect is excised with a narrow margin around and under it using a scalpel to remove a saucer-shaped disk of tissue. Step (3) The tissue is oriented, mapped, sectioned, and placed on slides for microscopic examination. Step (4) The remaining tumor is removed only from the mapped site in the second stage and placed on the slide for examination. The procedure continues in this fashion until there is no remaining tumor and margins are clear

Figure 11.2, Step 3: If tumor is present at any microscopic margin, the patient returns to have tissue removed only from the mapped site where tumor remains (second stage or layer 2). The procedure continues in this fashion until there is no remaining tumor and the margins are clear.

Figure 11.2, Step 4: The final defect is measured and photographed, and the Mohs surgeon typically reconstructs the wound on the same day. As mentioned previously, healing by second intention may occasionally be preferable to reconstruction. For complex tumors, subsequent management by a plastic or oculoplastic surgeon, otolaryngologist, or neurosurgeon may be required. This is generally arranged prior to the planned procedure.

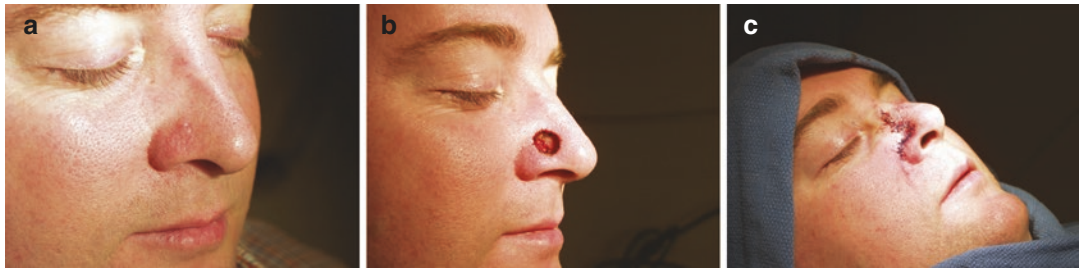

Fig. 11.3 (**a**) Basal cell carcinoma on the nasal sidewall. (**b**) Surgical defect following microscopic tumor clearance. (**c**) Same-day reconstruction with rhombic flap

Fig. 11.4 Microscopic examination of stained frozen sections is performed by the Mohs surgeon

Slide Preparation

Once the tissue is removed, oriented with hatch marks, and mapped, it will be processed by a histotechnician working within the surgical facility. The tissue is pressed down to flatten the skin so that the entire tissue margin is leveled for even sectioning, with preservation of the epidermis around the entire periphery of the specimen. The tissue is divided, and the ends of the pressed tissue specimen are dyed with colored inks to maintain orientation. These colors and the division of the specimen are also marked on the map so that orientation is coordinated between the patient (hatch marks), the specimen sections (hatch marks and colored dyes), and the written map. The tissue is embedded, frozen, sectioned, and mounted on slides (Fig. 11.5a, b), which are then stained, most commonly with hematoxylin and eosin and occasionally with toluidine blue or immunostains. The horizontal frozen sections are immediately examined under the microscope by the Mohs surgeon. It is important to mention

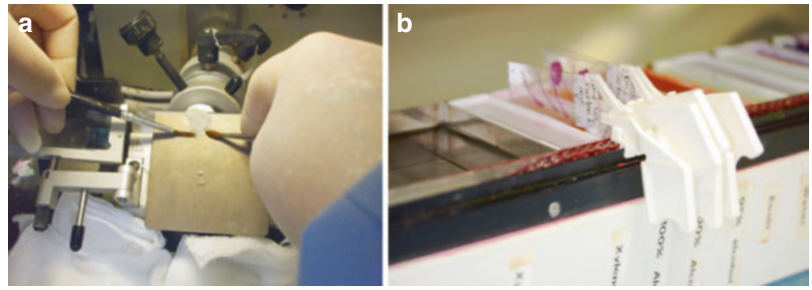

Fig. 11.5 (**a**) Frozen tissue is sectioned and placed on a slide. (**b**) These slides are then stained; in this image, an automatic stainer is being used

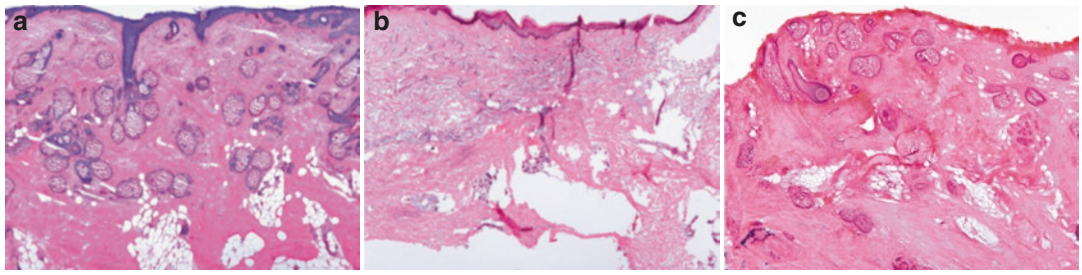

Fig. 11.6 Variations in histological slide preparation. (**a**) Good-quality frozen section stained with hematoxylin and eosin. (**b**) This poor-quality section would be difficult to interpret. Note that it has no clear adnexal structures and fat is not visible. (**c**) Section missing epidermis

that consistent high-quality slide preparation is essential to the success of the Mohs technique. While there may be some variability in tissue preparation or staining, if slide quality is poor or if portions of the epidermis or deep tissue are missing, the processing must be repeated to ensure examination of 100% of the peripheral and deep tissue margins (Fig. 11.6a–c).

Variations on the Mohs Surgery Technique

Classical Mohs surgery is performed with a scalpel beveled at 45° – a technique that is helpful for flattening the epidermis against a glass slide, but less ideal for wound reconstruction. Once a tumor-free margin is achieved, the surgeon may de-bevel or recut the defect at 90° prior to reconstruction. Conversely, there are surgeons who use a 90° angle for Mohs layers and avoid this step.

Several situations may require permanent, delayed formalin-fixed paraffin-embedded sections to confirm tumor-free margins. Tumors with histology that can be difficult to interpret on frozen sections, such as sebaceous carcinoma, often require permanent sections with tissue mapping. This "slow Mohs" procedure allows for confirmation of histology while still allowing for tissue mapping and several stages with delayed repair. Another situation in which the surgeon may employ permanent sections to confirm frozen section findings is to delineate tumor margins in the setting of a dense inflammatory infiltrate or to further characterize basaloid proliferations encountered incidentally on microscopic examination.

Some have advocated the use of immunohistochemical stains to define tumor margins on frozen sections [29]. These include anticytokeratin stains for BCC and SCC, MNF116 for BCC, and CD34 for DFSP [30]. The use of immunostains may also be used to evaluate melanoma in Mohs surgery. Studies exist regarding the use of MART-1, HMB-45, MEL-5, S-100, SOX-10, and other melanocytic immunostains for evaluation of melanoma on frozen section slides [31–38]. The standard surgical treatment of invasive melanoma is wide local excision, where surgical margins are determined by the Breslow depth of the tumor [39]. The role of Mohs surgery in this setting is still being defined [40, 41]. For tumors that are known to be locally aggressive or recurrent, including DFSP, Merkel cell carcinoma, and melanoma, the Mohs surgeon may take an extra margin of tissue around the microscopically clear defect for additional frozen sections or to be sent for permanent section processing. This "wide Mohs" variation is similar to wide local excision, with the added reassurance of 100% examination of all peripheral and deep tissue margins.

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) have been managed with Mohs surgery. Owing to the difficulty in assessing melanocytic atypia on frozen sections, eval-

uation of melanoma specimens is typically performed using permanent histological confirmation and/or adjunctive use of immunostains. Mohs surgery has found to be highly effective for the treatment of melanoma in situ, with low recurrence rates (0.34% or 2 out of 597 lesions) over the course of 2.8 years [41]. Zitelli et al. reported large prospective studies of Mohs surgery for head and neck melanoma and found recurrence rates comparable or even superior to historic recurrence rates with standard excision, particularly for in situ and thin melanomas (<0.76 mm) on the head and neck [31, 32]. The technique has been described and refined to include removal of a 3-mm margin surrounding the clinically apparent tumor, which is then sent for permanent section examination. An additional 3-mm Mohs layer is afterward removed for 100% margin examination in frozen sections with immunohistochemical staining. Although the authors have used both HMB-45 and MART-1, they found that the latter stained more consistently and reliably [32]. Mohs surgery will likely be used increasingly to treat melanoma as the use of immunostains becomes more common.

For many Mohs surgeons, however, LM and LMM are managed using staged surgical excision with rush permanent specimens or the "square" procedure described by Johnson et al. in 1997 [42]. In the "square" technique, a square or rectangular outline 0.5–1.0 cm around the clinical Wood's lamp margins is marked and a 2–4-mm wide strip of tissue is excised, tagged for orientation, and sent for permanent sections. The lesion is left intact on the patient while the cutaneous strip from the margin is being assessed, leaving the patient with a smaller wound while awaiting the histological interpretation. The geometric angles of the specimen are reported to increase accuracy of orientation for both the surgeon and the dermatopathologist. Geometric strips can be removed from any areas with positive tumor on subsequent permanent sections (similar to the "slow Mohs" technique). After confirmed marginal clearance, the entire lesion can be excised and the defect repaired.

Complications and Follow-Up

Serious complications following Mohs surgery are rare and generally avoided by completing a meticulous preoperative evaluation as outlined previously. With any surgery, there is potential for infection, hematoma/seroma formation, dehiscence, necrosis, scarring, and asymmetry. Fortunately, most Mohs surgeons do their best to perform meticulous reconstruction of their surgical defects – both on the head and neck and elsewhere – and are often able to achieve reconstruction with excellent preservation of facial symmetry and minimal scarring.

Wound infection following dermatologic surgery is low, with reported incidence rates averaging <3% [43]. Patients at higher risk for infection include those who are immunosuppressed, diabetic, smokers, or elderly. Patients undergoing long procedures, procedures requiring delayed repair or under significant tension, or repairs in contaminated or clean-contaminated locations (leg, groin, etc.) are also at higher risk for infection. These patients may require oral antibiotics to prevent postoperative wound infection. Some surgeons prescribe topical antibiotic ointment for wound care, although it has been shown that white petrolatum can be used without an increase in infection rate [44]. Complications are minimized by tailoring treatment to the individual needs of the patient, using sterile surgical technique, performing meticulous hemostasis following tumor removal, and choosing the best reconstructive option to optimize healing and minimize the potential for necrosis and scarring. Postoperative pain is typically minimal and managed with acetaminophen and/or other oral analgesics.

The surgical dressing generally remains in place for 24–48 hours. The patient is then responsible for wound care involving twice-daily cleansing, application of ointment, and covering the wound with a nonstick dressing. Sutures are typically removed in 1–2 weeks (depending on the surgical site), although certain flaps will require subsequent pedicle division, prolonging the wound healing process. Second intention

healing also requires dedication to wound care for a longer period of time. However, most patients can resume normal activities within 2–3 weeks following surgery and may be evaluated thereafter to ensure that the wound is healing properly. Patients may return to their primary dermatologist for follow-up skin examinations after they have healed.

Mohs Surgery Pearls

1. It is essential to pinpoint the biopsy site accurately before proceeding with surgery. Taking a photograph or making a diagram at the time of the initial biopsy or consultation visit may be helpful. Measuring the distance from the lesion to nearby anatomic landmarks can be useful as well. Allowing the patient to confirm the biopsy site by looking in the mirror and asking them to use a cotton-tipped applicator to point to the site at the time of surgery may be necessary if uncertainty remains regarding the exact location.
2. Correct orientation of the specimen with respect to the patient is critical. Making a pronounced double hatch mark at the 12 o'clock position facilitates orientation and mapping of the specimen.
3. If a biopsy slide is not available at the time of surgery, it may be helpful to take a frozen section biopsy of the tumor prior to debulking. Doing so enables the surgeon to compare suspected areas of positivity on the Mohs surgical slides with a known positive tissue sample and may provide additional important information regarding the histopathologic characteristics of the tumor.
4. Buffered lidocaine may be infiltrated nearly painlessly, while bupivacaine is extremely painful when infiltrated. If longer-acting anesthesia is required for patient comfort – as, for example, if tissue processing is expected to take several hours – be sure the patient has been completely numbed with lidocaine prior to infiltration of bupivacaine.
5. Be certain that your technician is proficient at preserving epidermis around the entire tissue specimen, that there are no holes in the center of the specimen, and that subcutaneous fat is not missing at the deepest portion of the specimen. If tissue dye is seen along the entire base of the specimen, the entire depth of the specimen has been preserved and the deep margin can be adequately visualized.

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Chapter 12
Principles of Cutaneous Flap Surgery

Tatyana R. Humphreys

The origin of cutaneous flaps dates back to 600 BC in India when crimes such as adultery were punished by amputation of the nose. Indian physicians such as Sushruta Samhita were called upon to correct the resultant deformity using cheek flap procedures [1]. The Indian method of forehead flap repair appeared centuries later. In Europe, the Indian method of rhinoplasty continued to be used through the fifteenth century. Italian surgeons such as Tagliacozzi utilized pedicled flaps from the arm for nasal reconstruction in the late sixteenth century [1]. It was not until the nineteenth century that further refinements in flap surgery occurred in Europe. In the twentieth century, the development of new suture materials and local anesthesia brought further innovations in closure of skin and soft tissue defects. With regard to closure of cutaneous defects, the appearance of the fresh tissue technique of Mohs micrographic surgery in the 1950s allowed for immediate wound closure following skin cancer removal using local cutaneous flaps.

The blood supply to the skin consists of two vascular networks, the deep and the superficial plexus [2, 3] (Fig. 12.1).

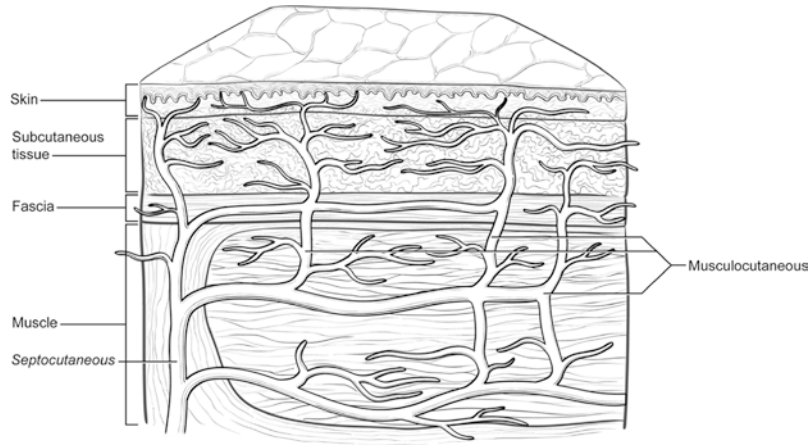

Fig. 12.1 Vascular supply to the skin. (Illustration by Alice Y. Chen)

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The deep plexus lies at the junction of the dermis and the subcutaneous fat, while the superficial plexus is located in the superficial portion of the reticular dermis supplying the capillary loops of the dermal papillae. Subcutaneous perforating vessels emanating from the main arteries that supply the skin of the face connect with the deep vascular plexus [2–4]. Cutaneous flaps can be classified based on their vascular supply: random pattern, axial, fasciocutaneous, and musculocutaneous (Fig. 12.2) [3].

Random pattern flaps derive their blood supply from the subdermal plexus supplied by musculocutaneous perforators. In contrast, axial flaps obtain their blood supply from a specific fasciocutaneous artery that runs beneath the longitudinal axis of the flap. Fasciocutaneous flaps are composed of skin, fat, and deep fascia, while musculocutaneous flaps include the same tissue layers with the underlying muscle [3, 4]. Random pattern and axial flaps are the most frequently employed by dermatologic surgeons [5]. Both flap types will be discussed in this

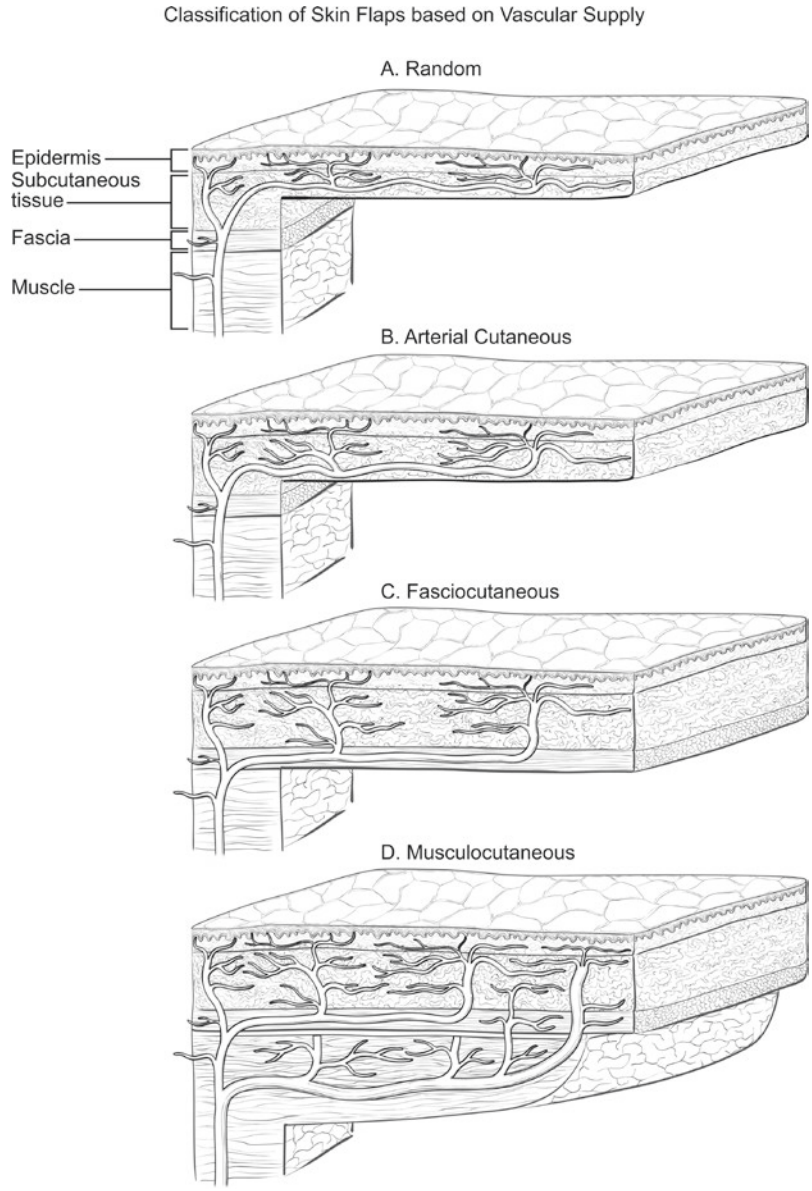

Fig. 12.2 Classification of cutaneous flaps. (Illustration by Alice Y. Chen)

chapter with an emphasis on surgical technique and aesthetic considerations. While basic flap types will be addressed, an exhaustive discussion of flap design is beyond the scope of this chapter.

Indications and Contraindications to Flap Closure

Cutaneous flaps are typically utilized to close defects when primary closure is not possible because of excess tension or distortion of free margins even after adequate undermining. Whenever possible, primary linear or curvilinear closure should be the preferred method of closure since even very large defects can be closed in this manner with adequate undermining. Whether primary closure is possible will depend on the degree of tissue laxity which varies considerably with age and anatomic location.

A flap should not be used because one can perform it but because it is necessary for optimal contour and cosmesis. Beginning surgeons are often eager to test their skills by performing a sophisticated flap, but experienced surgeons know that choosing the simplest best solution will yield the best result. A more complicated repair means greater potential for complications.

One contraindication to flap closure is failure to confirm negative tumor margins prior to closure. Immediate closure of a defect resulting from removal of skin cancer is only advised following Mohs micrographic surgery or other confirmation of negative margins; otherwise, a flap closure should be delayed. Re-excision of positive margins after a flap closure is much more likely to result in a recurrence.

Even with confirmation of negative tumor margins, the risk of recurrence needs to be assessed routinely prior to closure. A simpler repair may be more appropriate in the setting of a large high-risk squamous cell carcinoma with perineural invasion to allow for postoperative detection of recurrence. Skin grafts may be preferable to flaps with regard to detection of recurrent tumor because of the relative thickness of the overlying tissue.

Additional contraindications to immediate closure with a flap may include an avascular recipient bed such as exposed cartilage or bone lacking perichondrium or periosteum, respectively. In these situations, the surgeon might opt for delayed closure or use of an axial flap with its own vascular supply and less risk of ischemia.

Preoperative Considerations

Preoperative assessment and planning are essential for obtaining the best surgical result. The usual considerations in any cutaneous surgery also apply to flaps and include risk of intraoperative or postoperative bleeding, infection, and compromised wound healing. Most of these issues have been discussed in depth in preceding chapters, so the emphasis here will be specific to flap repair procedures.

Flap Design

Some general aesthetic principles must be considered when designing a flap. The surgeon should always strive to maintain symmetry. When designing a flap, the surgeon should seek to blend the edges and contours of the flap with its surroundings and recapitulate natural patterns rather than draw attention to itself.

When determining the best closure for a skin and soft tissue defect, a mental checklist can be used to guide you to the best design (Table 12.1).

Table 12.1 Considerations in flap design

Identify relaxed skin tension lines
Identify cosmetic unit boundaries
Identify reservoirs of skin laxity
Assess texture, thickness, and color of the skin surrounding the defect
Assess contour of the affected area

1. *Identify Relaxed Skin Tension Lines and Cosmetic Unit Boundaries*. Prior to administration of any local anesthetic, examine the patient in a sitting upright position to determine the location of preexisting wrinkle lines, cosmetic unit boundary lines (Fig. 12.3), and relaxed skin tension lines (Fig. 12.4) that can serve to camouflage incision lines. One should identify and mark these with a surgical pen prior to administration of local anesthetic which can cause tissue distortion.
2. *Identify Reservoirs of Skin Laxity Near the Anticipated Defect*. Typical reservoirs of tissue laxity are found at the glabella, melolabial crease, preauricular and jowl regions, but the amount varies considerably with age and gender.
3. *Assess Tissue Mobility*. Tissue mobility varies tremendously with location of the defect and age of the patient. Greatest mobility is found on the cheek and the least on the nose and scalp. Younger skin will be tauter, less distensible, and more likely to require a flap or graft for closure of a defect than that of an older patient. Undermining around the defect at the time of surgery can aid in further assessing tissue mobility and determining whether a flap closure is required. I generally recommend undermining *at least* 1.0 cm in all directions before abandoning primary closure as an option.
4. *Assess Texture, Thickness, and Color of the Skin Around the Wound and Potential Donor Sites*. The proper matching of the

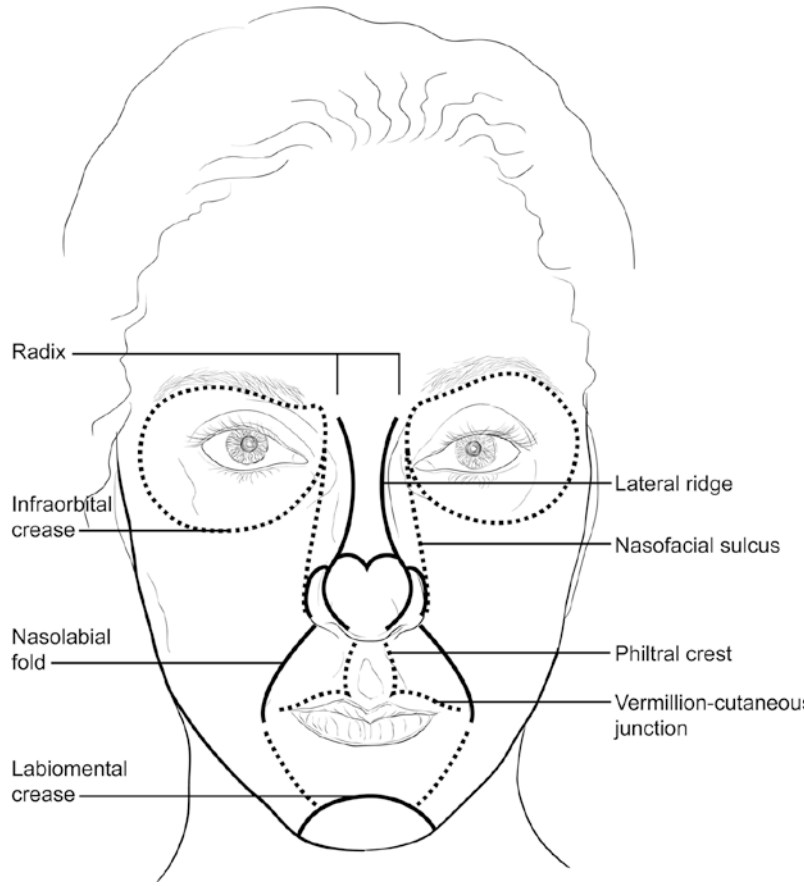

Fig. 12.3 Cosmetic unit boundaries. (Illustration by Alice Y. Chen)

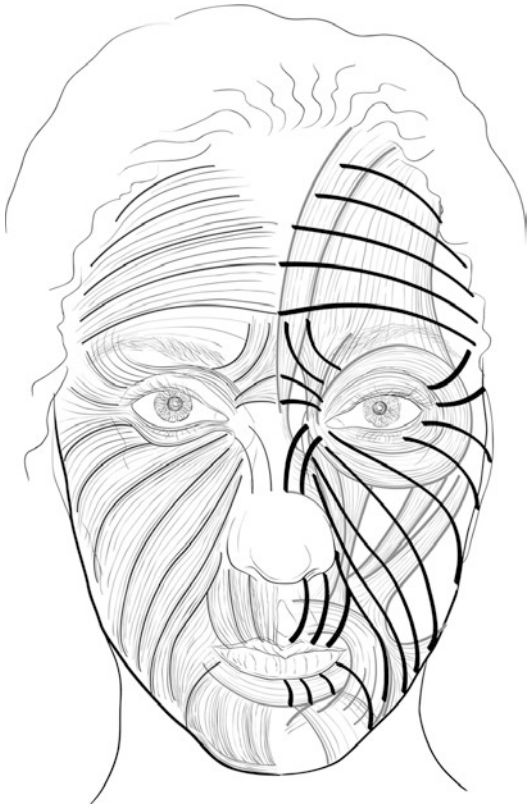

Fig. 12.4 Relaxed skin tension lines perpendicular to muscles of facial expression. (Illustration by Alice Y. Chen)

donor and recipient site is critical for optimal cosmesis. The flap design should allow movement of the skin of a similar color and texture from the donor site and recipient site. Even subtle disruption of local texture can draw attention to a scar especially on the nose.

5. *Assess the Contour of the Area Around the Defect*. Restoring contour, either convex or concave, is an important consideration in aesthetic reconstruction. A bulky medial canthus or flattening of the cheek can alter normal symmetry.

Random Pattern Flaps

Random pattern flaps can generally be divided into subtypes based on the principal direction of tissue movement: advancement, rotation, and transposition. In practice, many flaps will defy precise classification since they may demonstrate several types of tissue movement. While every defect has its unique closure solutions, certain flap types work best in specific anatomic locations because of cosmetic unit boundary lines and local tissue mobility (Fig. 12.5 and Table 12.2).

Advancement Flaps

Advancement flaps are the most basic type of flap since they create tissue movement along one directional vector, usually horizontal (Fig. 12.5 and Table 12.2). Advancement flaps have many variations depending on the location of the defect and the amount of tissue movement required. The movement of an advancement flap will create small pockets of redundant tissue at the pedicle base. These can usually be eliminated extending the length of the flap and applying the "rule of halves" when suturing skin edges of unequal lengths. The horizontal line of the "T" can be extended if necessary, to further distribute the dog ear along its length. The author prefers this method over excision of redundant tissue as a wedge. Advancement flaps can be single, double (H-plasty, A-T, O-T), or triple (Mercedes flap). Figure 12.6 demonstrates a Mohs defect on the forehead above the eyebrow following removal of a basal cell carcinoma (BCC). This defect was closed using a simple advancement flap above the brow with a horizontal direction to prevent alteration of the brow position. A burrows wedge must be removed from the superior aspect of the defect to allow advancement of the flap.

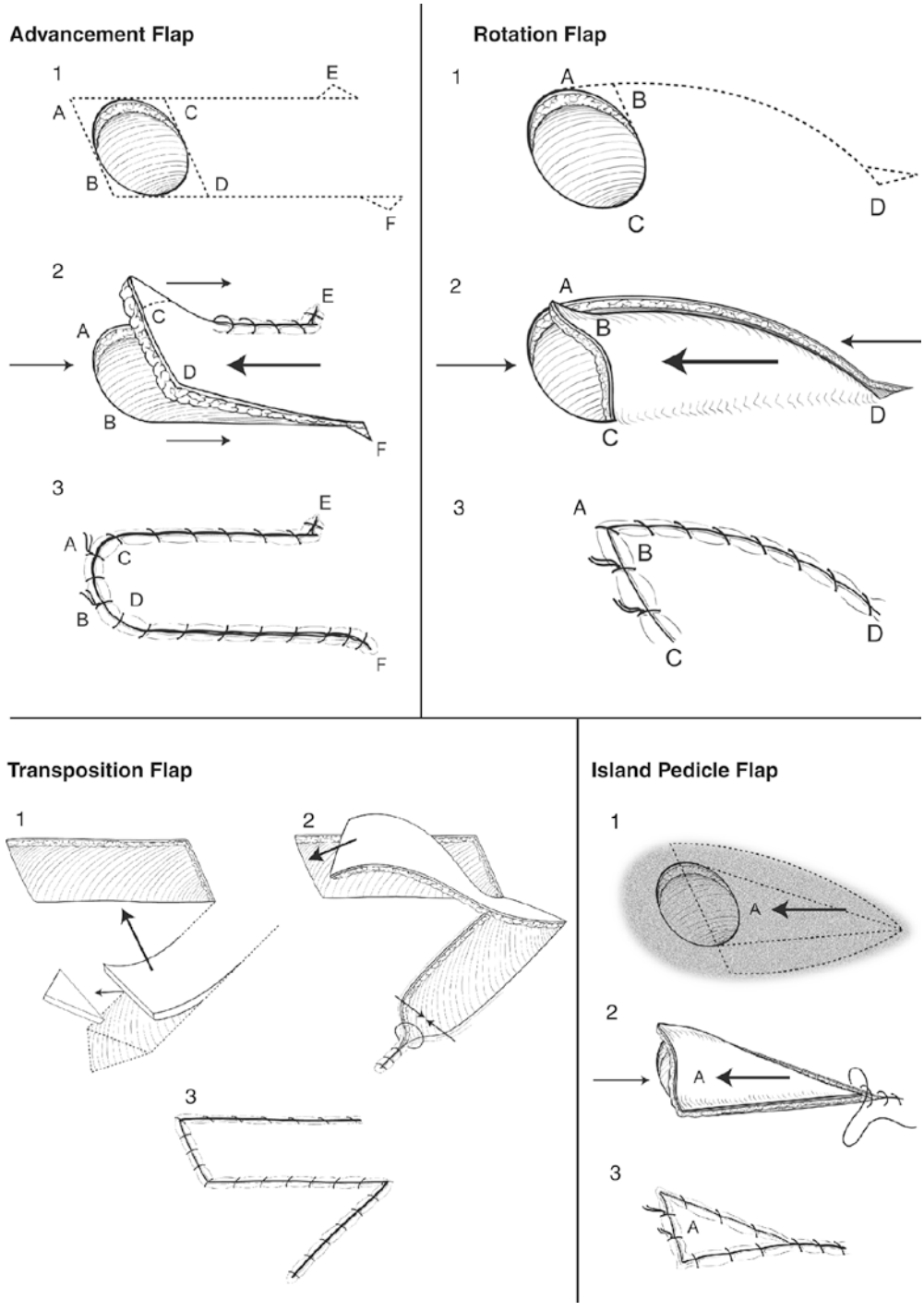

Fig. 12.5 General types of random pattern flaps. (Illustration by Alice Y. Chen)

Table 12.2 Commonly used cutaneous random pattern flaps

Advancement flap
Indications: • To create horizontal orientation of tension vectors and avoid upward displacement of free margins (the lip, eyebrow) • To achieve favorable placement of incision lines for maximal camouflage
Examples: O-L, O-T, H-plasty
Island pedicle flap
Indications: • Need for greater unidirectional tissue movement along subunit boundaries or free margins
Examples: • Lateral upper-lip large defects (nasolabial crease and vermilion border) • Midfacial defects • Medial canthus • Anterior pinna (trap door island pedicle from postauricular sulcus)
Rotation flap
Indications: • Camouflage of incision lines along curvilinear RSTLs or cosmetic unit boundary lines • Reduce risk of flap ischemia with broad-based pedicle
Examples: unilateral, bilateral (O-Z, Peng), spiral
Transposition flap
Indications: • Need for greater tissue movement between defect and best donor site • Complex contour considerations • Risk of retraction of free margin with advancement or rotation flap closure
Examples: melolabial transposition, rhombic, bilobed

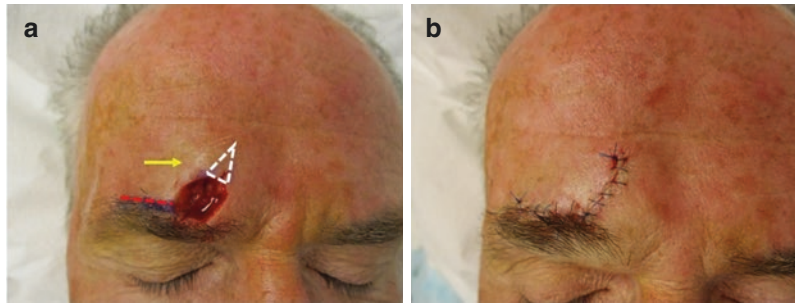

Fig. 12.6 Advancement flap (O-L type), forehead. (**a**) Mohs defect above medial eyebrow. The planned incision is along red dashed line. The standing cone created by the tissue movement is approximated by the white triangle. The direction of movement is shown by the yellow arrow. Undermining allows tissue movement toward the midline. Note that tension vectors are directed horizontally to prevent vertical displacement of the eyebrow. (**b**) Appearance immediately after placement of subcutaneous and superficial sutures

This simple advancement flap can also work well for closing defects of the nasal sidewall with the incision line placed along the alar groove (Fig. 12.7).

A bilateral advancement flap is useful if the amount of movement from a single advancement is not sufficient. A Mohs defect involving the eyebrow shown in Fig. 12.8 was closed using an H-plasty in order to realign the brow. Another variant of the bilateral advancement flap is the O-T or A-T (Fig. 12.9) which also functions well for preservation of a free margin (eyebrow or vermilion border) or cosmetic unit boundary line. In Fig. 12.10, a defect of the forehead is closed using an O-T advancement flap. The incision at the base of the flap is placed within the horizontal forehead lines for best cosmesis. The O-T advancement is particularly useful for closure of small-to-medium-sized defects of the upper lip since the closure line is camouflaged within the vertical lip lines while preserving the position of the vermilion border as shown in Fig.12.11.

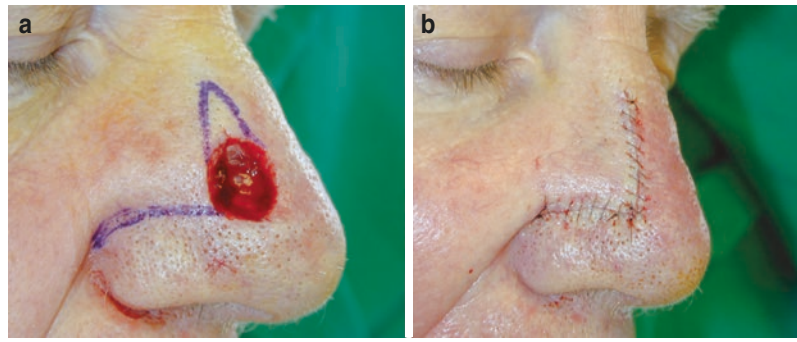

Fig. 12.7 Advancement flap (O-L), nose (**a**) Defect of nasal sidewall with outline of flap incision along alar groove and anticipated standing cone of redundant tissue superior to the defect. (**b**) Final appearance at closure

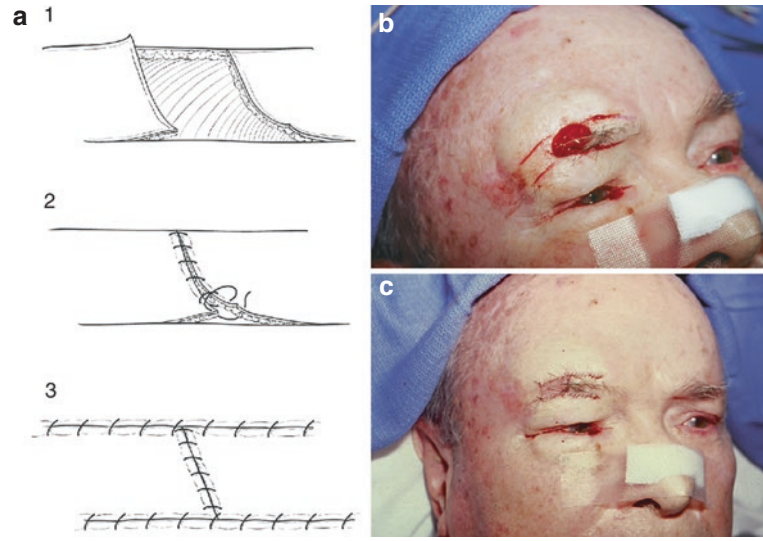

Fig. 12.8 (A) A schematic of the H-plasty advancement flap. Two arms of advancement flap are designed horizontally on either side of the defect (**a**). The two sides are advanced medially along a horizontal axis to the midline of the defect (**b**) to produce an H-shaped closure (**c**). (B) Bilateral advancement (H-plasty type). Defect of eyebrow following Mohs micrographic surgery (left). Flap incised along superior and inferior borders of the eyebrow, advanced to midline (yellow arrows). Final appearance after suture placement (right)

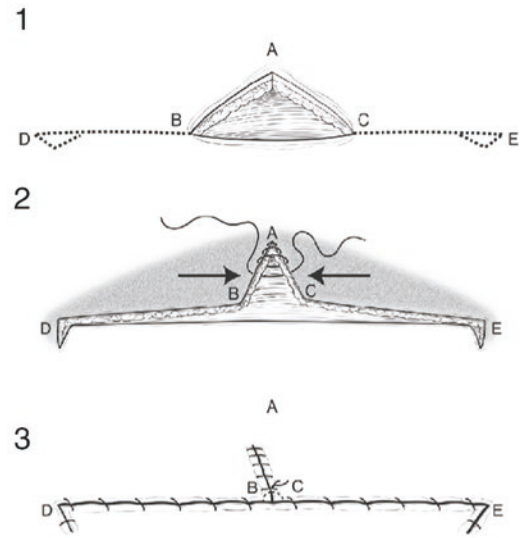

Fig. 12.9 Bilateral advancement flap (A-T, O-T). (**a**) Each side of the flap moves along one vector toward the midline of the defect (ABC). The base of the flap can be placed along RTSLs or cosmetic unit boundary line for camouflage. The dotted area represents the scope of undermining. Redundant tissue created by flap movement can be excised (D, E) or divided along the horizontal axis. (**b**) Final closure

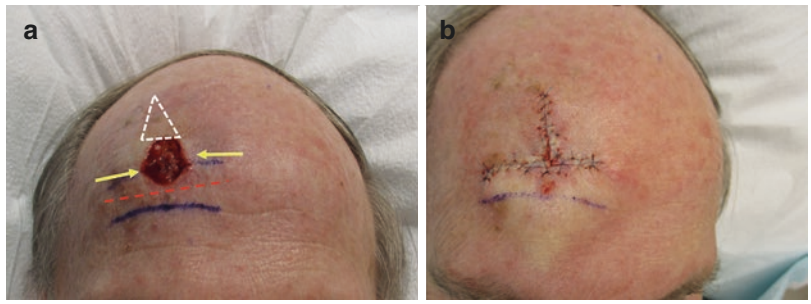

Fig. 12.10 Bilateral advancement flap (forehead). (**a**) Forehead defect following Mohs surgery. The planned incision line at the base of the flap is placed parallel to the horizontal RSTLs of the forehead. The standing cone above the defect is identified and excised. After undermining, tissue is advanced horizontally toward the midline of the defect. (**b**) Closure after suture placement

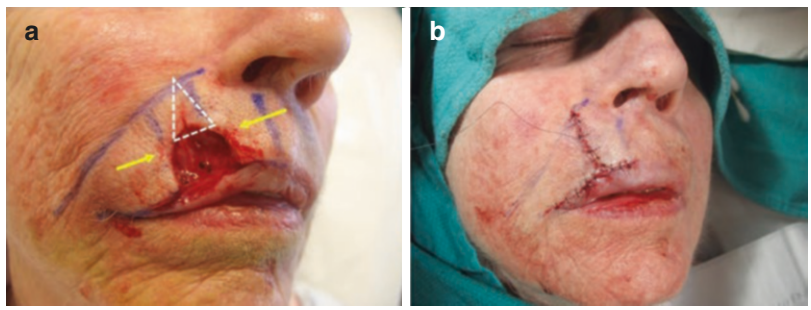

Fig. 12.11 Bilateral advancement flap (O-T), upper lip. (**a**) Defect of cutaneous upper lip and design of "O-T" advancement flap. The incision line is placed along the vermilion border and the standing cone excised vertically along relaxed skin tension lines of the upper lip; the flap edges advance medially. (**b**) Closure after suture placement

The Island Pedicle Flap

The island pedicle flap is a type of advancement flap that is completely incised along its periphery and derives its blood supply via the underlying subcutaneous plexus (Fig. 12.5, bottom right). A "V"-shaped island of skin is incised along its periphery leaving the underlying subcutaneous pedicle intact. The flap is moved unidirectionally toward the defect. Suturing produces a "Y"- or kite-shaped closure.

Because the skin edges are detached from the recipient site, greater mobility can be achieved in certain anatomic locations than flaps with intact cutaneous pedicles (Table 12.2). Island pedicle flaps can be advanced or transposed, tubed, or tunneled. When used to advance tissue along one directional vector, they can achieve increased movement while preserving cosmetic subunit boundaries and position of free margins such as the upper lip. Upper-lip defects that are too large to be closed using a single or double advancement flap without compromising the contour of the philtral columns can often be closed using an island pedicle flap by designing the borders along the vermilion border and nasolabial crease. A large Mohs defect on the upper lip (Fig. 12.12) is closed easily using an island pedicle flap incised along the subunit boundaries without displacement of the free margin.

In Fig. 12.13, a basal cell carcinoma involving the nasal sidewall and nasal facial sulcus was excised using Mohs micrographic surgery. Because of the laxity along the nasofacial sulcus and melolabial crease, the defect was closed using an island pedicle flap from this region. The pedicle should be released from the surrounding subcutaneous tissue enough to allow movement but not so much as to compromise the underlying blood supply. Using an island pedicle flap in this location preserves the normal contour and fullness of the cheek (Fig. 12.13c).

Defects involving the nasal sidewall portion of the medial canthus (Fig. 12.14) can also be closed using an inferiorly based island pedicle

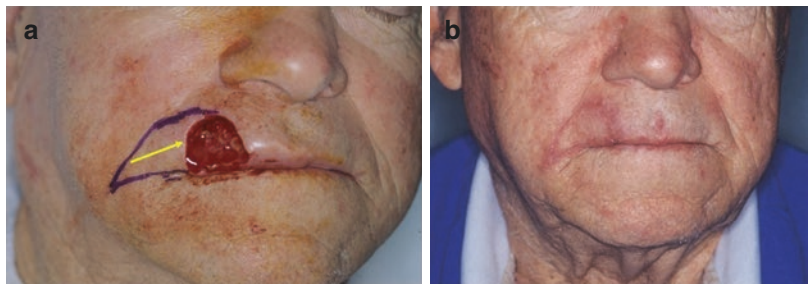

Fig. 12.12 Island pedicle flap (upper lip). (**a**) Defect of the upper lip and outline of island pedicle flap. The flap is incised along the entire perimeter placed along the melolabial crease superiorly and the vermilion border inferiorly and then advanced medially along a horizontal tension vector. (**b**) Appearance at 1 week postoperatively

flap. The leading edge can be anchored to the medial canthal tendon to provide greater stability and resist forces of scar contraction. Other applications of island pedicle flaps include the postauricular trap door flap where tissue is advanced through cartilage from the postauricular sulcus to repair defects of the concha and scapha [6].

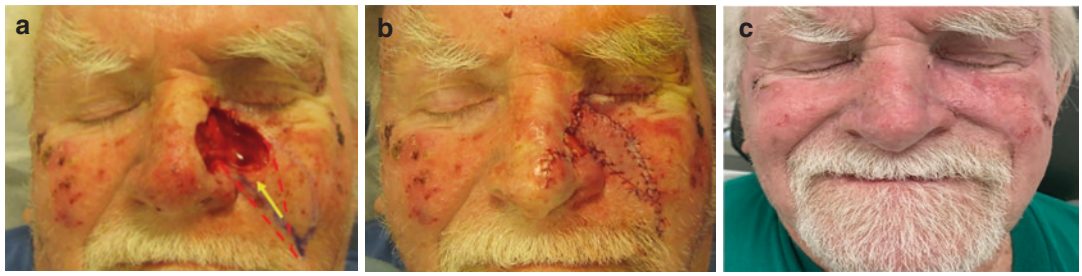

Fig. 12.13 Island pedicle flap (nasal sidewall and cheek). (**a**) An island pedicle flap is designed inferiorly to utilize tissue reservoir above the melolabial crease. Pedicle flap is advanced superiorly. (**b**) Appearance after closure. (**c**) Follow up after 2 months. Note that the fullness of the medial cheek has not been compromised

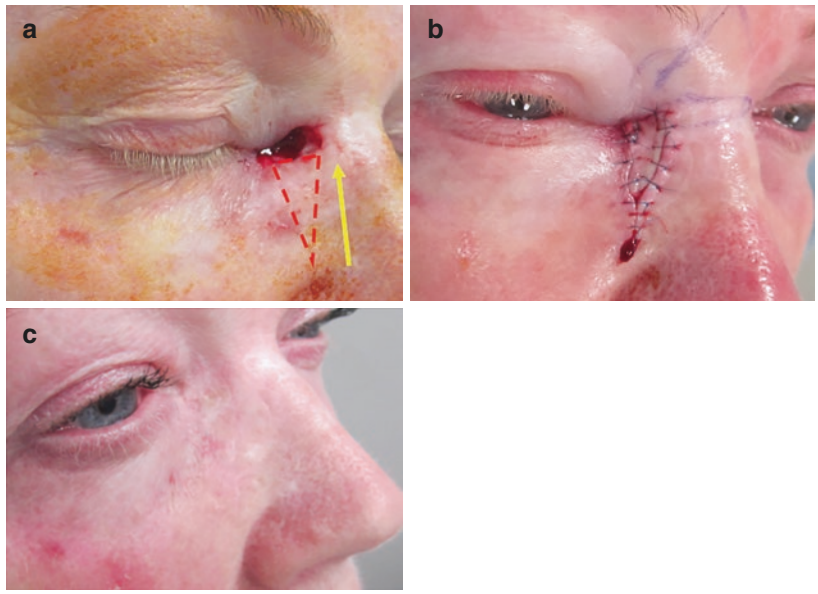

Fig. 12.14 Island pedicle flap (medial canthus). (**a**) Defect involving the medial canthus. The design of island pedicle flap is shown with the red dashed lines and the direction of flap movement shown by the yellow arrow. (**b**) Flap appearance after suturing. (**c**) Appearance at 4 months postoperatively. No webbing or disruption of normal concavity is seen

Rotation Flaps

Rotation flaps move tissue along a defined arc of rotation (Fig. 12.5, upper right).The flap is incised along an arc from A to D and undermined to the base. Note the broad base that preserves blood flow. The rotation pucker at the base of the flap can be divided along the length of the incision (rule of halves) or excised.

The curved incision line of a rotation flap is easily camouflaged in areas with curvilinear relaxed skin tension lines (RSTLs) such as the cheek (Table 12.2). Since rotation flaps have a broad pedicle with robust blood supply, they have a relatively low risk of ischemia compared to other flap types and can be used to close large defects. The rotational movement of opposing skin edges of unequal lengths can create a standing cone at the base which can be blended applying the rule of halves with subcutaneous and superficial sutures or excised. When executing a rotation flap on relatively immobile tissue like the scalp, the arc must often be extended much further than expected to achieve the required amount of tissue movement.

Because of their reliability and ease of concealment within curvilinear RSTLs, the author utilizes rotation flaps whenever possible in locations such as the cheek and chin. Large defects of the zygoma or lateral cheek are very well suited to closure with a rotation flap that can be extended onto the lateral cheek and preauricular sulcus. A large BCC was excised using Mohs margin control and subsequently closed using a rotation flap (Fig. 12.15). The closure is well camouflaged at 4 weeks (Fig. 12.15d). Chin

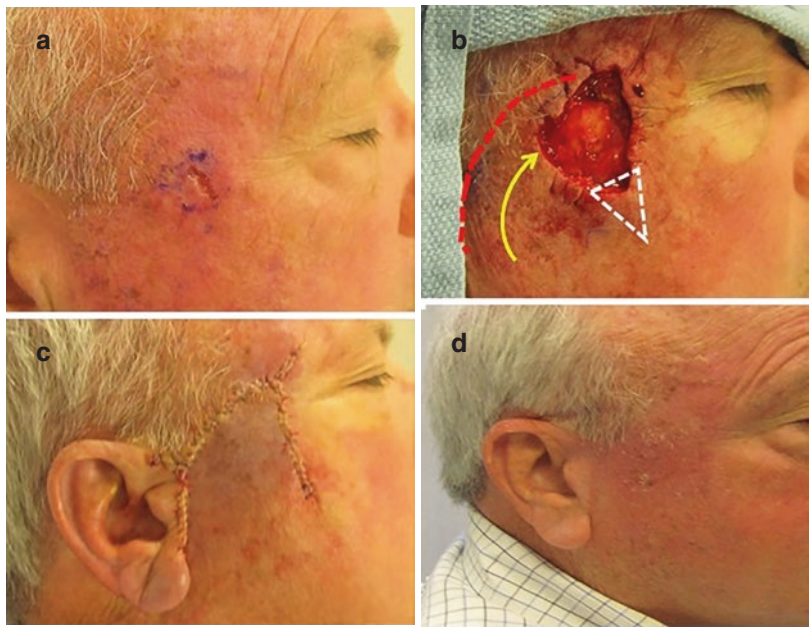

Fig. 12.15 Rotation flap, lateral cheek (**a**) Basal cell carcinoma, lateral cheek (**b**). Defect following Mohs micrographic surgery and flap design (incision line in red, standing cone in white, directional movement as shown by yellow arrow). (**c**) Appearance after suture placement. (**d**) Appearance at 4 weeks postoperatively. Note that the relatively large scar is almost invisible because of the placement along curvilinear relaxed skin tension lines

defects below the mental crease, another curvilinear boundary line, can be closed seamlessly using unilateral or bilateral rotation flaps. Figure 12.16 demonstrates the use of a rotation flap to close a Mohs defect along the orbital rim that could not be closed primarily without creating excess tension along the lower eyelid. The rotation flap redirects the tension of closure horizontally along the nasofacial sulcus. Tacking sutures placed on the underside of the flap to the periosteum of the nasal bone provide additional support against vertical displacement.

Rotation flaps are not only indispensable for closing larger defects of the cheek and chin but also very useful for smaller defects where curved subunit boundaries allow optimal camouflage of the incision. Even defects involving the lateral canthus and cheek can be closed using a rotation flap incised along the curvilinear RTSLs of periorbital and cheek lines (Fig. 12.17). Rotation flaps near the lid margins should be slightly oversized at the leading edge to compensate for any anticipated loss of height with the movement of the flap that can lead to downward pull of the lid margin.

Small-to-medium-sized nasal defects can also be closed using rotation flaps placed along subunit boundaries. Figure 12.18 demonstrates closure of defect on a rounded nasal tip using a bilateral rotation flap. Figure 12.19 demonstrates a small alar defect that is closed with a "spiral" variant of a rotation flap [7] placed along the alar groove. Small-to-medium-sized defects of the nasal sidewall may also be closed using a rotation flap along the junction of the superior nasal sidewall and dorsum.

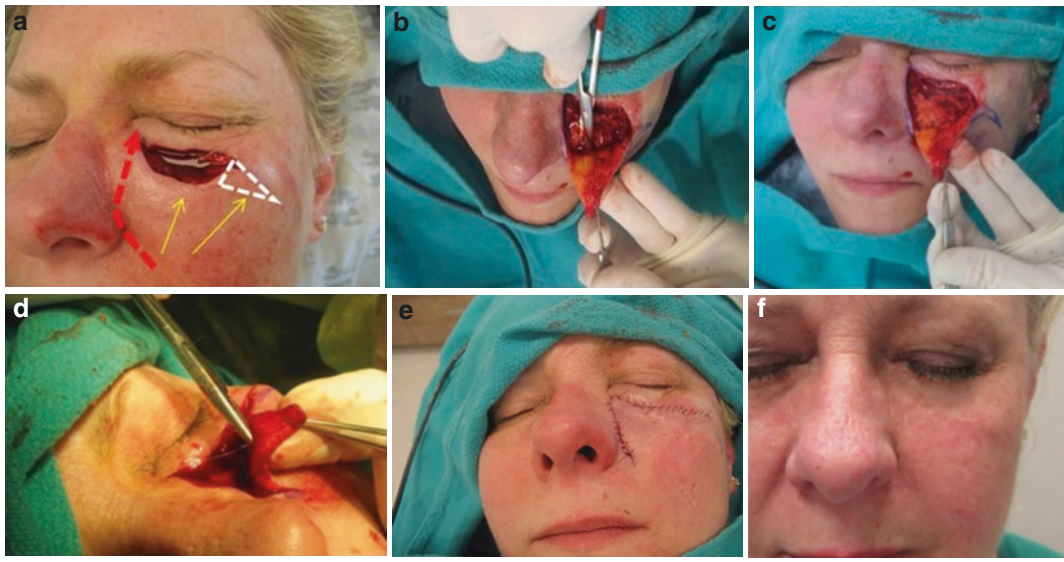

Fig. 12.16 Rotation flap, medial cheek and orbital rim. (**a**) Defect involving the upper cheek along the orbital rim. Rotation flap design using the boundary line of the nasofacial sulcus as the incision line and arc of rotation. The standing cone resulting from movement of the flap and suggested area of undermining are marked. (**b**) The flap is broadly undermined in the subcutaneous plane. (**c**) Flap after undermining. (**d**) Placement of subcutaneous tacking suture that is anchored to the periosteum of the nasal bone. (**e**) Superficial sutures (6.0 nylon) are placed to precisely align skin edges. (**f**) Appearance at 2 years postoperatively

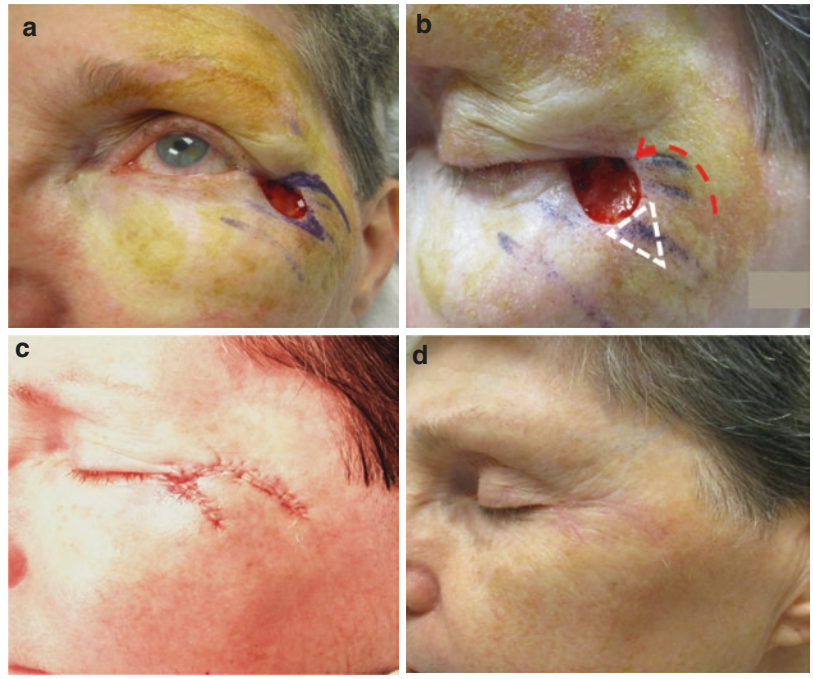

Fig. 12.17 Rotation flap, lateral canthus and cheek. (**a**) Defect on the lateral canthus and cheek, frontal view. (**b**) Lateral view with flap design (incision line and arc of movement shown in red). (**c**) Closure after suture placement. (**d**) Appearance after 3 months

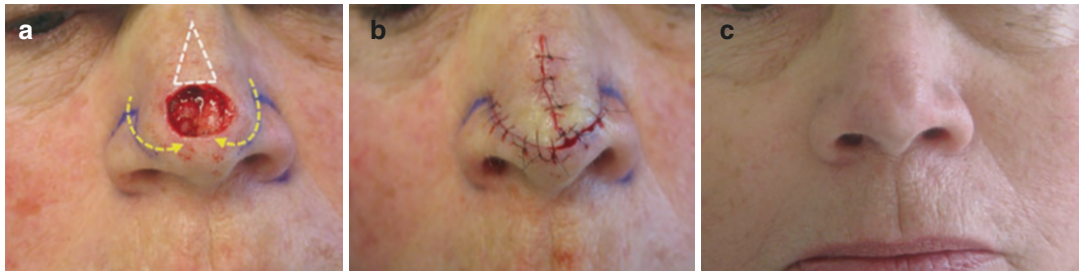

Fig. 12.18 Bilateral rotation, nasal tip (Peng flap). (**a**) Defect on nasal tip with rounded contour and flap design (incision line and arc of rotation shown in red). (**b**) Final closure. (**c**) Appearance after 4 months

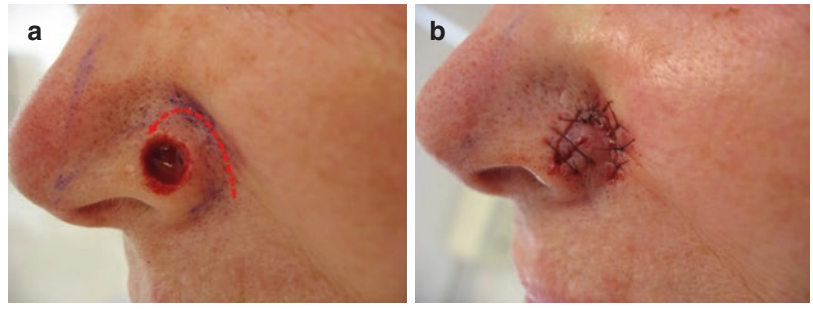

Fig. 12.19 Rotation flap, spiral type (ala). (**a**) Small defect on nasal ala. The rotation flap is designed with an excision just above the alar groove extending toward the alar base. (**b**) Completed closure

Transposition Flaps

Transposition flaps move tissue from recipient to donor site by crossing over intervening tissue (Fig. 12.5, bottom left). They enable the surgeon to utilize reservoirs of tissue laxity not directly adjacent to the defect such as the melolabial crease for nasal defects and the preauricular sulcus for auricular defects. Transposition flaps provide the greatest tissue movement and can be easily manipulated to restore contour (Table 12.2). They are most useful in repairing defects on sites with complex topography such as the nose and the ear. Transposing tissue creates a secondary defect at the donor site that requires closure. It is usually easier to close the secondary defect first to reduce the tension when closing the primary defect. The use of tacking sutures along the underside of the transposed tissue allows improved opposition with the recipient site and contour refinements.

Figure 12.20 demonstrates a Mohs defect of the nasal root and medial canthus that is closed with a simple transposition flap utilizing laxity at the glabella and natural furrows to camouflage.

Another common reservoir of tissue laxity is the melolabial crease. A flap from this location is frequently used for reconstruction of mid-alar defects. A basal cell carcinoma of the ala was excised using Mohs surgery (Fig. 12.21a, b). A melolabial transposition flap was used to close the defect (Fig. 12.21c–f). Tacking sutures at the alar groove were placed to preserve natural concavity and prevent tenting. Additional fat was removed at the base of the secondary defect to help recreate the natural crease. Cosmesis is excellent, and the closure of the secondary defect is well camouflaged within the crease.

The use of multilobed transposition flaps used in succession can increase the distance of tissue transfer. The bilobed transposition flap as described by Zitelli [8] is a masterful design and usually my first choice for closure of medium-sized defects involving the medial ala and nasal tip (Fig. 12.22). When properly designed, the contour results are outstanding, and removal of any standing cone of

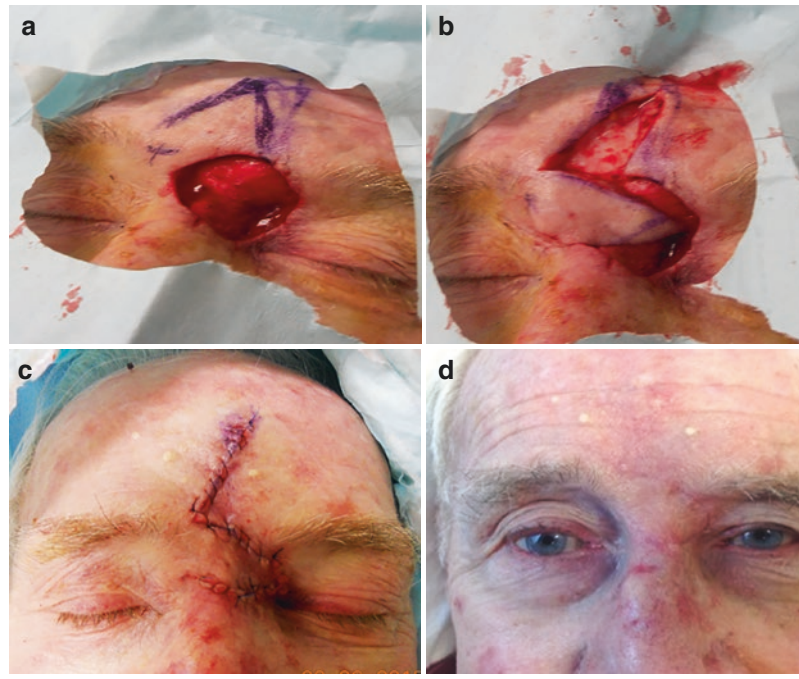

Fig. 12.20 Single-lobed transposition flap. (**a**) Defect of nasal root and medial canthus with transposition flap design on the glabella. The x denoted the position of the supratrochlear artery. (**b**) Flap from the glabella is incised, elevated, and transposed to cover the defect. (**c**) Closure after suture placement. (**d**) Appearance after 2 months

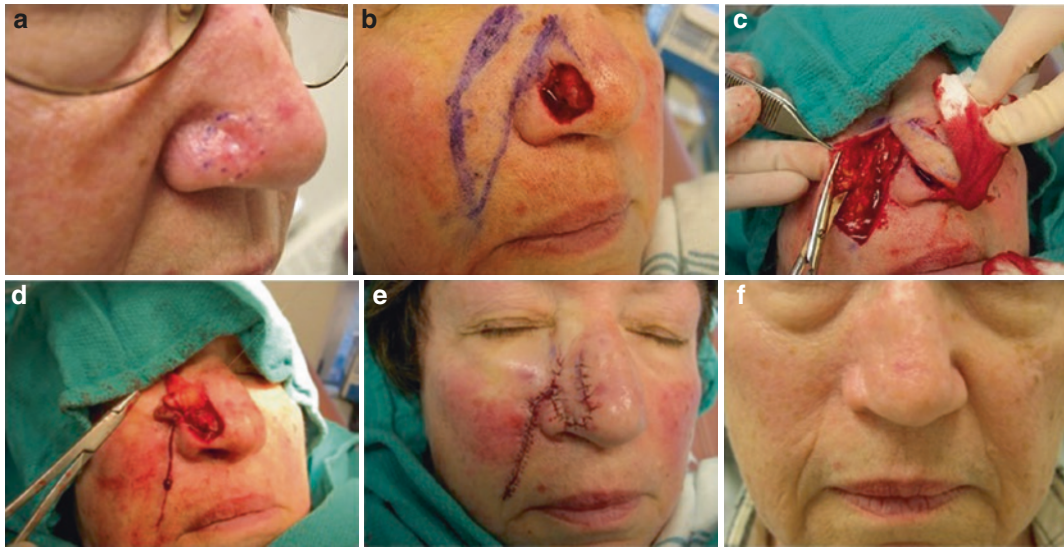

Fig. 12.21 Single-lobed transposition flap (melolabial type) closure of alar defect. (**a**) Basal cell carcinoma of the nasal ala. (**b**) Mohs defect with outline of melolabial flap and burrows triangle above the defect. (**c**) The flap is raised, and the secondary defect is closed first to minimize tension on the flap and allow for more precise placement. (**d**) Subcutaneous tacking sutures are placed to recreate the alar groove. Additional tacking sutures placed to oppose underside of the flap to the recipient bed. (**e**) Appearance after placement of superficial sutures. (**f**) Appearance 4 weeks postoperatively

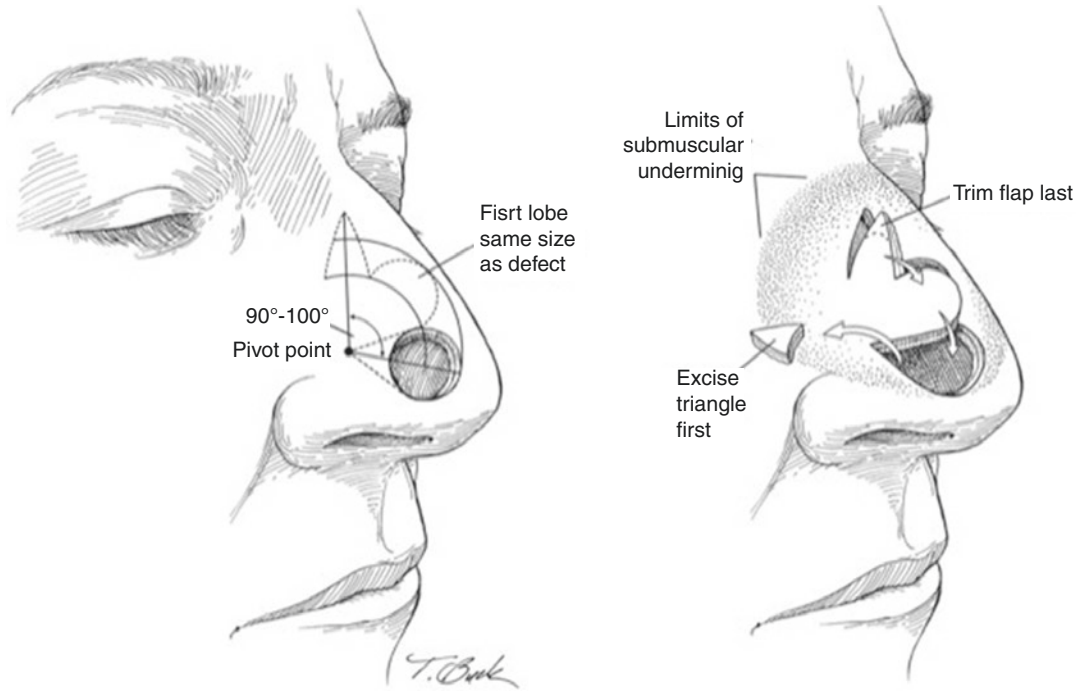

Fig. 12.22 Bilobed transposition flap, schematic. (**a**) A defect involving the nasal tip and alar junction. The pivot point of the flap is identified by approximating the burrows triangle along the alar groove. A line is drawn from the tip of the standing cone to bisect the defect. A second line is drawn from the pivot point at an approximately 90-degree angle adjusting for optimal placement. A third line is drawn at approximately 45 degrees between lines one and two. The two lobes of the flap are then drawn along these axes. The first lobe adjacent to the defect is the size of the defect, while the second lobe is smaller and the tertiary defect triangulated. (**b**) After excision of the burrows wedge and wide undermining in the submuscular plane, the first lobe is transposed into the defect and the second lobe into the secondary defect after trimming to size. The tertiary defect is closed primarily. Illustration by Todd Buck

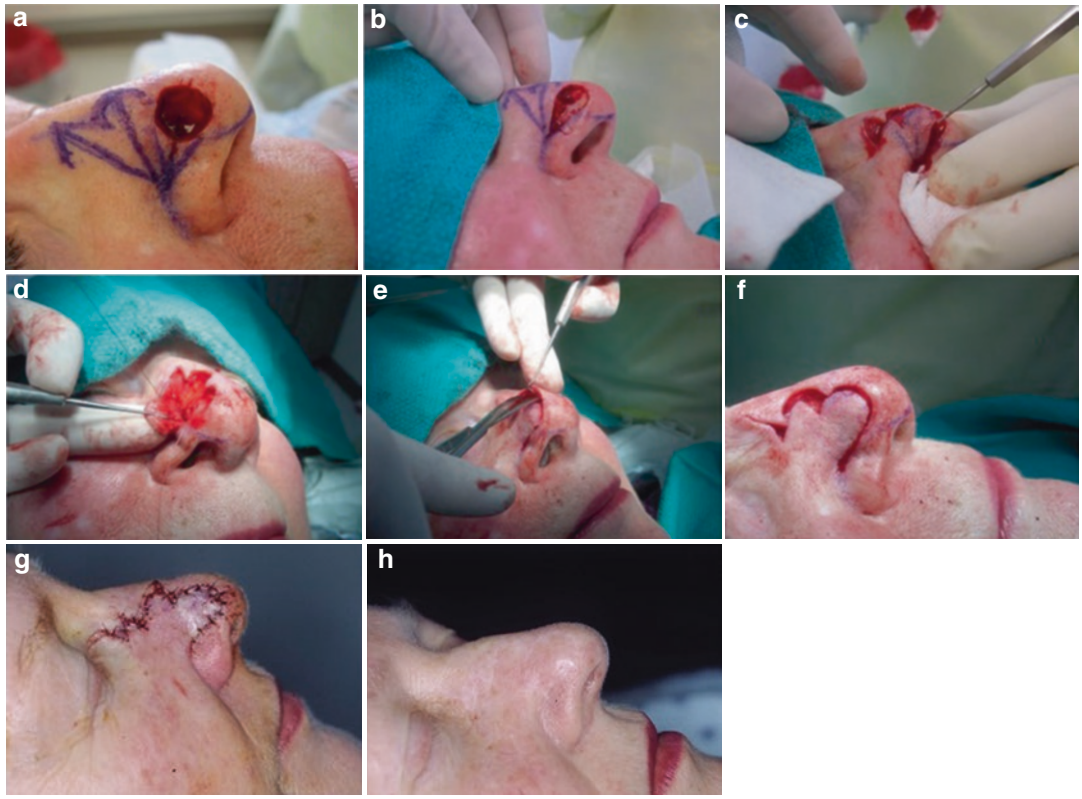

Fig. 12.23 Bilobed flap repair (**a**) Defect involving the nasal tip and medial ala. Design of bilobed flap marked with surgical marker. (**b**) Removal of standing cone at alar groove. (**c**) After incision and elevation of the flap in the submuscular plane, mobility is assessed with skin hook. Additional undermining toward nasal facial sulcus is performed as needed. (**d**) After thinning of the first lobe, deep tacking sutures are placed to secure the flap to the recipient bed to increase opposition and prevent tenting. (**e**) Undermining at periphery of defect. (**f**) Appearance after placement of subcutaneous sutures. (**g**) Final closure after superficial sutures. (**h**) Appearance 6 months postoperatively

tissue is well hidden in the alar groove (Fig. 12.23). Potential disadvantages of transposition flaps include greater likelihood of flap tip ischemia with a greater length-to-width ratio and "pin cushioning" or "trap dooring" with peripheral contracture of the flap. Pin cushioning can be minimized by undermining the periphery of the recipient site. The author generally avoids the use of angular transposition flaps such as the rhombic flap and its variants (Webster 30 angle and Dufourmental flaps) because angular scars tend to stand out rather than blend on most parts of the face.

Axial Flaps

Because axial flaps are supplied by a specific arterial branch, they are less vulnerable to ischemia than random pattern flaps and can be moved a greater distance from donor to recipient site [2]. The most common axial flap used in dermatology is the forehead flap which is typically used to reconstruct large defects of the nose, especially the nasal tip. The forehead flap is based on the vascular path of the supratrochlear artery which lies just medial to the eyebrow (Fig. 12.24). The

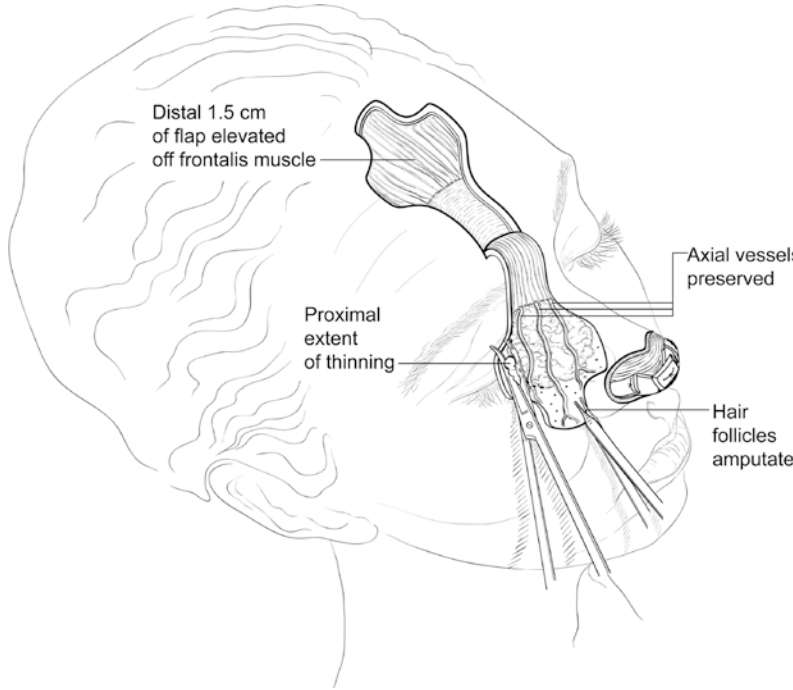

Fig. 12.24 Axial (paramedian) forehead flap design. (Illustration by Alice Y. Chen)

texture match is excellent, and the cosmetic results are usually superior to that of random pattern flaps. Several factors must be considered to determine whether a forehead flap is appropriate for the individual patient. Physical or psychological inability to undergo a multistage procedure may preclude the use of a forehead flap. Many patients are reluctant to have a tubed pedicle in place for the 3 weeks required for revascularization despite the usual superior long-term result compared to other closure choices.

The paramedian design based on one supratrochlear artery has the advantages of a narrower pedicle base and a greater arc of rotation than the traditional midline forehead flap [9, 10]. The path of the supratrochlear artery from the medial eyebrow to the forehead can be confirmed by Doppler ultrasound [9] or approximated anatomically. The supratrochlear artery is located at the glabellar furrow 50% of the time [11]. The remainder of the time it lies between 1 and 6 mm lateral to the crease created by the movement of the procerus and corrugator muscles. When designing a paramedian forehead flap, the pedicle should thus include the glabellar furrow and be 6 mm laterally toward the medial brow [11]. For optimal vascularity, the flap should extend onto the forehead directly superior to the pedicle rather than obliquely crossing over the midline [10].

Figure 12.25 demonstrates a basal cell carcinoma (Fig. 12.25a) and the resultant cutaneous defect of the nasal tip following Mohs excision (Fig. 12.25b, c). To design the flap, the distance from the pivot point at the origin of the pedicle at the medial brow to the nasal tip is measured and the flap length slightly oversized to compensate for length lost from movement from donor to recipient site. A template of the nasal tip unit can be fashioned from Telfa or aluminum foil and flattened onto the superior forehead to outline the flap. While the actual defect may not encompass an entire subunit of the nose, a superior aesthetic result may be obtained by enlarging the defect and replacing the entire subunit [1]. The flap is incised to periosteum, and the flap tip can be thinned for best contour. The underside of the pedicle is lightly

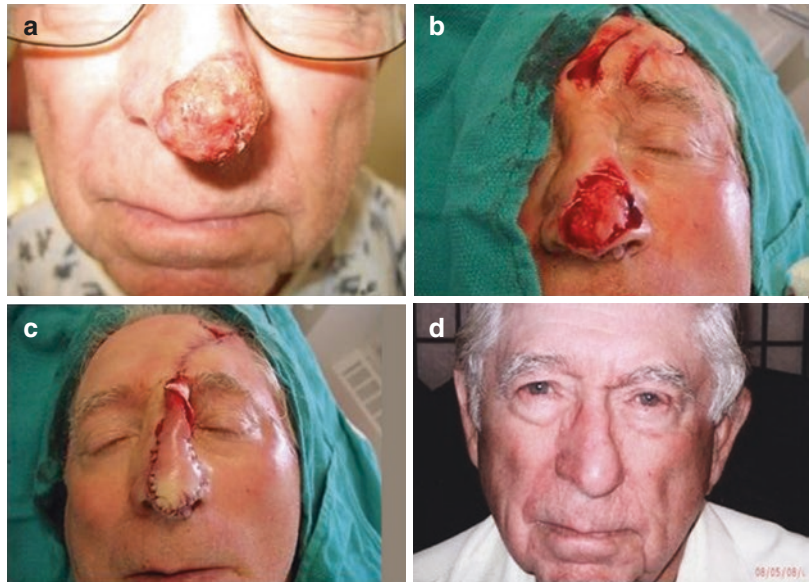

Fig. 12.25 Paramedian forehead flap closure of nasal tip defect. (**a**) Basal cell carcinoma of nasal tip. (**b**) Large defect involving the entire nasal tip and medial ala with incision of paramedian forehead flap to the periosteum. (**c**) Paramedian forehead flap closure after suturing of primary and secondary defect. (**d**) Flap appearance after 5 months after division and inset of pedicle

cauterized and wrapped in petrolatum gauze. Neovascularization at the recipient site is usually sufficient to sever the pedicle after 3 weeks. The flap is then completely inset and the severed pedicle reapproximated at its origin. Excellent cosmetic results can be achieved even with large skin and subcutaneous defects as seen in Fig. 12.25d. Large full-thickness defects involving the cartilage or mucosa will require additional structural support and lining for best results [1, 10].

Table 12.3 Surgical pearls for successful flap closure

Choose simplest closure design to minimize complications
Make contour the primary consideration in flap design
Antiseptic technique
Cauterize sparingly
Handle tissue gently
Meticulous suturing technique with use of deep tacking and basting sutures

Surgical Pearls for Cutaneous Flap Surgery

In planning a flap repair, several guiding principles will aid in achieving success (Table 12.3). In general, one should choose the simplest best solution to a reconstructive challenge. Bigger repairs can lead to bigger complications. Contour should always be the primary concern of any flap repair, and preservation of contour should occur with planning and execution.

An adequate skin prep with a broad-spectrum antiseptic is critical for flap procedures to reduce the risk of infection. Chlorhexidine offers broad bactericidal spectrum and longer duration of action than other antiseptics since it binds to the stratum corneum [12]. Contraindications to chlorhexidine are used on the eyelids and ear canal since prolonged exposure can lead to corneal and inner-ear toxicity. Oral antibiotics can be given for specific indications (prosthetic

device, immunosuppression, prolonged Mohs surgery, sites at higher risk of infection).

Generous use of local anesthetic offers the surgeons many advantages than just anesthesia. Diffuse infiltration of the tissue promotes ease of incision and reduces bleeding which results in better visibility and less tissue injury due to cautery [13]. Allowing the infused anesthetic to sit for 10–15 minutes prior to the flap procedure can help maximize the vasoconstrictive effect of the epinephrine [14].

Some undermining of a flap and the surrounding tissue is usually required to reduce tension, facilitate movement, and redrape or redistribute tissue. Undermining should be performed prudently to minimize tissue injury and optimize flap movement. Inadequate undermining will result in excess tension on the flap tip and poor contour, while excessive undermining can result in reduced blood supply and increased risk of bleeding and tissue injury due to cautery. The ideal tissue plane for undermining will depend on the location of the flap and the underlying vascular supply. On most areas of the face, undermining is performed in the subcutaneous fat. However, when performing flaps on the nose, submuscular undermining can improve blood supply and flap viability. On the scalp, undermining in the subgaleal minimizes bleeding since it is an avascular plane that separates easily.

Tissue handling should always be gentle. Skin hooks are very useful for manipulating tissue with minimal trauma but can be hazardous to the inexperienced user. Tissue forceps must be used with care to prevent inadvertent crush injury especially to the flap tip which is the most vulnerable. Cautery should be used only sparingly to focal areas of bleeding at the wound depth and not to the skin edge since bleeding usually resolves with suturing and overly aggressive cauterization can result in ischemia and tissue necrosis.

Defatting of the flap tip, especially in the case of transposition flaps, can improve contour, prevent trap dooring, and reduce the need for secondary revision. Recent literature also suggests that it can increase flap survival [15] by diverting blood flow cutaneous to the distal flap tip. The use of tacking sutures to oppose the undersurface of the flap to the defect is critical for optimal contouring but increases contact with the recipient bed. Subsurface tacking sutures are often more effective than horizontal subcutaneous sutures at the opposing wound edges for optimal closure.

Any type of tissue movement or transfer will create standing cones of redundant tissue. Advancement and rotation flaps will create pockets of redundant tissue away from the defect site, while transposition flaps will require removal of additional tissue adjacent to the defect for placement. Skin edges of unequal length should be divided over the length of the incision using the rule of halves whenever possible. If a rotation or advancement pucker is still present, then a standing cone of tissue can be removed. With a few notable exceptions (such as the bilobed flap), excision of "dog ears" is best accomplished toward the end of the procedure after tissue redistribution has been completed. Frequently, standing cones of tissue are smaller than anticipated after undermining and applying the rule of halves. Alternatively, tissue mobility and flap movement may be less than anticipated, and discarding tissue prematurely may cause unnecessary difficulty in closing the wound.

Complications in Cutaneous Flap Reconstruction

Adverse sequelae such as infection, bleeding, and hematoma are risks of any cutaneous surgical procedure and are described in depth in a preceding chapter. This section will describe complications more specific to cutaneous flap repair. Good flap design and gentle tissue handling are critical for good outcomes. However, complications may still occur, and the ability to identify patients or repairs that are at greater risk is important to managing them effectively with early intervention. Surgical patients should be routinely con-

tacted by the office 24 hours postoperatively and inquiries made regarding pain, bleeding, and understanding of wound care instructions. Patient complaints should carry a low threshold for reevaluation in the office since problems such as seroma, hematoma, or ischemia can be minimized by early intervention and supportive care. Flap complications can be categorized as acute or delayed.

Acute Complications

Flap ischemia is the result of inadequate blood flow and perfusion pressure. Random pattern flaps are at greatest risk because they are initially dependent on blood flow from small arterioles that is more easily compromised. Flap ischemia can be caused by a variety of factors that include surgical technique and intrinsic patient factors (Table 12.4). With regard to flap design, random pattern flaps are typically thought to be at risk for ischemia if the ratio of the flap length to the width of the pedicle exceeds 4:1, but venous congestion may also be a cause of poor flow [2]. Excess tension at the flap tip or edges is a common cause of tissue ischemia.

Tissue injury may also occur with rough handling or excessive cauterization. Tissue manipulation should be minimized to avoid crush injury especially at the tip. Skin hooks or delicate-toothed forceps should be used gently. Forceps should be used for guiding not for grabbing. Cautery should be used very selectively to reduce the risk of thermal injury and loss of perfusion. The author uses radio-frequency current directed through fine-toothed forceps to specific bleeding points at the base of the wound. Cautery to the skin edges should be avoided since it may lead to tissue necrosis.

Table 12.4 Causes of flap ischemia

Cause	Prevention
Excess tension at flap tip or edges	Optimize flap design, use tension-bearing subcutaneous sutures
Tissue trauma	Gentle handling of tissue, minimize cautery
	Use of correct suturing technique
Nicotine-induced vasoconstriction	Smoking cessation 2–4 weeks preoperatively
Avascular wound bed	Delayed closure

Correct suturing technique can also maximize contact of the flap with the recipient bed resulting in reduction of dead space and risk of hematoma. Deep "basting" or "tacking" sutures from the underside of the flap to the wound base should be placed parallel to direction of blood flow from the flap pedicle and never perpendicular so as not to compromise perfusion. Ideally, minimal tension should be exerted at the wound edges. Superficial sutures should be secure but not tight to prevent "cutting in" with postoperative swelling which in turn can lead to infection or wound edge necrosis. In addition to meticulous suturing technique, the use of a carefully applied pressure dressing for 24–48 hours postoperatively can greatly reduce swelling and fluid collection that can put the flap at risk.

Patient risk factors for flap ischemia include smoking and diabetes. Smokers should be encouraged to stop or decrease their smoking for a minimum of 2–4 weeks before surgery in order to reverse the vasoconstrictive effect [16]. Delayed reconstruction for several weeks may allow the wound to granulate and reduce the risk of flap necrosis. Inadequate vascularity of the recipient bed as is seen with cartilage lacking in perichondrium or exposed bone can also lead to flap failure which can be prevented by allowing the development of granulation tissue at the wound bed before repair.

Management of the Ischemic Flap

Patients with flap repairs that are deemed to be at increased risk for ischemia should be reevaluated early (24–48 hours) so that a timely intervention can be made. If evidence of ischemia is present, the cause should be identified

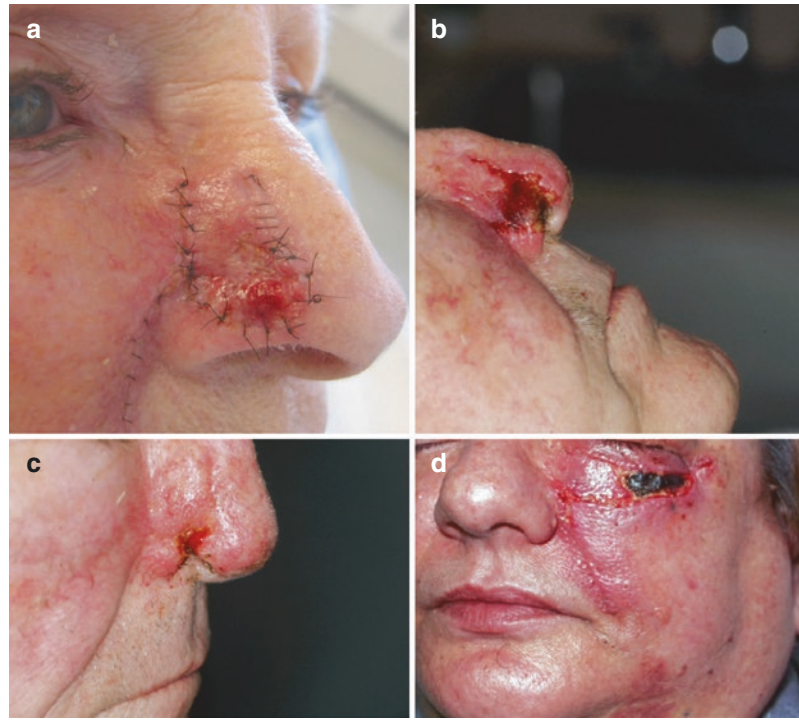

Fig. 12.26 Flap ischemia and necrosis. (**a**) Mild flap ischemia with superficial epidermal sloughing at flap tip. (**b**) Tip necrosis of melolabial transposition flap associated with smoking. (**c**) Secondary notching of alar rim. (**d**) Flap tip necrosis (eschar) of transposition flap associated with diabetes and smoking

and corrected. Any tight or constricting sutures can be removed and any fluid collection beneath the flap evacuated. Mild ischemia manifested by epidermal sloughing (Fig. 12.26a) can be managed by supportive care with topical antibiotics and a dressing until the surface re-epithelializes. Antibiotics are indicated if secondary infection is present or likely to occur. Management of full-thickness tissue necrosis as seen in Fig. 12.26b is more controversial. Traditional surgical teaching instructs the surgeon to avoid debridement and allow an eschar to form and separate. However, conservative debridement of obviously nonviable tissue can facilitate wound healing and remove a potential reservoir of bacterial colonization. Patients can be seen at weekly intervals to facilitate wound debridement and reinforce wound care. The placement of focal guiding sutures can help re-oppose separated edges more quickly. Full-thickness necrosis (Fig. 12.26c) will likely result in contraction or notching which may require later revision (Fig. 12.26d).

Delayed Complications

Persistent telangiectasia and wound contracture (Fig. 12.27a, b) are the most common long-term sequelae of flap surgery. Since angiogenesis is part of the tissue reparative process, prominent telangiectasia or erythema can persist in vascular areas of the midface especially in patients prone to rosacea (Fig. 12.27a). While most postoperative redness will resolve spontaneously, persistent erythema or telangiectasia can be treated with a long-pulsed dye laser or intense pulsed light (IPL) at monthly intervals. Trap dooring or pin cushioning, ectropion, and displacement of other free margins such as the alar rim and lips with the contractile phase of wound healing generally appear around 4 weeks postoperatively. Pin cushioning occurs most frequently with transposition or interpolated pedicle flaps (Fig. 12.27b). While scar contracture is the main cause of pin cushioning, it can also be caused by the use of a bulky flap that is too thick for the recipient site as in the case of a melolabial transposition flap for nasal repair. The risk of pin cushioning can be reduced by siz-

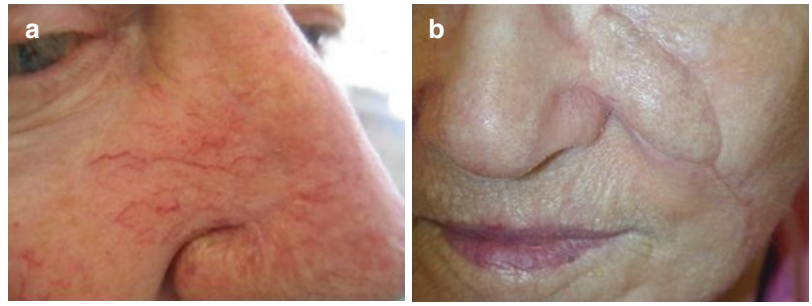

Fig. 12.27 Delayed flap complications. (**a**) Persistent telangiectasia along nasal flap. (**b**) "Pin cushioning" of interpolated pedicle flap at 2 months post-op

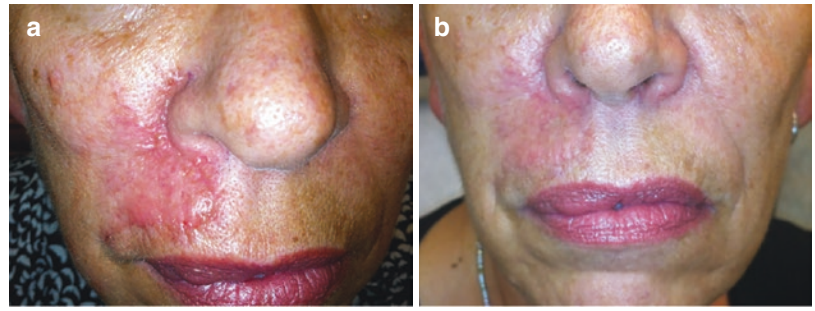

Fig. 12.28 (**a**) Pin cushioning and telangiectasia of upper-lip transposition flap. (**b**) Improvement with ILK, pulsed dye laser, and massage

ing the flap appropriately to the recipient site (same size or slightly smaller), defatting, and undermining the periphery of the recipient site. Gentle massage of the flap starting at 2–3 weeks postoperatively can reduce swelling and prevent contracture. Patients with nasal flap repairs should return for a postoperative check 4–6 weeks after surgery. Mild induration or pin cushioning can be reversed with focal use of intralesional Kenalog (ILK) 10 mg/ml to indurated areas and repeated monthly as needed.

Figure 12.28 demonstrates telangiectasia and induration of a transposition flap on the upper lip that resolved with ILK and long pulsed dye laser treatment.

Contraction of a flap can also cause displacement of free margins such as the alar rim, vermilion border, and eyelid. Optimal flap design and suturing techniques can reduce the risk of margin displacement. In the case of large or full-thickness defects on the nose, the use of cartilage grafts can stabilize the alar rim. Failure to adequately repair lost nasal lining or provide structural support can result in unopposed wound contracture and a poor cosmetic result that requires revision. Early contracture can be reversed with ILK repeated at monthly intervals.

Ectropion is not infrequent with periorbital flap repair. Excess tension on the lid margin may not be apparent at the time of the repair, but subsequent contracture of the scar can produce ectropion at around 4 weeks postoperatively as shown in Fig. 12.29. This is particularly true in the case of elderly patients whose lid laxity should be assessed preoperatively using the "snap" test. If a significant lid lag is noted, one should consider additional means of support to resist the forces of contracture such as a canthopexy, suspension, or fixation of the lateral canthus to the lateral orbital rim or adjacent soft tissue.

When repairing defects adjacent to the orbital rim, the flap should always be designed to avoid downward pull on the lower lid and redirect tension vectors along a horizontal axis. Anchoring sutures placed in the subcutaneous tissue or periosteum are useful for suspension of periorbital flaps. Mild ectropion can often be ameliorated with Kenalog injection at the site of contraction. Persistent ectropion may require a revision to restore volume and lid position using a transposition flap from the ipsilateral upper eyelid (Fig. 12.29b) or skin graft.

Prominent scarring or ridging is another complication that occurs on sebaceous areas of the

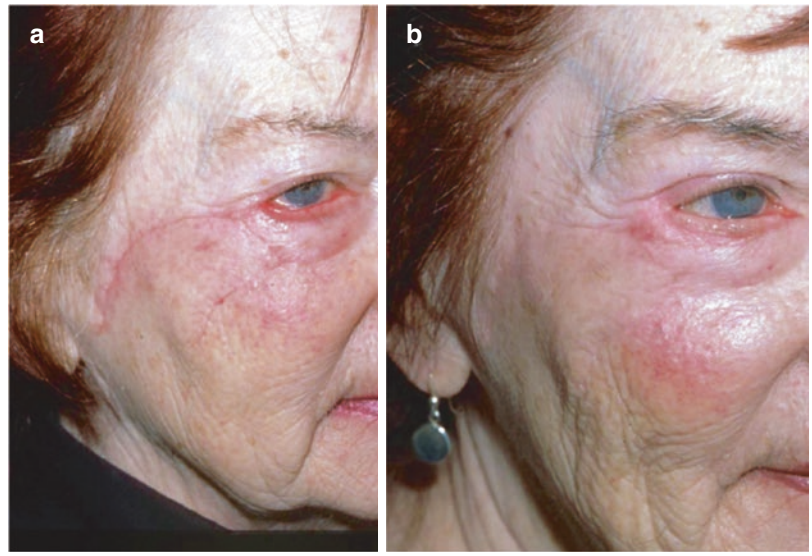

Fig. 12.29 Ectropion. (**a**) Delayed ectropion associated with large cheek rotation flap, 4 weeks postoperatively. (**b**) Correction following a transposition flap from the upper eyelid

nose, especially in male patients with preexisting rosacea. If meticulous suturing fails to produce a cosmetically acceptable result, resurfacing by fractionated or ablative laser or manual dermabrasion can greatly approve the appearance of a prominent scar.

Summary

Flap repairs of cutaneous and subcutaneous defects can yield excellent results in restoring contour and appearance. Preoperative planning with regard to flap design and placement is critical to success. Meticulous surgical technique is essential for maintaining flap viability. Despite proper planning and technique, complications can occur, and surgeons performing flap repairs should be thoroughly prepared to manage them.

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Chapter 13
Techniques in Skin Grafting

Deborah F. MacFarlane

Free skin grafting, defined as the severing of a piece of skin from its local blood supply and transfer to another location, is thought to have originated in India approximately 2500 years ago. However, it was not until the nineteenth century that the first accounts appeared in Western literature [1].

The goal of this chapter will be to provide the practitioner with an understanding of the physiological processes involved in skin grafting, be it with full-thickness, split-thickness, free cartilage, or composite grafts. This knowledge coupled with attention to meticulous hemostasis, careful tissue matching, and postoperative management is essential to achieving an excellent outcome.

General Principles

Graft survival is dependent upon the establishment of a blood supply from the recipient site and occurs over a series of stages. It is essential that this process is appreciated if graft survival is to be achieved.

During imbibition (from Latin *bibere* "to drink"), which occurs during the first 24–48 h, the graft absorbs transudate from the recipient bed and becomes edematous [2]. The graft is initially held in place by fibrin, which is eventually replaced by granulation tissue. Over the next 48–72 h, inosculation occurs with the development of vascular anastomoses between the recipient bed and donor site [3]. By 4–7 days, capillaries have grown from the recipient bed to the graft in the process of neovascularization, and full circulation has been restored to the graft [4]. Restoration of lymphatic circulation also occurs within this period. Two to four weeks following grafting, reinnervation occurs, and full sensation may take several months or even years to return to normal [5].

Full-Thickness Skin Grafts

Composed of the epidermis and the entire dermis, including adnexal structures such as hair follicles and sweat glands, full-thickness skin grafts (FTSGs) are especially useful for the repair of defects of the nasal tip, dorsum, ala, lateral nasal sidewall, lower eyelid, and ear [6]. When close attention is paid to skin color, texture, and thickness, FTSGs can provide an excellent cosmetic result (Fig. 13.1).

Wound contraction is minimal with FTSGs and dermal adnexal structures are left intact. Recipient sites must be able to provide a rich vascular supply for capillary ingrowth as well as fibroblasts for graft adherence. In general, avascular structures such as exposed bone, cartilage, tendon, and nerve, which have had their periosteum, perichondrium, peritenon, or perineurium removed, are unable to support FTSGs [8].

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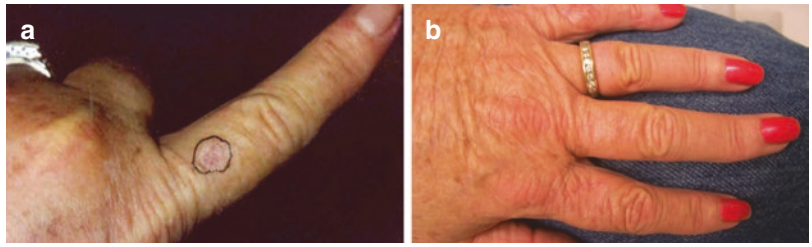

Fig. 13.1 (**a**) Squamous cell carcinoma on the base of the left index finger prior to Mohs surgery. (**b**) Appearance of FTSG 1 month postoperatively. Note careful matching of color and texture between donor skin (upper inner arm) and recipient site provides a cosmetically very acceptable result. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

Technique

Preoperative Planning

A thorough preoperative history should be taken to identify medications and dietary supplements that may increase the risk of bleeding. It cannot be stressed enough how vital hemostasis is to graft success, and any medication or supplement that is not essential should be stopped at least 1 week prior to surgery [9, 10]. Since a threefold risk of graft necrosis has been observed in patients smoking more than one packet of cigarettes daily compared with nonsmokers or those smoking less than a packet daily [11], all smokers should be encouraged to cease or decrease cigarette smoking markedly several days prior to surgery and to continue this for at least the first postoperative week. Patients should similarly be advised that they will need to curtail physical exercise; this is especially important when dealing with FTSGs on the lower extremities of elderly patients. One may consider hospitalization in such circumstances (Fig. 13.2).

Donor Site Considerations

In order to maximize esthetic outcome, like skin is always best repaired with like skin. The importance of this step cannot be over-emphasized.

> Time should be spent matching donor skin with that of the recipient site, taking into consideration not just color, but also texture, thickness, extent of photodamage, and degree and direction of hair growth (Fig. 13.3), if appropriate.

> Burow's graft from the supero-medial brow and placement of the FTSG so that the eyebrow hairs are carefully aligned with adjacent hairs

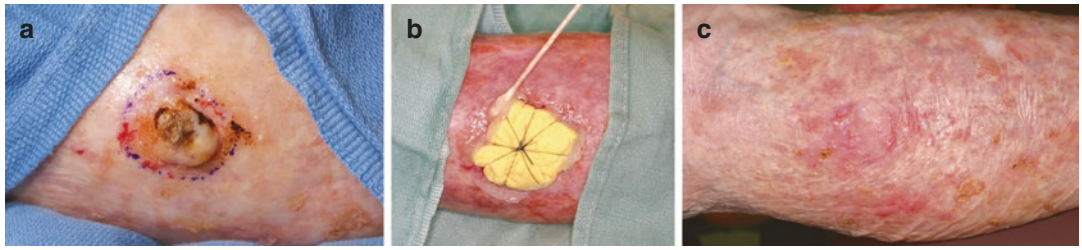

Fig. 13.2 (**a**) A large squamous cell carcinoma on the leg of a 93-year-old albino African-American woman prior to Mohs surgery. (**b**) A bolster is placed over the FTSG and the patient is hospitalized for 1 week of bed rest. The daily application of antibiotic ointment to the wound periphery, commencing on postoperative day 2, is demonstrated. (**c**) Appearance of the FTSG 89 weeks later. Note the patient's varices. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

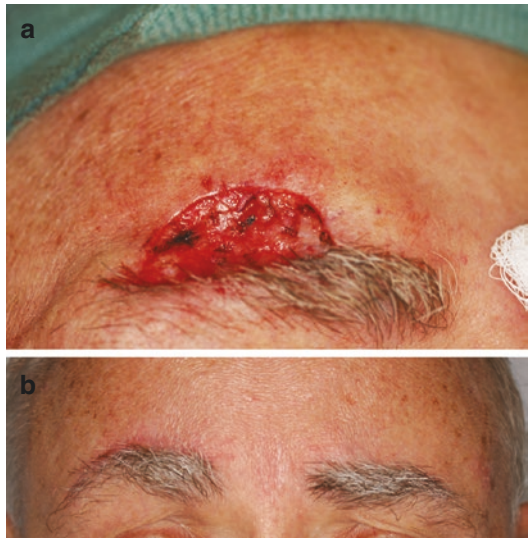

Fig. 13.3 (**a**) A large defect involving the superior aspect of the eyebrow is apparent following three stages of Mohs surgery for a recurrent SCC. (**b**) Appearance of the brow 2 months after complex linear repair and Burow's graft from the supero-medial brow and placement of the FTSG so that the eyebrow hairs are carefully aligned with adjacent hairs

Skin grafts taken from excess upper eyelid skin can be used to repair lower eyelid defects. However, grafts of this especially thin skin should be oversized by at least 100% to prevent contraction and possible ectropion [12]. The preauricular region is a good source of a thicker skin with a degree of sun exposure that can be used to repair nasal defects, and the donor site heals nicely (Fig. 13.4) [13].

Skin taken from the nasolabial fold may also be used to close small nasal tip defects and may often supply a degree of sebaceous quality. The donor site heals imperceptibly, and the author recommends this over preauricular skin, which is less sebaceous, may often have fine hairs, and may not provide as close a color match (Fig. 13.5).

Conchal bowl grafts provide another option where a sebaceous texture is needed, as with the nasal tip on some patients [14]; however, it may take weeks for the donor site to granulate in and patients should be aware of this.

A graft taken from skin adjacent to the surgical defect, known as a Burow's graft, often provides an ideal match with respect to both color

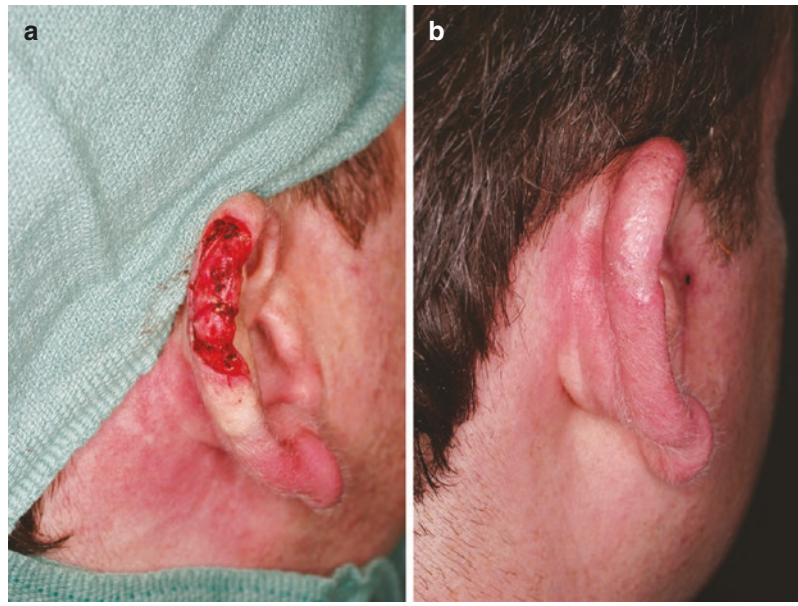

Fig. 13.4 (**a**) Defect following two stages of Mohs surgery to remove a BCC on the ear of a young male. Note some notching of the auricular cartilage where the BCC was adherent. (**b**) Appearance of the ear 2 months following surgery. There is a small crust at the preauricular donor site

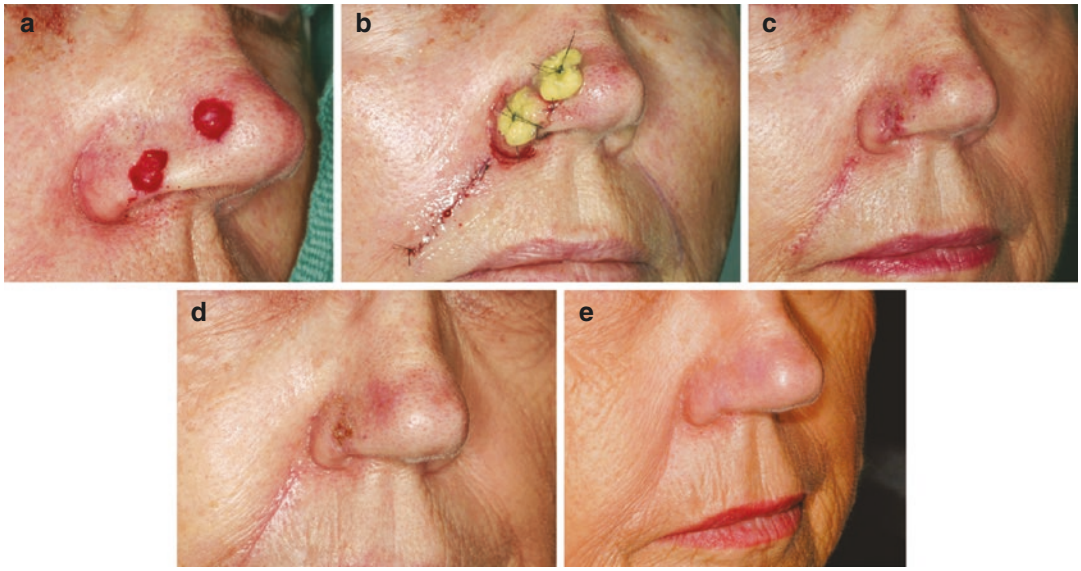

Fig. 13.5 (**a**) Defects on the nasal wall following Mohs surgery for two basal cell cancers. (**b**) FTSGs are taken from the right nasolabial fold. (**c**) Appearance at suture removal 7 days later. The crust is left undisturbed and the area redressed for another week. (**d**) Appearance at 2 weeks—the FTSG is left open. (**e**) Appearance 5 months following surgery

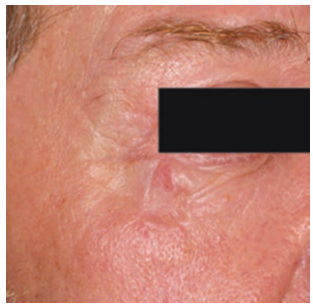

Fig. 13.6 SCC in situ has occurred within this FTSG taken from the patient's right upper eyelid after oculoplastic repair of a Mohs defect beneath the patient's eye 18 months prior. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

and texture [15]. As there are several reports of skin cancers being accidentally transferred in donor skin, a careful examination should be made of prospective donor skin to exclude malignancies (Fig. 13.6) [16].

Often a better color match is provided by using skin with a certain degree of photodamage. Clavicular skin, for instance, may be used for larger defects requiring FTSGs of sun-damaged skin; however, these grafts need to be carefully placed to avoid an unattractive scar [17]. Similarly, skin can also be harvested from the forearms or wrists to repair defects on the fingers or hands (Fig. 13.7).

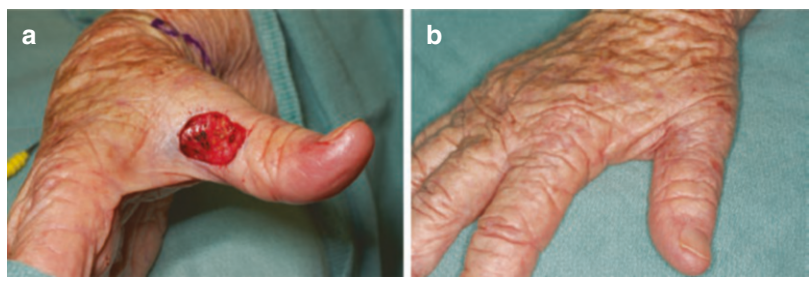

Fig. 13.7 (**a**) Wound defect following Mohs surgery for a squamous cell cancer. Note that donor site (inner wrist) has been selected for color match. (**b**) FSTG appearance 2 months later

Skin may be harvested from the abdomen; however, the color and texture match may be less desirable, and, for the author, this is the place of last resort. Care should be taken to place the excision in an area free from trauma due to clothing.

Procedure

There are many techniques used in the construction of full-thickness skin grafts. What follows is the author's personal technique (Fig. 13.8a–i).

Hemostasis of the recipient site is essential for graft survival and electrocautery must be precise and meticulous. Once the wound is dry and the recipient site chosen, a template can be manufactured from any sterile and flexible material. The author uses Telfa, which is placed on the recipient site and firmly pressed into the contours of the bed. Any blood present is absorbed onto the Telfa, forming an outline that is then cut out. The author does not personally cut FTSGs larger than the defect, except in the ocular area as described previously. Next the template is outlined on the donor site prior to local anesthesia. The FTSG is then excised down to superficial fat, placed in a sterile saline-filled container, and the donor site is repaired. The FTSG is next defatted until the dermal surface is white and shiny. This is facilitated by placing the FTSG on a piece of gauze, dermal side up, and trimming with sharp scissors (Fig. 13.8d).

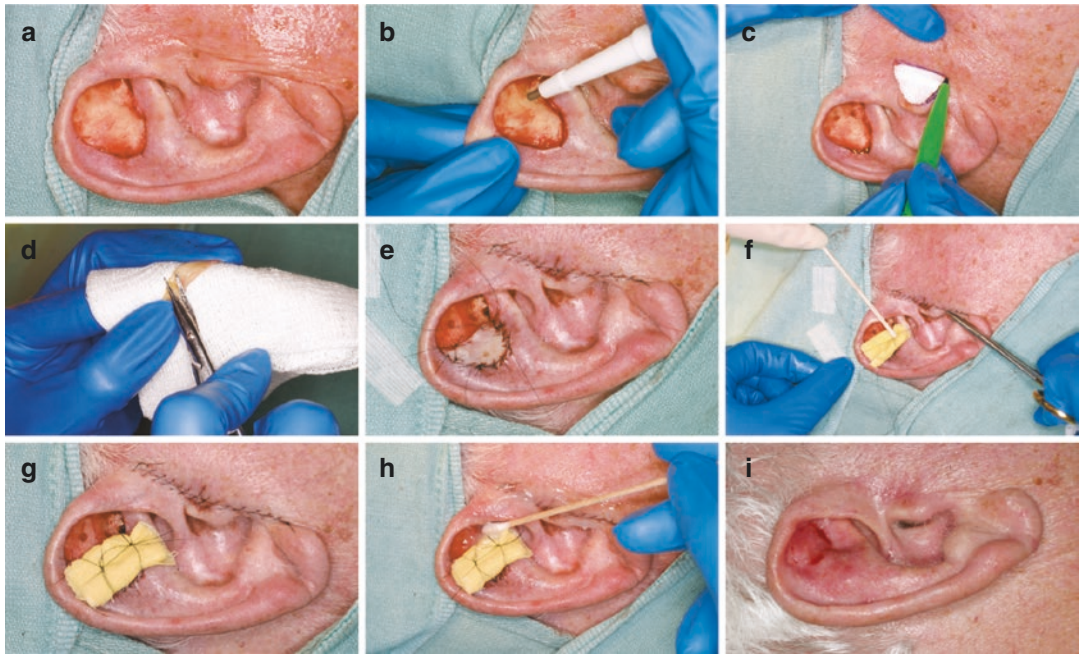

Fig. 13.8 (**a**) Defect following four stages of Mohs surgery for a BCC, which necessitated removal of perichondrium in the superior aspect of the defect. (**b**) A 2 mm punch is used to punch through the denuded cartilage to facilitate ingrowth of granulation tissue from the posterior aspect of the ear. (**c**) A Telfa template of the defect is outlined on the preauricular area, which has been chosen as a suitable color and texture match. (**d**) Gradle scissors are used to defat the graft. (**e**) A running 6-0 Ethilon suture has been placed around the periphery of the defatted FTSG. Long ties are placed at symmetric points on the FTSG and anchored to the drapes with Steri-Strips. (**f**) A Xeroform bolster is tied in place. (**g**) The finished bolster. (**h**) Antibiotic ointment is applied to the exposed cartilage and around the perimeter of the bolster. This is then covered with a protective dressing (Telfa, gauze, and Hypafix), which is left untouched for 48 h. Thereafter antibiotic ointment is applied daily and the wound dressed similarly following suture removal 7 days after surgery. (**i**) Appearance of the FTSG 4 weeks later—the superior aspect of the defect has granulated in fully and blends imperceptibly with the FTSG. The shape and appearance of the ear are fully restored. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

The author has observed that overly thinned FTSGs will later result in an unattractive hypopigmented appearance.

Immobilization

It is essential that FTSGs be kept in direct contact with the recipient bed if the previously described physiological processes are to occur successfully.

Next a running suture is placed around the perimeter of the FTSG. Basting sutures are not used as they are felt to contribute toward a "pincushion" effect. A bolster can be manufactured from Xeroform and tied securely over the FTSG (Fig. 13.8f, g). A thick layer of antibiotic ointment is placed around the perimeter of the bolster (Fig. 13.8h), and the entire area is covered with Telfa and Hypafix. In a comparison of 96 full-thickness skin grafts dressed with either tie-over bolsters of petrolatum gauze (47 grafts) or non-bolsters dressed with petrolatum gauze only (49 grafts), the author noted that graft success did not differ between the groups. This applied for grafts up to 5 cm [18]. For this reason the author prefers not to use bolsters with the exception of large external auditory canal grafts which the author will bolster and, on occasion, use a T-stent [19]. Ultimately the choice as to whether to use a bolster or not relies upon physician preference and surgical site [20].

Postoperative Care

The patient is instructed to change the dressing after 2 days and to apply the antibiotic ointment to the perimeter of the bolster or dressing, to replace the dressing, and to continue this process thereafter until suture removal. Using this technique, bolster or dressing and suture removal are both extremely easy. It is important to caution patients that following suture removal a graft is still delicate and that trauma such as a hot shower on the area should be avoided for an additional 1–2 weeks. For this reason the author instructs patients to continue to keep the grafted area covered with antibiotic ointment, Xeroform, and an occlusive dressing for a further week. It is extremely important to caution patients to avoid UV exposure in the postoperative period. The author recommends that instead of applying sunscreen to the FTSG and donor site, that the patient use Desitin. Sold over the counter, the major ingredient in this cream is zinc which provides UV protection without some of the ingredients in sunscreens which can result in irritation [21].

Special Situations

Be aware that skin grafts less than 1 cm in diameter can survive due to vascular re-anastomoses, which form solely from the edges of the wound [22]. However, other solutions are needed for larger grafts. When an immediate FTSG is needed to cover bare cartilage, fenestrating the cartilage and lifting a hinge flap have been found to increase graft survival [23].

> The author often uses a 2 mm skin punch to punch out the cartilage (Fig. 13.8b), allowing the ingrowth of granulation tissue, and then waits 2–3 weeks until sufficient granulation has occurred (Fig. 13.8i).

It is advisable to position these punches so that the support function of the auricular cartilage is not compromised, and it is essential that the patient keep the area moist with an ointment like mupirocin (less chance of contact dermatitis) and covered with a layer of Xeroform and an occlusive dressing, which is changed daily. Nonsteroidal anti-inflammatories are useful to relieve pain due to the chondritis, which often occurs following manipulation of auricular cartilage. Other authors have documented the benefits of delaying FTSGs [24, 25]. The author has not uncommonly performed auricular FTSGs 2–3 weeks following surgery when sufficient granulation has occurred.

Complications

Partial or complete graft failure may be due to excessive electrocautery of the recipient bed, hematoma, infection, and disruption of graft-bed

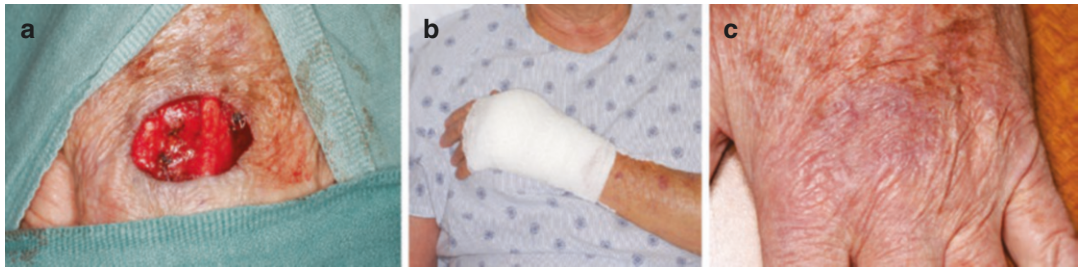

Fig. 13.9 (**a**) Defect appearance following Mohs surgical removal of a large SCC on the dorsum of the hand of a farmer. (**b**) Avoidance of strenuous activities was emphasized. (**c**) FTSG appearance 3 months following surgery

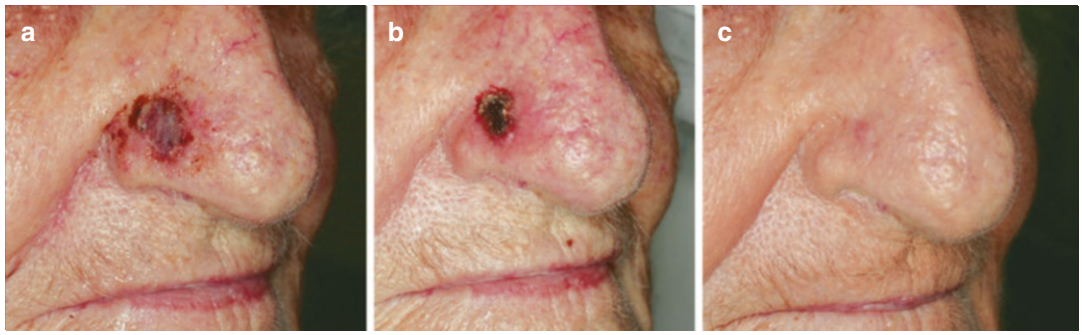

Fig. 13.10 (**a**) Appearance of FTSG on a patient's nasal ala at 1 week. The patient is reassured and told that the area will dry out and become darker in color. (**b**) Appearance 1 week later. (**c**) Appearance 6 weeks following surgery

contact. Attention to hemostasis, careful bolster design, and stressing the importance of avoiding strenuous activities should help reduce the risk of such failure (Fig. 13.9).

Another complication is necrosis; this is usually superficial and not full-thickness.

> If graft necrosis occurs, it is important not to debride the region of necrosis. Instead, advise patients that the graft is acting as a dressing, that new skin is growing underneath, and that it is important that they refrain from manipulating the area and should just let it dry out and lift off (Fig. 13.10).

Debridement of the necrotic area will only interfere with this process. Graft elevation can be treated with intralesional corticosteroids after several months have elapsed. DuoDERM strips may be applied nightly by patients to help smooth out any contour irregularities.

Split-Thickness Skin Grafts

Split-thickness skin grafts (STSGs) consist of the epidermis and a portion of the dermis. Dependent upon the amount of dermis included in the graft, they vary from 0.25 to 0.75 mm in thickness and are categorized as thin (0.0125–0.275 mm), medium (0.275–0.4 mm), or thick (0.40–0.75 mm).

Equipment

A variety of methods and instruments are available to harvest STSGs. The simplest STSG is the pinch graft, which may be 1 cm or less in size, harvested using forceps and a scalpel blade or small scissors, and is especially useful for non-healing leg ulcers. The Weck blade has a guard that helps the harvesting of a uniformly thick piece of skin, but requires some experience.

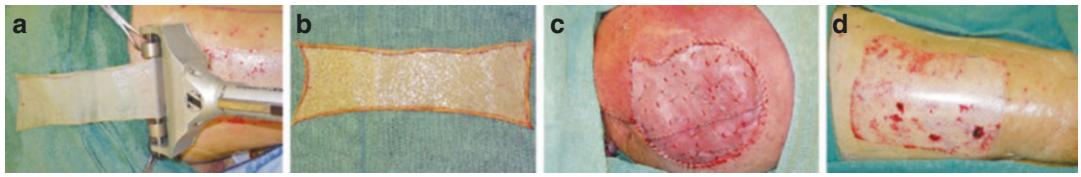

Fig. 13.11 Harvesting of an STSG using the Zimmer dermatome. (**a**) As the Zimmer dermatome glides over the donor skin of the anterior thigh, the graft emerges [27]. (**b**) Note how the edges of the STSG curl inward toward the dermal side of the graft and that the latter has a shiny appearance. (**c**) The graft is attached to the recipient bed. Note the fenestrations that allow for the drainage of any blood and serum. (**d**) An Opsite dressing is placed over the wound. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

Powered dermatomes are used to harvest larger more uniform pieces of skin. The Davol Simon dermatome is battery operated and cuts 3-cm-wide grafts at 0.015 in [26]. Larger dermatomes include the Brown and Padgett dermatomes and the Zimmer dermatome. The latter is less operator-dependent, consistently harvesting grafts of predefined width and thickness (Fig. 13.11a) [27].

Technique

Following donor site selection, the area should be shaved of hair and anesthetized. Local infiltration with 1% lidocaine with epinephrine or tumescent anesthesia with 0.1% lidocaine with epinephrine (1:1,000,000) may be used. The donor site is next cleansed with an antiseptic such as povidone iodine or chlorhexidine gluconate, which should then be removed with saline, and the skin dried and draped. Typically, the skin is then coated with a thin layer of mineral oil to facilitate movement of the dermatome. The skin is pulled tightly ahead of the path of the dermatome by an assistant using dry gauze pads or special wooden paddles (tongue blades) to provide traction on the slippery skin surface.

Following harvesting, the STSG is transferred to sterile saline-soaked gauze. As the graft is so thin, it is easy to confuse the dermal and epidermal sides; the epidermal side of the graft has a duller appearance, the dermal side has a shinier appearance, and the edges of the STSG tend to curve inward toward the dermal side when the skin is lying downward (Fig. 13.11b). In order to increase the surface area of the STSG, it may be placed through a mechanical mesher.

Thorough hemostasis is essential and recipient beds should be freshened up by scoring with a scalpel. Bare cartilage can be fenestrated with a 2 mm punch as previously described, and bone lacking periosteum may be burred away to expose the blood vessels of cancellous bone.

Split-thickness skin grafts should next be attached securely to the recipient bed. The perimeter is typically secured with sutures or staples, while basting sutures are placed centrally. Any overlapping skin will desiccate and drop off, so careful trimming of the STSG edges to fit the recipient bed is unnecessary. The graft can be fenestrated in several places to allow for the drainage of any blood and serum (Fig. 13.11c).

Dressing

Once secured, the graft is then dressed with a nonadhesive dressing such as N-Terface and covered by a pressure dressing or bolster. Suture and staple removal can be performed 7–10 days later.

Donor Site Care

The donor site heals by granulation and usually causes more postoperative pain than the grafted area. Once the skin around the donor site is dried, an adhesive such as Mastisol is applied around

the wound and allowed to dry; an Opsite dressing is placed over the wound (Fig. 13.11d), secured around the perimeter with paper tape, followed by a gauze dressing and Ace wrap. In the first 24 h postoperatively, it is common for a large amount of serosanguineous material to accumulate beneath this dressing. This fluid can be aspirated and a new Opsite applied. Donor sites typically take 7–21 days to re-epithelialize, and the dressing should remain in place for this period. Other donor site dressings include Xeroform gauze, which was one of the earliest dressings, Adaptec gauze (Johnson and Johnson, New Brunswick, NJ), Jelonet (Smith & Nephew, Montreal, Quebec, Canada), Reston (3 M Health Care, St. Paul, MN), Kaltostat (ConvaTec, Princeton, NJ), Allevyn polymer foam (Smith & Nephew, Largo, FL), and honey [28].

Benefits of Opsite include decreased donor site pain and improved visualization of the donor site. In addition, the wound is kept moist and healing facilitated.

Postoperative Complications

Early complications, as with FTSGs, include infection, hematoma or seroma formation, and graft movement. Any infection should be cultured and treated with antibiotics. Color mismatch between the STSGs and surrounding skin is common, and STSGs and donor sites often become hypo- and hyperpigmented. Patients should be advised that this commonly occurs and that they should avoid exposure of the graft and donor site to the sun and apply broad-spectrum sunblock to both areas. Dryness of the STSG can be treated with emollients.

The very thinness of STSGs often contributes to a greater tendency to contract and a less cosmetically acceptable outcome. STSG contraction is unpredictable, and they should therefore be used with caution near the eyes, oral commissure, and nasal alae. Hypertrophic scarring of the graft and donor site may be treated with intralesional steroids. The donor site often requires postoperative care to granulate and may be painful.

Vacuum-Assisted Closure (VAC)

Subatmospheric pressure dressings, commercially available as the vacuum-assisted device (VAC), have been shown to accelerate wound healing [29–32] (Fig. 13.12a). This has been especially effective in the management of skin grafts on the lower extremities. Consider VAC for the patient with poor distal circulation. The application of a negative pressure to the wound bed through a foam dressing increases dermal perfusion, promotes granulation, removes excess exudate and periwound edema, and reduces bacterial count. The ideal pressure setting is negative 125 mmHg on continuous or intermittent pressure. Fluid is connected in a canister, and the dressing only needs to be changed every 2 days. Portable VACs are available for ambulant patients. VAC is contraindicated in malignant wounds, untreated osteomyelitis, exposed arteries or veins, or large amounts of necrosis. VAC has significantly increased skin graft take when used as a bolster over the freshly grafted wound (Fig. 13.12b).

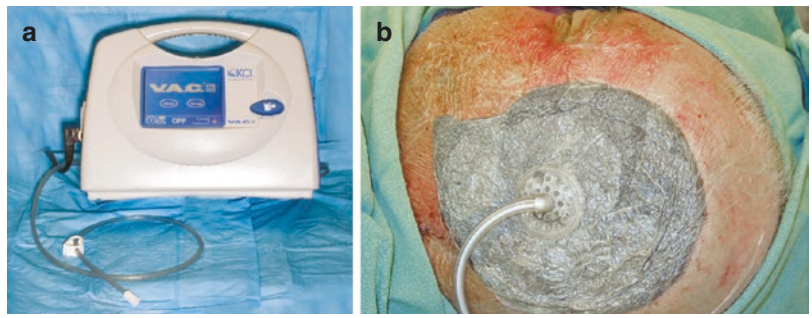

Fig. 13.12 (**a**) A wound VAC. (**b**) a VAC is used as a bolster and will stay in place for a week. (Reprinted from MacFarlane [7], © 2006, with permission from Elsevier)

Free Cartilage Grafts

The free cartilage graft is a portion of cartilage covered by its perichondrium and typically used for the reconstruction of cosmetic free margins such as the alar rim or lower eyelid [33]. The ear is most commonly used for free cartilage grafts in dermasurgery, and the concha and antihelix are common donor sites. The author's preferred donor site is the posterior conchal bowl, which is easily accessed without distortion of the auricular shape, and the donor site scar is easily hidden.

Technique

The donor site is incised; the skin overlying the cartilage is undermined to expose the perichondrial surface of the conchal bowl (Fig. 13.13a); the desired length of cartilage, slightly oversized, is incised as a 2–3-mm-wide strip, which is dissected from the anterior skin and placed in sterile saline (Fig. 13.13b); and the donor site is then sutured.

To secure the graft, the soft tissue of the recipient bed is undermined medially and laterally and the graft inserted into the pockets so that it fits snuggly (Fig. 13.13c). In addition, the graft may be secured with an absorbable 5-0 suture. Once the graft has been stabilized, a nasolabial flap or FTSG is then placed (Fig. 13.13d).

Dressing

A pressure dressing over the conchal bowl will help minimize the chance of hematoma. The external suture line is dressed with antibiotic ointment and covered with an occlusive, nonadherent dressing.

Complications

Donor site complications can include sterile chondritis, infection, and distortion. Sterile chondritis can be treated with nonsteroidal anti-inflammatory medication. If infection is sus-

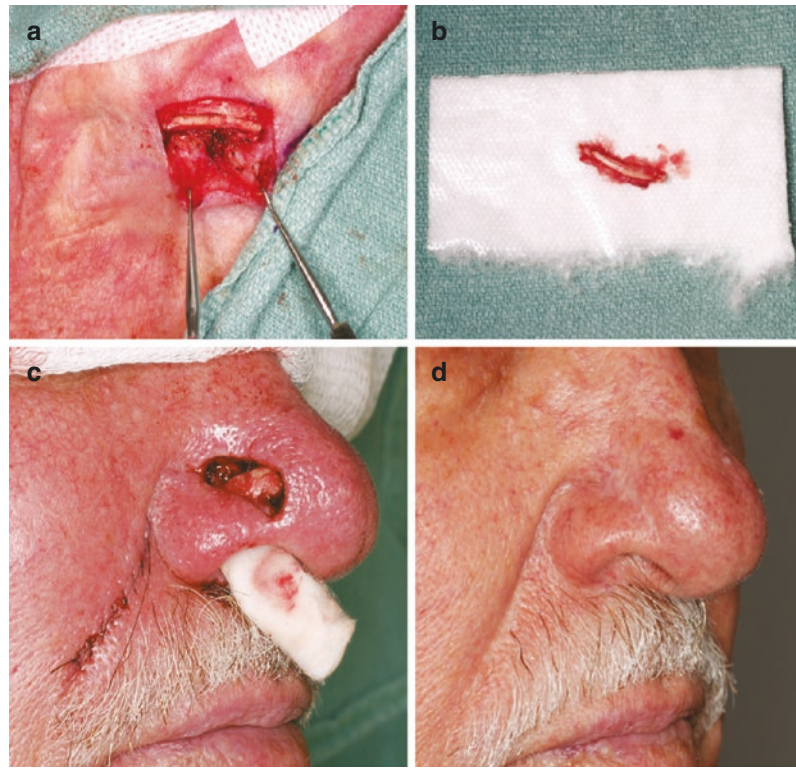

Fig. 13.13 (**a**) The postauricular cartilage is exposed. Note the Hypafix tape that is used to hold the ear forward while the graft is obtained. (**b**) A 2–3-mm-wide and slightly oversized strip of cartilage is harvested. (**c**) The graft is secured in place. Note an FTSG is harvested from the right nasolabial fold. (**d**) Appearance of the nose 6 months later

pected, broad-spectrum antibiotics (quinolones are commonly used) should be started after cultures have been taken. Complications of free cartilage grafting include infection; hematoma; and graft displacement, distortion, and extrusion [34].

Composite Grafts

Composite grafts contain tissue from two or more germ layers. In dermatologic surgery they generally consist of skin and cartilage, which are used in the reconstruction of full-thickness defects of the alar rim in addition to nasal tip defects with cartilage loss [35, 36]. They may also comprise skin and fat or skin and perichondrium [37, 38]. Composite grafts used to repair full-thickness defects are dependent upon revascularization solely from the wound edges. It is important, therefore, that no portion of such grafts should be more than 1 cm from the vascular source and these grafts are therefore limited in size to 1–2 cm in diameter [39].

Following graft placement, the tissue undergoes a series of changes in appearance. Initially it is white in color, then after about 6 h, it becomes pink as graft vessels anastomose with those of the recipient site. Between 12 and 24 h, the tissue becomes blue due to venous congestion, and by 3–7 days, it becomes pink again, indicating that the graft has survived [39]. Donor sites include the crus, triangular fossa, scapha, conchal cavum, and cymba of the ear and are usually allowed to heal by secondary intention. Reconstruction of full-thickness nasal defects can be challenging. Due mainly to the presence of cartilage, the auricular chondrocutaneous graft provides structural support and has only a slight tendency to contract.

Technique

The donor and recipient sites should be anesthetized and then prepped with chlorhexidine solution. Any granulation tissue should be removed from the recipient site and the edges freshened if the wound has had time to partially heal. A template is then made of the recipient site and placed onto the donor site; the graft is next harvested and placed in sterile saline. The chondrocutaneous graft may be sized to simply fill the defect or especially designed with cartilaginous wings to provide additional stability. If a winged or tongue-in-groove technique is used, then the traced graft is lengthened by several millimeters at each end, and the graft including this extra tissue is excised. Once the graft is harvested, the skin is removed from each strut exposing the cartilage. Pockets are made in the alar defect, and the graft is then positioned so that the cartilage wings interlock with the recipient bed. The mucosal surface is sutured first with a 6-0 absorbable suture. The skin is closed with 6-0 nonabsorbable sutures, which may be removed in 1 week's time.

Dressing

The author recommends securing the graft with intranasal packing, which can be manufactured from a Xeroform-covered dental roll.

The external suture line is dressed with antibiotic ointment and covered with an occlusive, nonstick dressing.

Donor Sites

Defects of the helical crus may be repaired in linear fashion or with rotation or transposition flaps if necessary. Defects of the helical rim may be excised in wedge fashion and grafts taken from the scapha, triangular fossa, conchal bowl, or cymba granulate well.

Postoperative Care

Antibiotics are prescribed preoperatively and for a few days following surgery. Ice packs should be applied to the surgical site for the first 3 days. Patients should be advised as to the delicate nature of these grafts and to avoid strenuous activity. They should also be aware that these grafts have a higher rate of failure than other grafts and that multiple revisions are common.

Dermabrasion or laser resurfacing may be used at 6 weeks to 6 months to improve the color and/or texture match between the graft and adjacent skin.

Complications

Composite grafts are more prone to necrosis than other graft types [40]. Disadvantages include a higher risk of failure, size limitations, and limited donor sites.

Summary

A thorough knowledge of the various techniques used in skin grafting is essential for successful soft tissue reconstruction. Careful attention to detail and planning should ensure an excellent outcome.

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Chapter 14
Nail Surgery and Malignant Tumors of the Nail Unit

Julia O. Baltz, Richard K. Scher, Nathaniel J. Jellinek, and Deborah F. MacFarlane

Anatomy

As many as 10% of patients seek dermatologic care for a nail disorder [1]; therefore, it is important that dermatologists be comfortable performing nail surgery.

A thorough understanding of nail anatomy is crucial for successful nail surgery and will help to reduce any apprehension the clinician may have when operating on the nail unit. The components of the nail unit include the matrix, proximal and lateral folds, plate, bed, hyponychium, and four grooves—proximal, distal, and two lateral.

The most central and defining structure in the nail unit is the nail matrix which produces the nail plate and is found beneath the proximal nail fold and proximal nail plate. The lunula is the visible portion of the distal matrix. The proximal portion of the matrix produces the dorsal nail plate, while the distal portion of the matrix produces the ventral nail plate. Therefore, a distal matrix biopsy is less likely to cause a split nail than a proximal one [2]. Distal matrix biopsy, however, is more likely to result in erythronychia. Maximum care must be exercised when performing surgery on or near the proximal nail matrix due to risks of leaving a permanent split nail. The proximal nail fold is a modified extension of the dorsal digital skin that forms a fold over the matrix. It is continuous with the lateral nail fold that forms the side borders of the nail plate. The nail plate extends about 5 mm proximal to the cuticle where it fits into the proximal nail groove, the roof of which is the undersurface of the proximal nail fold; the floor is the matrix. The nail plate fits laterally into the lateral nail grooves formed by the junction of the lateral nail folds and the nail bed. The nail bed begins at the distal portion of the lunula (matrix) and extends distally to terminate at the hyponychium. There is no subcutaneous tissue in the nail unit, and when one is cutting through this structure, the underlying periosteum of the distal phalanx may be exposed. The distance from the nail plate surface to the periosteum is only 1–3 millimeters (Fig. 14.1). The tendon of extensor digitorum communis crosses the distal interphalangeal joint (DIPJ) to insert onto the proximal dorsal portion of the terminal phalanx, approximately 12 mm proximal to the cuticle; incisions should be planned to avoid this area [3]. The blood and nerve supplies of the nail unit are provided by branches of the radial and ulnar arteries and nerves and run the length of each finger. It is important to remember this circulatory and neural pattern when anesthetizing and operating on the nail unit (Table 14.1).

> Vascular supply runs laterally in the finger; therefore, compress any bleeding vessels by applying lateral pressure to the finger and elevating it.

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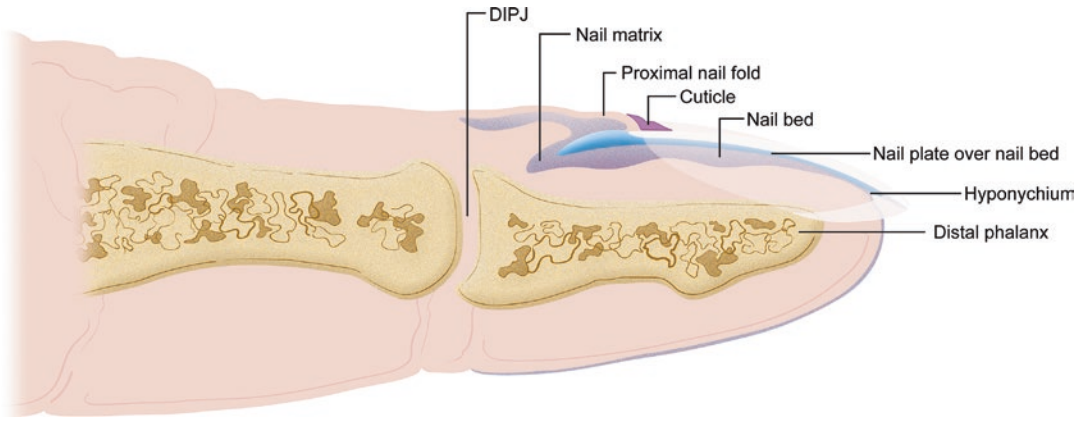

Fig. 14.1 Anatomy of the nail unit

Table 14.1 Anatomic danger areas

Matrix: Beneath cuticle, damage to proximal part may cause permanent nail dystrophy
Underlying periosteum: Only several millimeters beneath nail plate
Vascular and nerve supply: Run laterally
Extensor Digitorum Communis tendon: Inserts on proximal part of terminal phalanx, approximately 12 mm proximal to cuticle

Preoperative Considerations

A careful medical history and physical examination prior to the surgery will reduce complication risk (Table 14.2). If possible, nail surgery should be avoided in those who have end-stage peripheral vascular disease or uncontrolled connective tissue disorders that compromise circulation. This includes Raynaud's phenomenon, particularly when surgery on the toenails is considered. Details of previous surgical procedures, underlying illness, current medications, and allergies should be elicited. Anesthesia may be affected by monoamine oxidase inhibitors, beta-blockers, or phenothiazines, although this is rarely a relevant finding. Anti-tetanus immunization status should be ascertained. The risks, benefits, and alternatives to surgery should be discussed in detail with the patient and consent obtained. Patients should be aware of the risk of permanent nail dystrophy. Preoperative X-rays should be obtained when the condition is suspected to involve the bony phalanx [4].

Table 14.2 Preoperative considerations prior to nail surgery

Details of illness causing nail dysfunction
Medical history: Peripheral vascular disease, diabetes, connective tissue disease, Raynaud's, arthritis, bleeding diatheses
Previous surgical procedures
Prosthetic joints or heart valves
Drug history: Check for allergies. Monoamine oxidase inhibitors (MAOIs), β-blockers, and phenothiazines may affect anesthesia. Aspirin, antiplatelet agents, or anticoagulants may prolong bleeding. Systemic or topical steroids may delay healing. Check for use of herbal medicine/vitamins
Anti-tetanus immunization status

If there is evidence of active infection, elective procedures should be deferred until successful treatment with antibiotics.

Nail surgery should be performed under aseptic conditions. The surgical site should be thoroughly scrubbed with an antiseptic surgical cleanser.

Instruments

Several instruments are essential for performing nail surgery (Fig. 14.2). An elevator or a dental spatula is useful in separating the nail plate from the nail bed and the proximal nail folds. The nail splitter is designed for transverse or longitudinal nail avulsion, with its smooth lower anvil-shaped

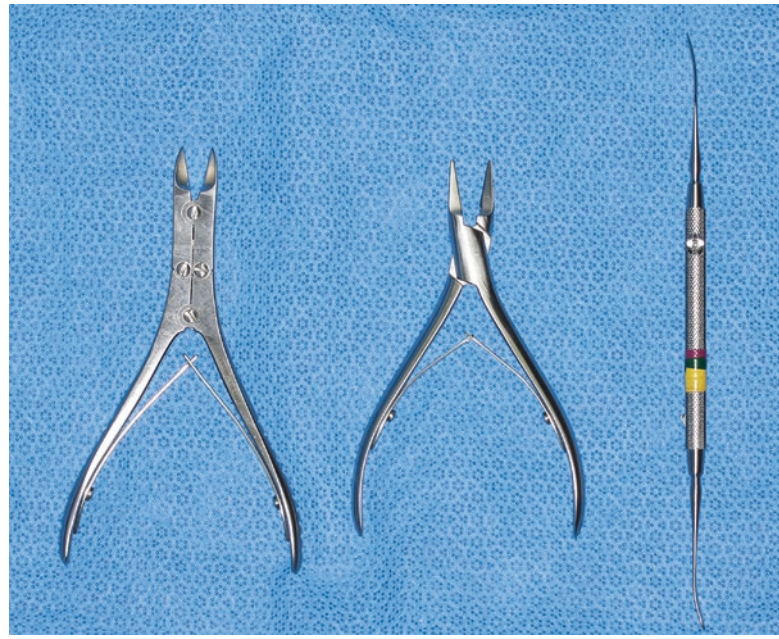

Fig. 14.2 From *left* to *right*: dual action nail nipper, English anvil nail splitter, elevator

section to cleave under the nail plate over the nail bed and a sharp upper blade for cutting through the nail plate. The nail nipper allows close and accurate nail cutting in an atraumatic manner. This instrument has a tapered neck that conforms to the patient's nail and allows simple plate cutting procedures to be done without anesthesia. The ordinary nail clipper should only be used for routine nail trimming as it is rigid and requires the patient's nail to conform to the instrument, often producing pain.

A nail-pulling forceps is practical for gripping the plate prior to avulsion once it has been separated from its attachments, although a hemostat or needle driver may be sufficient. A variety of skin hooks or rake retractors are used to retract the proximal nail fold to allow for maximum exposure when performing matrix surgery.

Tourniquet

A sterile Penrose drain secured with a hemostat at the finger base will provide a safe tourniquet for the approximately 15 minutes which most surgeries take. Alternatively, a sterile glove with the fingertip portion cut and finger portion rolled back to the digital base may be used. Postoperative reperfusion of the distal digit should be ascertained and tourniquet time documented in the medical record.

Radiographs

Preoperative radiographs are suggested when the condition may involve the bony structure of the phalanx.

Anesthesia

Adequate anesthesia is vital for successful nail surgery. Sedation is usually unnecessary. To avoid a vasovagal response, patients should be in a reclining position. The limb should be cleansed well and a sterile field obtained.

A buffered solution of 1 or 2% lidocaine hydrochloride is most commonly used as a local anesthetic. Mepivacaine hydrochloride, 1 or 2%, has also been used as an anesthetic. It may be used

in patients sensitive to lidocaine and has the added advantage of longer action and better hemostasis.

More recently, ropivacaine has been advocated as an ideal agent for digital anesthesia, with relatively quick onset, long duration of action, and inherent vasoconstrictive properties.

> Bupivacaine can be added at the end of the procedure if significant postoperative pain is expected.

A cryogen spray such as 50% ethyl chloride/50% dichlorotetrafluoroethane (Fluro-Ethyl, Gebauer Company, Cleveland, OH), ethyl chloride, or fluoroethyl can be utilized 1–2 s prior to needle insertion to diminish pain. Traditionally, anesthesia of the nail unit has been achieved by the use of a distal or proximal digital nerve block or a combination of both. The authors more commonly use the distal wing block or distal digital block for most surgeries.

Distal Wing Block

Technique

A 30-gauge needle is used to inject at the junction of the proximal and lateral nail fold (Fig. 14.3a).

Slow infusion will help minimize pain. The injection proceeds distally and inferiorly to include the lateral digital nerve and its branches. Without removing the needle, one should inject across the proximal nail fold to block the transverse nerve branch and then inject the other lateral side of the digit, placing each subsequent injection into a previously anesthetized site. Finally, after anesthesia is complete, additional anesthetic may be injected into the tip of the digit, particularly for procedures on the distal portion of the nail unit (Fig. 14.3b).

A sufficient quantity of anesthetic may cause moderate blanching, aiding hemostasis. Typically between 1 and 3 ml of anesthesia are needed.

In the traditional digital block, anesthesia is infused into the lateral digit at the base of the finger, and approximately 1–2 cc of anesthetic is injected into each side of the digit. With either technique, the surgeon should wait for approximately 10–15 min for complete anesthesia. If the patient has a history of peripheral vascular disease, is elderly, or has diabetes mellitus, vasospasm due to excess anesthetic must be avoided. While anesthesia is performed under clean conditions—the skin prepped with alcohol and clean gloves used—all nail surgery including punch biopsies should be performed under sterile conditions.

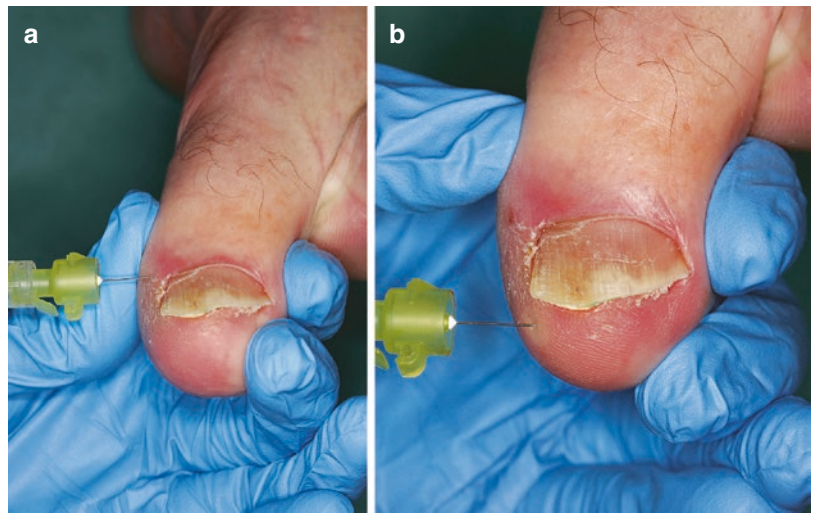

Fig. 14.3 (**a**) Local anesthetic infiltration is commenced at the junction of the proximal and lateral nail fold and then continued across the finger just below the proximal nail fold. (**b**) Additional anesthetic is injected into the digit tip

Distal Digital Block

Technique

Equally popular, the initial injection and wheal are created at the proximal/lateral nail fold junction as in the wing block. The needle is advanced behind the slow injection of fluid, angling volar, to reach the volar branch of the digital nerve that innervates the nail bed and most of the nail apparatus. The fluid bolus of injection must be observed to extend volar past the mid-lateral line to achieve complete anesthesia. Given the distal location, a 3–5-minute wait is all that is usually required to complete anesthesia.

Nail Avulsion

Nail avulsion may be necessary to expose the nail bed and matrix in order to perform a matrix biopsy or to excise nail unit tumors. In only rare conditions (i.e., retronychia) is nail avulsion performed for therapeutic benefit.

Nail avulsion may be partial or total. The nail plate is attached to the digit at two locations: the nail bed and the proximal nail fold.

Technique

Insert the nail elevator beneath the free edge of the nail and advance proximally (Fig. 14.4a). Resistance will be felt until reaching the matrix. The elevator then is used to separate the proximal nail fold from the dorsal plate, lysing the cuticle connection. Finally, the elevator is inserted into the lateral nail sulci. Grasp the nail plate with a hemostat and remove the nail with a pulling and twisting motion (Fig. 14.4b, c).

Bleeding is minimal and the patient has little discomfort once the anesthetic has worn off.

Repeated avulsion may cause a thickening of the nail plate, with increased transverse curvature (predisposing to pincer nail deformity and ingrown nail), especially on the great toenail.

Punch Biopsy of the Nail Bed

Punch biopsy of the nail bed is one of the most commonly performed procedures on the nail unit. A nail bed biopsy may be performed with or without avulsion of the nail plate. Sometimes partial nail avulsion is sufficient to expose the area.

Technique

To avoid nail avulsion, make a sharp 3 mm punch through the nail plate until the dorsal phalanx is met (Fig. 14.5).

It is useful to soften the nail plate by soaking in warm water for 10 minutes prior to the procedure. Use iris or gradle scissors to recover the specimen.

Forceps are best avoided as they can crush the specimen. In the two-punch technique, use a larger punch through the nail plate and a smaller punch through the nail bed. There is generally little bleeding as the anesthetic bolus tends to

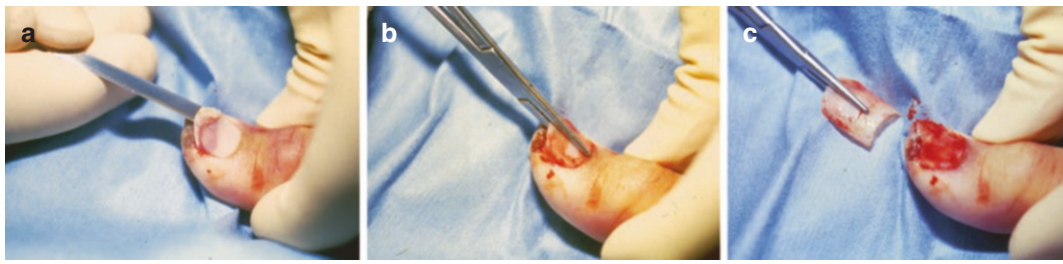

Fig. 14.4 (**a**) Nail elevator is advanced proximally to separate nail plate from nail bed. (**b**) Hemostat is used to grasp nail. (**c**) Nail plate is completely avulsed

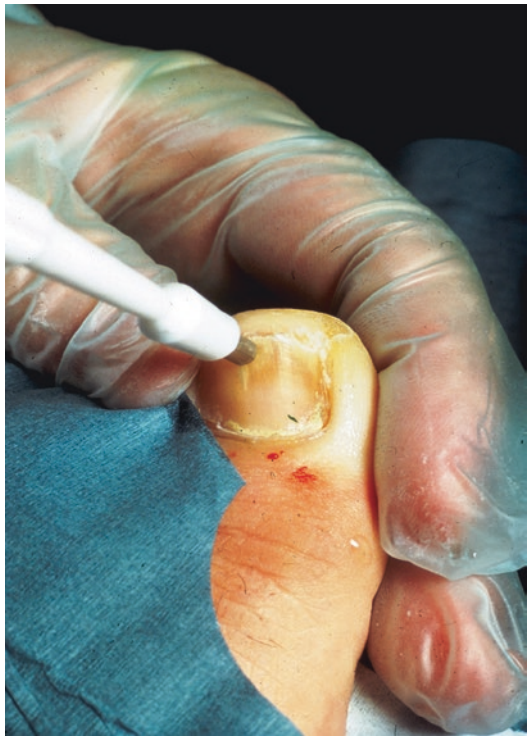

Fig. 14.5 Punch biopsy through nail plate. Photograph courtesy of Richard K. Scher, M.D.

compress the arteries in the operative field; alternatively, a tourniquet is used or an assistant simply compresses the lateral digital arteries during the procedure. A small focus of onycholysis occasionally may result but is unusual.

To provide better visualization or to perform a larger nail bed biopsy, the nail may be avulsed. It is useful to score the area to be biopsied first with the punch. Once the exact location has been confirmed, the punch is placed back onto the scored area and twisted until periosteum is met.

For larger lesions, an elliptical excision can be used, or a traditional wedge biopsy performed on the nail bed. Orient the ellipse longitudinally, no greater than 3 mm wide, with care to avoid the matrix (if uninvolved in the disease process). Hemostasis can be obtained in nearly all cases with pressure. However, in exceptional cases 35% aluminum chloride in 50% isopropyl alcohol or oxidized cellulose may be applied to the site for hemostasis. Monsel's solution may cause a tattoo effect that can affect pathologic interpretation. Suturing is not necessary since the biopsy site granulates quickly without nail distortion.

Nail Matrix Biopsy

Indications for nail matrix biopsy include longitudinal melanonychia, longitudinal erythronychia, full-length nail plate deformities, and matrix tumors. Nail matrix biopsies are most commonly performed for melanonychia, and the various techniques and their indications are presented here.

> Nearly all cases of primary melanocytic melanonychia originate from the nail matrix, so the foundation of biopsy technique must include sampling from this germinative tissue. Two first-line approaches are the punch biopsy and matrix shave biopsy. These are detailed below.

The punch is the most straightforward approach [5]. Advantages include minimal manipulation of nail tissues (i.e., no avulsion required), efficiency, and general high diagnostic yield. Disadvantages include a high likelihood of incisional biopsy leading to persistent melanonychia, risk of sampling bias, and full-thickness matrix injury that can predispose to split nail postoperatively (particularly when the pigment involves, and biopsy is taken from, the proximal matrix).

Punch Biopsy of the Nail Matrix

Technique

An elevator is first used to loosen the attachment of the proximal nail fold to the underlying plate (Fig. 14.6b). Oblique incisions are created in the proximal nail fold, which is reflected proximally (Fig. 14.6c). This step exposes the proximal nail

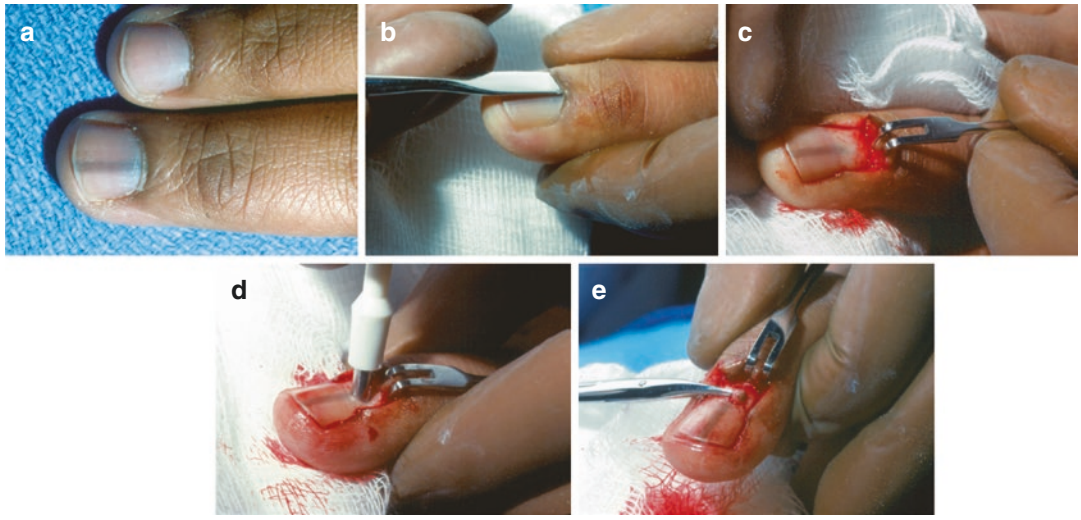

Fig. 14.6 (**a**) Longitudinal melanonychia striatum in the nail plate of the middle finger. (**b**) An elevator is used to loosen the attachment of the proximal nail fold to the underlying nail plate. (**c**) The proximal nail fold is reflected to expose the matrix. (**d**) A 3 mm punch is used to biopsy through the nail plate and through the matrix down to the underlying periosteum. (**e**) The biopsied nail matrix is then sent to pathology. Photographs courtesy of Richard K. Scher, M.D.

plate, under which the matrix can be visualized. In most instances, even through the nascent plate, the origin of melanonychia can be appreciated grossly. This pigment must be the target for biopsy. It is a good standard practice with this and in all cases of melanonychia to observe this pigment and document its presence with a surgical assistant; in cases of melanocytic activation (and not proliferation), it can be reassuring to the pathologist, surgeon, and patient that the area of pigment was indeed the correct site for biopsy.

A 3, 3.5, or 4 mm punch can be used, depending on the width of the pigmented band. The punch is scored over the origin of pigment and twisted through the nail plate and matrix until hitting periosteum (Fig. 14.6d). The punch instrument should be removed delicately—occasionally the matrix and plate separate with the plate remnant remaining in the instrument. The matrix (or matrix plus plate) specimen is then gently freed from its base using gradle or other fine-tipped scissors. Forceps are never required and will simply crush the tissue. All specimens are placed in formalin (two jars if plate and matrix separate) and sent for permanent section pathologic processing.

The matrix/plate defect is left to heal by second intention. The reflected nail fold is returned to the anatomic position and may be reapproximated with tissue adhesive, adhesive strips, or suture.

Shave Biopsy of the Nail Matrix (Tangential Matrix Excision)

The matrix shave (or tangential matrix excision) is a slightly more involved surgery and the authors' preferred approach in most cases. This technique was originally described by Hanecke and Baran in 2001 [6]. Advantages include exposure for direct (as opposed to indirect through the proximal plate) inspection of the matrix (which facilitates accurate biopsy with margins), opportunity to perform an excisional biopsy (to minimize risk of recurrent pigment), less sampling bias, and less scarring.

Indeed, wide pigmented bands can be excised with this technique, resulting in little to no dystrophy [7].

Technique

Oblique incisions are created and the proximal nail fold reflected proximally as with the punch biopsy. A full plate avulsion or alternatively a partial proximal or lateral curl plate avulsion is performed, and the plate reflected away from the nail bed and matrix, exposing the entire matrix [8] (Fig. 14.7a).

The origin of the pigmented band is observed clinically in the matrix. Usually this finding is obvious (although always enhanced with loupe magnification and good surgical lighting in a bloodless field); rarely there will be only subtle pigment appreciated. The surgeon may use the nail plate to map proximally to locate the source of the pigment.

The pigmented lesion is scored with a scalpel blade with 1–2 mm margins, usually in the shape of a rectangle. A Teflon/silicone-coated 15 or 15c blade is then turned horizontally and the lesion excised in the superficial dermal plane. In addition, injection of anesthesia into the matrix can tumesce this tissue and facilitate excision in the appropriate superficial plane. It is not infrequent for there to be an area of dermal adhesion that prevents rapid tangential excision. Use of a cotton-tipped applicator for counter traction (or occasionally forceps, although they may produce crush artifact) can stabilize the tissue to assist in completing the excisional biopsy. The ideal thickness of the specimen should be less than 1 mm [9].

Given its tendency to curl when placed in formalin, the specimen is placed on paper (the authors use a nail map in a standard cassette) and then in formalin and sent for permanent section pathologic processing (Fig. 14.7b).

As the defect is partial thickness and highly vascularized, matrix reconstruction is unnecessary, and the defect is left to heal by second intention. The plate is returned to the anatomic position, the nail fold is released on top of the plate, and skin and plate are sutured into position. Rapidly absorbable suture will minimize discomfort at suture removal.

This technique results in minimal scarring and a high diagnostic yield; however, recurrent pigment is frequent [10].

The authors suspect that there is some autologous grafting of remnant matrix melanocytes (present on the reflected proximal plate overlying the matrix) that, when returned to the wound, act as a split-thickness skin graft and

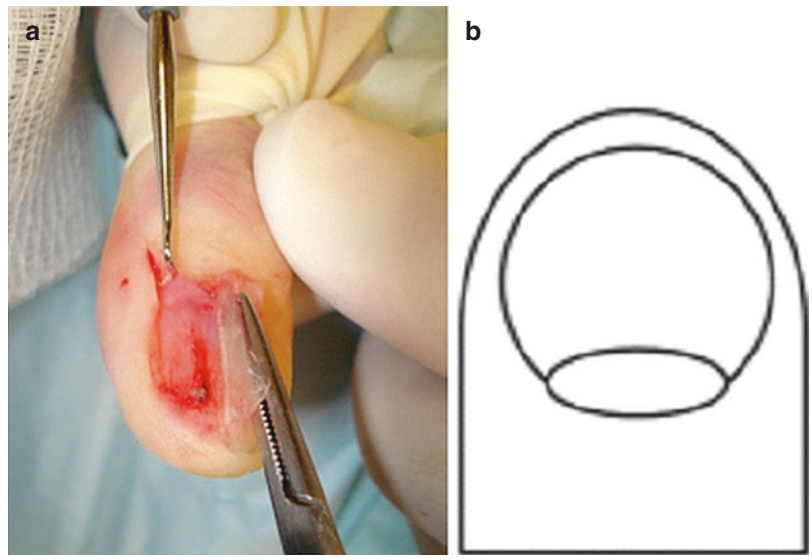

Fig. 14.7 (**a**) Visualization of the nail matrix after lateral plate curl. (**b**) Nail map for orientation during histologic processing. Photographs courtesy of Nathaniel J. Jellinek, M.D.

place activated or proliferating melanocytes back into the surgical site, resulting in pigment regrowth. This process can be interrupted in several ways: removing the section of nail plate containing possible matrix remnants or by curetting the ventral plate prior to placement over the matrix. There are inherent advantages to keeping the plate in vivo post biopsy: it prevents dorsal pterygium as a complication, it acts as a biologic dressing to accelerate healing and minimize discomfort, and it immobilizes the surgical site as a pseudo-splint postoperatively. In cases when the plate is removed, the authors advocate the use of a fashioned "faux nail" from a nasopharyngeal tube to splint the nail bed and prevent pterygium [11].

The normal healing after matrix shave biopsy has been demonstrated in picture series. It can take a year or more to accurately predict the degree of nail scarring, if present at all. Most frequently, a band of erythronychia at the site of biopsy, with minimal to no nail plate disturbance, is apparent [12].

In cases of melanoma in situ, en bloc (wide local) excision of the nail unit is increasingly becoming standard of care [13]. As the tangential shave biopsy typically does not create a full-thickness scar, dissection over the dorsal phalanx and extensor tendon is more easily performed, allowing for margins free of tumor and/or transected proximal margins in the matrix or at the cul-de-sac.

Lateral Longitudinal Excision

Lateral longitudinal excision is a fusiform variant designed around the entire lateral nail apparatus [14]. This technique can be used to excise laterally located melanocytic lesions, although over time the authors have moved away from this practice in favor of the matrix shave. The lateral longitudinal excision creates a significant scar that can complicate any subsequent wide local excision and does not afford improved diagnostic yield over the matrix shave. Furthermore the lateral longitudinal excision can lead to an acquired malalignment of the nail, an undesirable outcome especially in those pigmented lesions that are benign [15]. It is the authors' current practice to utilize this technique mainly in the setting of difficult to diagnose inflammatory nail conditions.

For each of the procedures above, detailed wound care instructions are reviewed with the patient. Acetaminophen plus ibuprofen are adequate for pain control. Antibiotics are not typically required.

Dressings

Pressure is the first and second line to obtain hemostasis. For minor surgical procedures, cleanse with alcohol or dilute hydrogen peroxide and apply a petrolatum-based ointment and a simple adhesive dressing to be changed daily. Vaseline gauze is especially useful in more extensive nail surgery with exposed dermis/bone, as it keeps the wound moist and can be easily removed. This can be covered with a layer of Telfa or gauze, and this in turn can be secured by the longitudinal placement of surgical tape (Table 14.3).

> Digits should not be wrapped circumferentially, as this may produce vasoconstriction, edema, and vascular compromise.

Table 14.3 Dressings

Cleanse area with dilute hydrogen peroxide or chlorhexidine
Apply antibiotic ointment
Cover with Vaseline gauze and a layer of Telfa secured with paper tape
Outer dressing may include surgical tape placed in longitudinal fashion
Surgitube may be used to make a protective, bulky dressing
Sling, Reese, or Zimmer boot immobilize and protect

Several layers of Surgitube dressing may be applied and secured. Bulky dressings will absorb external trauma and reduce excessive movement. Where appropriate, use of a sling or orthopedic boot may provide additional protection and immobilization. Immobilizing the digit with a splint can assist in pain control and prevent trauma. The patient should be instructed to keep the limb elevated as much as possible and to avoid using the affected digit. If unusual pain, edema, throbbing, or bluish discoloration is noted, the dressing should be removed at once and the surgeon contacted immediately.

Complications

Complications are uncommon in nail surgery. These may include hematoma, infection, and nail deformity. Postoperative infection in the distal phalanx may cause superficial infection, acute purulent tenosynovitis, osteomyelitis, and septic arthritis. When infection occurs, culture the organism and treat with appropriate antibiotics and soaks. Most complications of nail surgery may be avoided by paying careful attention to sterile technique and gently handling the tissue, in particular the matrix, returning the nail plate (when appropriate) after biopsy, and providing detailed wound care instructions and postoperative follow-up [16].

Malignant Tumors of the Nail Unit

Changes to the clinical appearance of the nail unit as a result of injury, infection, and benign and malignant neoplasms may be similar, further highlighting the importance of procedural intervention for diagnosis and appropriate treatment. A brief overview of malignant tumors of the nail will follow. Please note that discussion of treatment will refer to surgical options. Some nail tumors including verrucae may be amenable to topical and intralesional treatment. For further discussion of these modalities, see Chapters 2 and 5.

Verrucae

Although it is rare that a verruca may transform into a squamous cell carcinoma, the clinical appearance may be similar for the two. Various case reports exist of SCC either treated as verrucae or left untreated for long periods of time [17, 18, 19].

> Any lesion of the nail unit that does not respond appropriately to treatment, is long-standing, or has an unusual presentation should be biopsied.

Bowen's Disease

Bowen's disease, or squamous cell carcinoma in situ, is an uncommon condition usually seen on the thumb, index, and middle fingers of men older than 60 years. It can occur in both a periungual and ungual location and primarily affects nail folds, with potential extension into the rest of the nail unit, including the nail bed [20]. Bowen's disease of the nail is human papillomavirus (HPV)-associated in at least 60% of cases, and exposure to tobacco, radiation, chemicals, and arsenic ingestion have also been implicated. Patients with epidermodysplasia verruciformis and dyskeratosis congenita are also at increased risk. This is a low-grade malignancy with moderate potential for recurrence but low potential for metastasis [21, 22, 23].

Treatment

Mohs surgery has been reported with a wide range of recurrences. This likely reflects both continued presence of high-risk human papillomavirus and the technical difficulties and unique anatomic challenges of the nail apparatus; therefore, some authors suggest an additional surgical margin; however, the authors feel that Mohs surgery can be performed safely and with durable cure rates while also having the advantage of tissue sparing [24]. Photodynamic therapy (PDT) has been successfully used, albeit in small case series, and is not considered first-line therapy [25, 26].

Follow-up to evaluate for recurrence is essential, and one should examine all 20 digits and perform a lymph node exam. The anogenital area should also be examined, and female patients should be monitored for cervical cancer due to the strong association with HPV 16 [27, 28].

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common malignant tumor of the nail unit [29]. It occurs most commonly in men after the fifth decade, predominantly on the fingernails [30] (Fig. 14.8). While most commonly found in the nail bed, SCC may arise in any part of the nail unit [31]. As this entity is often slow growing with subtle clinical findings, it can be misdiagnosed as onychomycosis, onycholysis, verruca, nail deformity, subungual exostosis, chronic osteomyelitis, paronychia, or onychogryphosis [32–34]. Unresponsiveness to treatment, bleeding, and ulceration should raise suspicion [35]. Metastasis is rare. Risk factors are similar to those for Bowen's disease. Incidence of bony involvement is reported in 16–66% of cases; therefore, an X-ray prior to surgery is prudent [36].

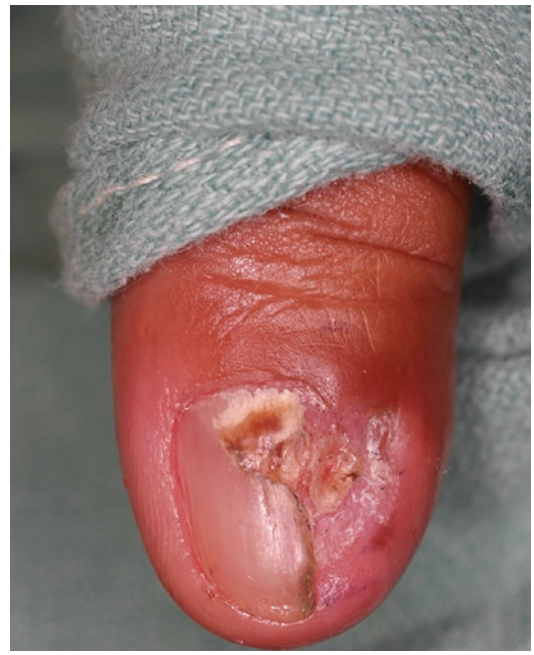

Fig. 14.8 A 45-year-old Hispanic male presented with a 2-year history of a lesion on the left thumbnail, which had been treated with over-the-counter antifungal creams. Biopsy confirmed SCC and the patient underwent Mohs surgery

Treatment

The treatment of choice is Mohs surgery with cure rates up to 92–96% [37] (Fig. 14.9a, b).

Amputation at the interphalangeal joint proximal to bone invasion is recommended for SCC with bony involvement that cannot be cleared with local excision [38]. Long-term follow-up is important as late metastasis has been reported [39].

> Obtain an X-ray prior to surgery of SCC involving the nail unit.

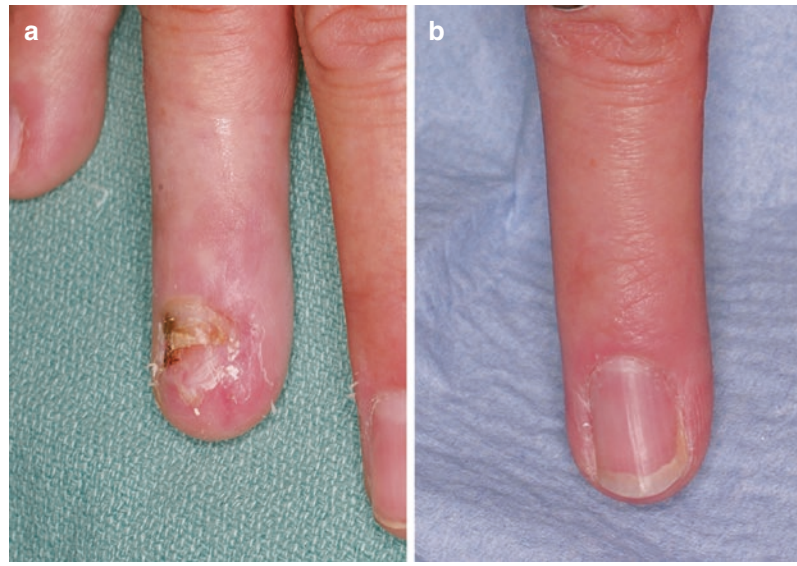

Fig. 14.9 (**a**) A 47-year-old female with a 1-year history of a suspected wart on the right ring finger. Biopsy confirmed SCC and Mohs surgery was performed. (**b**) Appearance 6 months following surgery

Subungual keratoacanthoma (KA) and well-differentiated SCC share similar clinical and histologic findings. Unlike cutaneous keratoacanthomas, KA of the nail unit is not prone to spontaneous regression and, due to rapid growth, is known to cause pressure-induced erosions of the distal phalanx. Due to this destruction, surgical treatment is necessary. The bony erosions typically resolve with definitive treatment [40, 41].

Verrucous Carcinoma

While extremely rare in the nail unit, verrucous carcinoma may mimic many benign conditions clinically including subungual verruca, leading to diagnostic confusion and delay [42, 43]. While more indolent than SCC, the typical delay in diagnosis and proximity to bone allows for osseous in 9 to 36% in some series [44, 45].

Treatment

Mohs surgery is the preferred treatment modality in the absence of bony involvement. Amputation is indicated for osseous invasion due to the rare but real risk of metastasis. Radiotherapy is controversial. Some have advocated for radiation for unresectable tumors; however, reports of transformation into high-grade SCC with metastasis argue against this treatment [46, 47, 48]. There has been one report of resolution with intra-articular methotrexate infusion [49].

Basal Cell Carcinoma

Basal cell carcinoma (BCC) of the nail unit is rare and has a wide variety of presentations that can lead to misdiagnosis or delayed diagnosis. Periungual BCC can mimic chronic paronychia, herpetic whitlow, pyoderma gangrenosum, as well as other neoplasms common to the nail apparatus [50, 51].

Treatment

There have been no reports of metastasis and Mohs surgery is the recommended treatment [52].

Metastatic Tumors

Subungual metastatic tumors are most often due to extension from a bony metastasis. Primary tumors of the lung account for the majority of

subungual metastases (41%), followed by tumors of the genitourinary system (17%) and breast (9%) [53]. Lung metastases most often affect the fingers, while colorectal and genitourinary metastases affect the toes. Symptoms consist of painful swelling and nail plate distortion [54]. These typically cause pain due to their rapid growth. An X-ray will often show radiologic changes.

Treatment

Subungual metastases usually represent disease progression in known cancer patients and rarely are the presenting sign of an undiagnosed malignancy. These lesions portend a poor prognosis, and treatment is tailored to the underlying process [54].

Melanoma

Nail unit melanoma is seen infrequently, making up 1.5% of melanomas in Caucasians and up to 20% of melanomas in patients of Asian and African decent [55]. Melanomas are most often seen in patients in their fifth to seventh decades and occur most commonly on the thumb and great toenail where they usually present as longitudinal melanonychia [56, 57]. Periungual pigment, which represents radial growth phase of melanoma onto the periungual tissue, may or may not be present and should not be considered as a diagnostic requirement [57, 58]. Up to a third of nail unit melanomas are amelanotic, and clinicians should have a low threshold for biopsy of a single dystrophic nail not responding to treatment [56, 59, 60].

The presence of bands of longitudinal melanonychia greater than 3 mm wide, with variegate color and proximal widening (triangle sign), or periungual pigment in any patient warrants a diagnostic biopsy of the nail matrix [61].

Treatment

Treatment of nail unit melanoma is evolving. Mounting evidence supports digit-sparing surgery for in situ nail unit melanoma as an alternative to amputation with low recurrence rates and improved quality of life [13, 62]. Some clinicians advocate for Mohs surgery, while others prefer en bloc excision of the nail unit with serial sectioning of the specimen to confirm clearance, ideally with 6 mm margins on all sides [63, 64, 65].

Invasive melanoma may necessitate distal amputation (Fig. 14.10a, b) with bone or joint involvement. The utility of sentinel lymph node biopsy for nail unit melanoma is based on the same criteria for primary cutaneous melanoma. Advanced disease is treated with chemotherapy or immunotherapy [66].

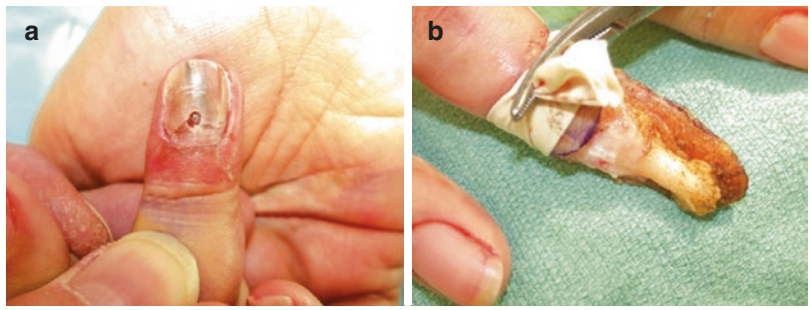

Fig. 14.10 (**a**) Appearance of the nail in an Asian female who presented with a biopsy-proven melanoma in situ. Given the clinical appearance, which was suspicious for invasive melanoma, the case was referred to melanoma surgery. (**b**) Following intraoperative lymphatic mapping and sentinel lymph biopsies (negative), an initial 5 mm margin was taken and sent for rapid pathologic interpretation, which confirmed an acral lentiginous melanoma 0.85 mm Breslow depth. A complex 1-cm-wide excision was performed, and this photo was taken prior to amputation of the distal phalanx. The fingertip was later repaired

Summary

For a variety of reasons discussed, the diagnosis of malignancy in the nail unit may be difficult and/or delayed. Practitioners, however, should have a very low threshold for performing biopsies on those tumors that have failed to respond to treatment or where malignancy is suspected.

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Chapter 15
Practical Management of Melanoma

Emily Z. Keung and Mark F. Naylor

Abbreviations

AJCC	American Joint Committee on Cancer
CLND	Completion lymph node dissection
CNB	Core needle biopsy
CNS	Central nervous system
CT	Computed tomography
DFS	Disease-free survival
FNA	Fine need aspiration
LDH	Lactate dehydrogenase
MIS	Melanoma in situ
MRI	Magnetic resonance imaging
MSLT	Multicenter Selective Lymphadenectomy Trial
MSS	Melanoma-specific survival
NCCN	National Comprehensive Cancer Network
PET/CT	Positron emission tomography/computed tomography
RLN	Regional lymph node
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SPECT	Single-photon emission computed tomography
SRS	Stereotactic radiosurgery
T-VEC	Talimogene laherparepvec
WBRT	Whole brain radiation therapy
WLE	Wide local excision

Melanoma incidence continues to rise at an alarming rate. More than 100,350 new cases and over 6,850 deaths are predicted for 2020 in the United States [1]. In general, patients who present with localized disease and thin primary melanomas (≤1.0 mm in thickness) have excellent prognosis with >95% 5-year survival [2]. Prognosis for patients with regional disease involvement is heterogeneous, ranging from 93% for those with stage IIIA melanoma to 32% for those with stage IIID disease [2].

Proper management is predicated on accurate staging in accordance with the American Joint Committee on Cancer (currently the 8th edition AJCC Cancer Staging Manual) [3]. Recommended staging and management of melanoma including surgical management, regional lymph node basin assessment, and local and systemic treatments can be found in the National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma, a constantly updated cancer treatment resource for clinicians [4]. This chapter presents a broad and practical overview and approach to the patient with suspected or proven melanoma.

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Clinical Presentation and Initial Assessment

Medical History

A thorough history should be taken from the patient with a suspected melanoma. Established risk factors for the development of melanoma (a personal or family history of melanoma, skin type I or II, a childhood history of sunburns, the presence of large numbers of melanocytic nevi, atypical nevi, the presence of congenital nevi, extensive use of sun beds, extensive history of sunburns or sun exposure, or genetic syndromes associated with a melanoma predisposition) and a detailed history of the lesion should be obtained. A systems review also should be performed.

Physical Examination

A complete physical examination should be performed, including a skin examination of the whole body with examination of the mucous membranes and scalp. The "ABCDE" mnemonic has been found to increase sensitivity when performed by individuals who have been trained in the technique (Fig. 15.1) [5]. Lesions that are morphologically suspicious should be photographed or diagramed and biopsied [4]. Careful attention and examination of the locoregional area and a lymph node exam should be routinely performed.

In vivo imaging in the clinic can be useful in the diagnosis of melanoma [6–8]. Traditional oil/glass or polarized light dermoscopy are particularly cost-effective aids in deciding whether or not to

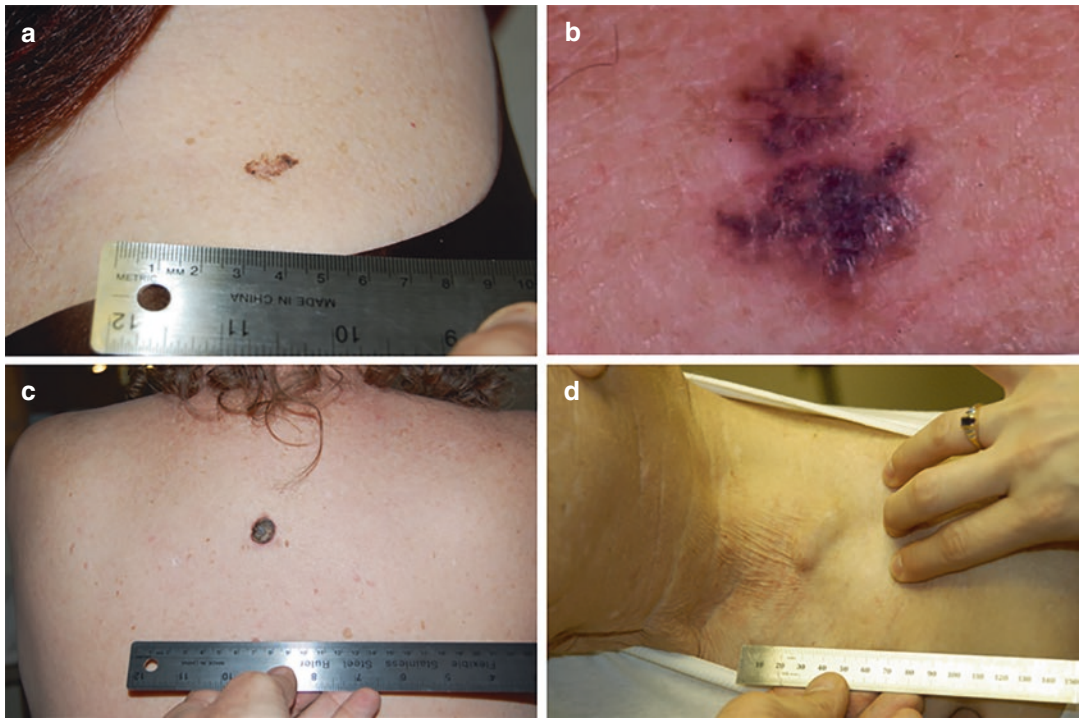

Fig. 15.1 Examples of melanoma in situ and invasive melanoma. (**a**) The macular character and variations in color are apparent in this melanoma in situ on a patient's neck. (**b**) The asymmetric shape, scalloped borders, and variety of colors typical of a superficial spreading melanoma are seen on this patient's shoulder. (**c**) A nodular melanoma is apparent on the back of this middle-aged male. (**d**) This 72-year-old male had an ocular primary with hepatic and dermal metastases

perform an excisional biopsy. One or more dermatoscopic features suggestive of melanoma would influence the decision toward biopsy.

Biopsy

Excisional biopsy (elliptical, punch) may be performed to completely remove a small suspicious lesion with narrow margins to provide the pathologist with a complete specimen for adequate diagnostic evaluation. Careful attention should be paid to the orientation of the excisional biopsy with definitive treatment in mind (e.g., a longitudinal orientation in the extremities) [4]. The pathologist then establishes the diagnosis, the maximum thickness of the tumor, and the presence of other factors that may influence staging and subsequent clinical decision-making and management, such as the presence of ulceration, mitotic rate, and lympho vascular invasion. Ulceration, which for staging purposes is determined microscopically, will typically upstage a lesion of a given thickness [3]. For larger lesions, or those that will be technically or esthetically difficult to remove as a complete specimen, it is reasonable to perform a non-excisional biopsy (such as a punch or incisional biopsy) to first establish the diagnosis [4].

Imaging and Laboratory Tests

Radiologic Imaging

Imaging has limited value in the initial workup of patients with primary cutaneous melanomas in the absence of clinically evident stage III disease [4, 9]. Nodal basin ultrasound prior to sentinel lymph node biopsy (SLNB) (see below, "Sentinel Lymph Node Biopsy") can be discussed with and considered for patients with an equivocal regional lymph node exam and those with biopsy-confirmed primary melanoma with high-risk features (such as those (<0.8 mm thick with ulceration or >0.8 mm thick with or without ulceration) [4, 10–14].

The workup of patients with suspected stage III/IV melanoma may include magnetic resonance imaging (MRI) of the brain with contrast and extracranial imaging with positron emission tomography/computed tomography (PET/CT) or CT with contrast [4, 10]. Please see Chap. 18 for a discussion of the strengths and limitations of these modalities.

Fine needle aspiration (FNA) is used in the cytological diagnosis of melanoma metastases and may be used in combination with ultrasound, CT, or PET/CT (see Chap. 18).

Laboratory Investigations

Similarly, bloodwork is of limited value in the initial workup of asymptomatic patients without clinical suspicion of regional or distant metastatic disease [4]. However, appropriate laboratory testing will help establish the overall health of the patient and provide a baseline against which changes can be measured in the future. Lactate dehydrogenase (LDH), in particular, should be measured for staging purposes in patients who may have advanced melanoma as it is used in staging of patients with distant metastatic disease and is a prognostic factor in these patients. LDH has consistently been shown to be predictor of poor response to immunotherapy and is an adverse prognostic factor in patients with advanced melanoma [15–21]. Additionally, current NCCN guidelines do not recommend mutational analysis or multigene testing of primary melanomas unless it will guide systemic therapy or if required for consideration of clinical trials [4].

Staging of Melanoma

Management of melanoma is dependent on staging [3, 4], as patient prognosis, risk of disease recurrence and risk of regional and distant metas-

tasis are stage-specific [2]. Stage 0 lesions are in situ (pre-invasive). Stage I disease has a low risk for recurrence/progression and includes thin melanomas (≤1.0 mm with or without ulceration) and intermediate thickness melanomas (>1.0–2.0 mm) without ulceration and without nodal, in-transit, microsatellite/satellite, or distant metastasis. Stage II disease includes intermediate thickness melanomas (>1.0–2.0 mm) with ulceration and melanomas >2.0 mm thickness with or without ulceration and without nodal, in-transit, microsatellite/satellite, or distant metastasis. Patients with stage III disease have regionally metastatic melanoma without distant metastasis, while those with stage IV melanoma have distant metastatic disease beyond the regional lymph nodes. For details of staging melanoma and stage-specific prognosis, refer to Gershenwald et al [2, 3].

Management of Melanoma In Situ (Stage 0)

Biopsy and Diagnosis of Melanoma In Situ

Melanoma in situ (MIS), also known as lentigo maligna, Hutchinson's melanotic freckle, or simply Hutchinson's freckle, has a much better prognosis than invasive melanoma. Fatalities do not normally occur unless it transforms into an invasive melanoma (Fig. 15.1a). MIS always has the potential to progress to invasive melanoma, particularly if left untreated for many years, and perhaps more so if there is significant ongoing sun exposure to induce a transforming genetic event. The lateral spread of these lesions can be quite extensive, and lesions can be many centimeters in extent. This makes it at times technically and esthetically difficult to excise and examine the entire primary tumor pathologically. An important guiding principle when dealing with suspected stage 0 lesions is to try and exclude invasive melanoma. For this reason, it is best to excise the entire lesion as an excisional biopsy with at least 1–2 mm margins of clinically normal skin for pathological evaluation.

In situations where a simple excisional biopsy is technically difficult (a very large lesion extending several centimeters), or when the resulting scarring may be unacceptable to the patient and consideration is being given to non-surgical therapy with imiquimod [22–25], we recommend that several areas within the lesion that are the most suspicious for invasive melanoma be biopsied using an incisional or punch technique (see Chap. 1). With each technique, it is imperative to try and biopsy the area most clinically suspicious for invasive melanoma: usually the thickest or, for flat lesions, the darkest areas as determined visually, or by dermoscopy or confocal microscopy, if available. While there are disadvantages to these techniques, the most notable being sampling error, advantages are that a full-thickness specimen is obtained, and the pathologist is directed, by virtue of the limited area of the specimen, to the location the clinician considers most clinically suspicious. If using the punch technique, it is a good idea with an extensive lesion to sample the two or three most suspicious areas within the lesion to further reduce the possibility of missing an invasive melanoma. The small defect created by a 3 mm punch is ideal for biopsying larger lesions in most areas. Smaller punches (2 mm) are acceptable if concern over the resulting cosmetic defect is going to prevent biopsy.

Excision of Melanoma In Situ

The standard treatment of MIS is wide local excision (WLE) with 0.5–1.0 cm margins recommended by the current NCCN guidelines [4]. If excision with a 5 mm margin is difficult, or the scarring unacceptable (such as on a young adult's face), a narrower margin can be accepted, although retrospective and prospective studies have demonstrated improved rates of complete histologic clearance with greater margins. Mohs micrographic surgery and staged excision with or without immunohistochemical staining have been used to treat lentigo maligna and MIS in anatomically important areas [26–30]. For a more detailed discussion of the Mohs technique, refer to Chap. 11.

Non-Surgical Treatment of Melanoma In Situ

Although surgical excision is the standard of care for MIS, in cases where resection is not possible either due to MIS location or extent or due to patient comorbidities, topical treatment with imiquimod is an alternative [4, 22–25]. Imiquimod is a toll-like receptor (TLR) agonist that can be used to stimulate immune responses against melanoma. The topical 5% cream has been used as a monotherapy for treating these lesions. A clearance rate of 70–90% can be achieved with use of this drug with low recurrence rates (0–4%) in reported series [31–35]. However, it is important that patients are counselled that surgery, the standard of care, is still the most reliable means of therapy in the absence of evidence to the contrary. Imiquimod does, however, offer a reasonable alternative if surgery is problematic.

Imiquimod cream is applied to the area of the MIS and for 5–10 mm beyond the visible border for a period of 3–6 months [22]. Although an intense application frequency (6–7 applications per week) results in the best clearance rate, application frequency can be adjusted depending on the severity of the inflammatory response and the tolerance of the patient if the total number of treatments is high (>60 applications) although fewer applications may also work [36]. It is generally advisable to try and achieve a visible degree of erythema in and around the tumor [37]. Daily application may not be tolerated by some individuals as local side effects can be considerable at this frequency. Three times a week application appears to be almost as effective as daily, if continued long enough [36]. Both cumulative dose and treatment intensity affect tumor clearance rates [34]. However, more intense application frequencies are not tolerated as well, so patient compliance has to be balanced with high efficacy, and a greater number of applications over a longer period of time are likely to lead to better compliance than the same number of applications in a shorter period of time. Duration of treatment of less than 6 weeks is not recommended since relapses are more likely. Fewer relapses are seen with treatment for 3 months or longer [36]. After the completion of therapy, it is good practice to biopsy the most clinically suspicious areas of previous involvement to look for any persistence of tumor using special stains for melanoma such as Mart-1.

Additionally, both imiquimod and radiotherapy [37–39] have been used as adjuvant treatment in selected patients with positive margins after optimal surgery.

Challenges of Melanoma In Situ Management

A pathologist may miss a small area of early invasion, even with the entire specimen to examine. Variations in appearance in different areas of the same tumor, not infrequently combined with a disconnect between morphology and clinical behavior, lead to pathological under-diagnosis of in situ melanomas, even with the best dermatopathologists [40–48]. Given the difficulty of making this diagnosis pathologically, it is good practice to follow patients considered for this diagnosis, even in the face of a negative biopsy. In situations where the pathology belies the clinical aggressiveness of the tumor, the only way to make the correct diagnosis is to observe a growth rate or other clinical behavior that is inconsistent with a benign lentigo. Patients with MIS, treated with any method, should have regular follow-up to look for recurrences and/or new primary lesions.

Management of Primary Melanoma (Stages I and II)

Definitive Excision of Primary Melanoma

Once the diagnosis of malignant melanoma has been made (see section “Clinical Presentation and Initial Assessment”), the treatment of pri-

mary melanoma includes (1) definitive excision with adequate negative margins and (2) staging of the regional lymph node basin for primary melanomas with high-risk features at increased risk of regional metastasis (such as those <0.8 mm thick with ulceration or >0.8 mm thick with or without ulceration).

The current NCCN guidelines recommend a 1.0 cm margin for T1 (≤1.0 mm in thickness), 1.0–2.0 cm margin for T2 (>1.0–2.0 mm in thickness), and 2.0 cm margin for T3–4 (>2.0 mm in thickness) primary melanomas [4]. These recommendations are based on prospective randomized trials, with no data to demonstrate any oncologic benefit of surgical margins exceeding 2 cm [49–57]. It has been common practice among some surgeons to excise all primary melanomas to the level of, but not including, the underlying muscle fascia. However, unlike margins, the importance of depth has not been prospectively studied in a randomized trial, and excisions to the muscle fascia may not always be necessary [58, 59].

Staging the Regional Lymph Node Basin

While most metastases are clinically occult, the regional lymph node (RLN) basin is the most common site of melanoma metastasis. The sentinel lymph node biopsy (SLNB) procedure is the standard method for RLN basin evaluation and staging in patients with T1b or thicker cutaneous melanoma and identifies patients with clinically occult RLN metastases [60]. The sentinel lymph node (SLN) status is a significant prognostic factor for disease-free survival (DFS) and melanoma-specific survival (MSS) as shown in a number of landmark studies, including the Multicenter Selective Lymphadenectomy Trial (MSLT) [61–63]. As discussed above (see "Clinical Presentation and Initial Assessment") and if radiology expertise is available, ultrasonography of the regional lymph node basin with FNA biopsy of any suspicious lymph nodes may also be discussed and considered for patients with T1b or higher T stage melanomas prior to SLNB [4, 11–14]. SLNB is not indicated for patients with clinically suspicious RLN on ultrasonography or with clinically palpable RLN that are confirmed to contain metastatic melanoma by FNA or core needle biopsy (CNB). Additionally, SLNB is not indicated in those with distant metastatic disease as prognosis and treatment of these patients is dictated by their stage IV disease.

As a technique to identify regional metastatic disease [60], SLNB is based on the concept that in most cases melanoma will first metastasize to the regional lymph nodes. The idea is that the lymphatic fluid from the tumor drains first to one or more SLNs in one or more adjacent lymph node basins. The technique identifies the first regional lymph node in the lymphatic drainage of the primary tumor site—the "sentinel" node. Typically, 1–4 h prior to surgery (or prior to surgical incision), patients receive an intradermal injection of 0.5–1 mCi of technetium Tc 99 m sulfur colloid. A handheld gamma counter is used intraoperatively to localize the SLN. In addition, to facilitate intraoperative identification of SLNs, 1–3 ml of isosulfan blue may also be injected intradermally around the tumor or biopsy site approximately 20 min before the mapping procedure. The sentinel node is then intraoperatively identified, excised, and examined histologically (Fig. 15.2). In certain areas of the body—namely, the head/neck and trunk—the lymphatic drainage can be variable [64, 65]. We recommend obtaining preoperative lymphoscintigraphy for patients with truncal melanomas to identify the draining regional lymph node basins containing the SLNs to be excised and inform surgical positioning on the day of surgery [4, 66]. For patients with head/neck melanomas, we recommend obtaining single-photon emission computed tomography (SPECT)/CT which fuses nuclear medicine and CT images to provide important anatomical information for the surgeon performing SLNB [4, 67, 68].

Concern has been expressed that a definitive excision performed prior to a SLNB may alter the

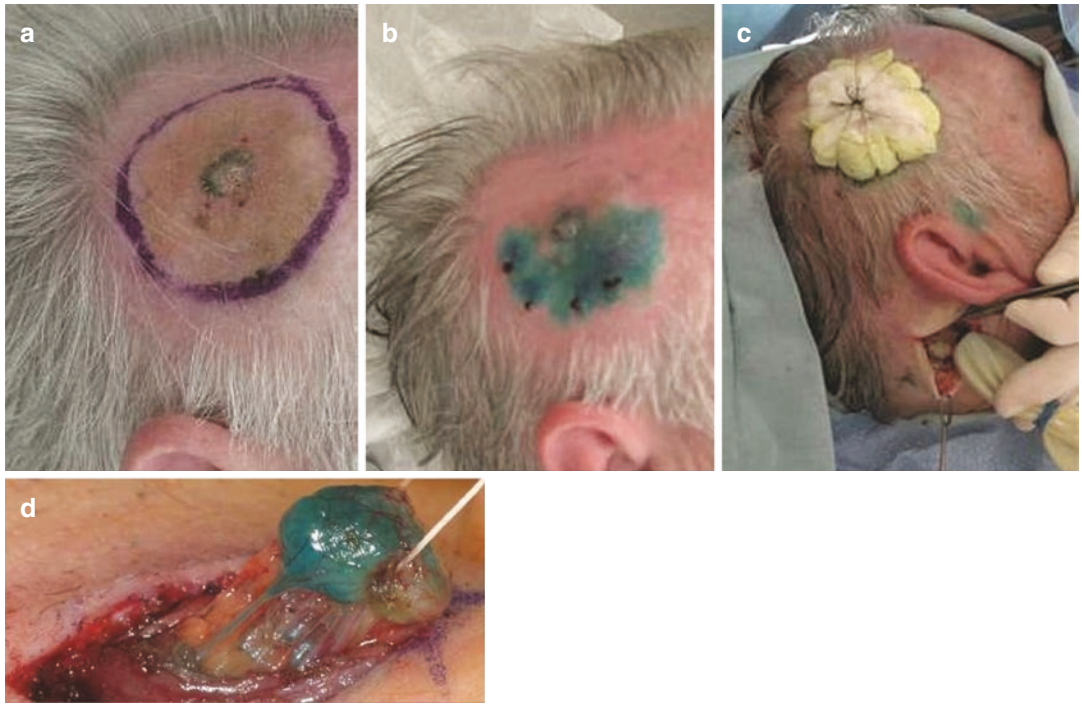

Fig. 15.2 Sentinel lymph node biopsy. (**a**) A primary melanoma on the scalp prepped for definitive excision and sentinel lymph node biopsy. Photograph courtesy of Dr. Brad Garber. (**b**) Appearance following injection of Tc-99 and blue dye. Photograph courtesy of Dr. Brad Garber. (**c**) Localized first by the Geiger counter probe, the sentinel lymph node (SLN) can be seen (*blue-yellow* nodule) in the dissection site and later confirmed by the high number of counts it emits. The primary melanoma site is seen on the scalp with a temporary packing placed after definitive excision. Photograph courtesy of Dr. Brad Garber. (**d**) Intraoperative identification of a sentinel lymph node (SLN). Intradermal injection of a vital blue dye around the intact melanoma or biopsy site leads to uptake of the dye by the lymphatic system and transport of the dye to the draining regional nodal basins, thereby allowing the identification of SLNs. (Copyrighted photograph courtesy of Jeffrey E. Gershenwald, M.D., and the UT MD Anderson Cancer Center)

lymphatic drainage from the primary tumor site, making the information from that SLNB less reliable. The evidence suggests that a previous wide local excision does not appear to adversely affect the ability to detect lymphatic metastases [4, 69], although the utility of lymphatic mapping and SLNB in patients who have undergone extensive reconstruction of the primary excision site is yet to be defined. However, these authors and current NCCN guidelines strongly recommend that, whenever possible, patients undergo concomitant wide local excision and lymphatic mapping with SLNB as this provides the patient with a single operation for the best opportunity for RLN basin staging and avoids the costs and potential-associated morbidity of two surgical procedures [4, 69].

SLNB is associated with a low complication rate (<5–10%) and significantly lower when compared with completion lymph node dissection (CLND) [4]. Potential complications include wound dehiscence, infection, seroma, hematoma, lymphedema, nerve injury, thrombophlebitis, and allergic reactions to the blue dye used [4].

Patients identified to have clinically occult RLN metastasis/positive SLNB may then benefit from or be candidates for CLND and/or adjuvant systemic therapy (see "Management of Melanoma with Regional Metastasis") [4].

Management of Melanoma with Regional Metastasis (Stage III)

The Role of Completion Lymph Node Dissection

Until recently, CLND was recommended for most patients with a positive SLNB. However, two recently reported multicenter RCTs (DeCOG-SLT, MSLT-II) [70, 71] designed to address the question of whether immediate CLND in patients with a positive SLN improves MSS compared to nodal observation did not demonstrate a survival benefit with CLND. Although CLND provided prognostic information and improved regional control, it was associated with increased lymphedema compared to nodal observation for patients with a positive SLN. As a result, fewer SLN-positive patients are undergoing CLND, particularly with the availability of effective adjuvant immune checkpoint therapies (see "Adjuvant Therapies for High-Risk Melanoma").

NCCN guidelines recommend either active nodal basin surveillance or consideration of RLN dissection for SLN-positive melanoma [4].

Adjuvant Therapies for High-Risk Melanoma

Patients at high risk for recurrence but without any detectable disease may be offered treatment following surgery to reduce their chance of recurrence and to improve survival. Antineoplastic treatment given in this situation is termed "adjuvant therapy." Historically, cytotoxic chemotherapy and interferon-based systemic therapy have been ineffective and poorly tolerated as adjuvant therapy for melanoma [4, 72–75].

In the past decade, however, the adjuvant treatment landscape for high-risk melanoma has changed dramatically with the introduction of molecularly targeted therapies (BRAF and MEK inhibitors [4, 76]) and immune checkpoint inhibitors (anti-CTLA [14, 77, 78] and anti-PD1 antibodies [4, 79, 80]). There is also great excitement and interest in evaluating targeted therapies and immune checkpoint inhibitors in the preoperative (neoadjuvant) setting for locally and regionally advanced melanoma [81–88]. It is critically important for clinicians to understand, discuss, and be comfortable recognizing and managing the potential complications associated with targeted therapies [4, 89] and immunotherapies [4, 90, 91], which can be permanent, severe, and life-threatening. Toxicities of BRAF/MEK inhibitors can be systemic (fever, hypertension, fatigue), gastrointestinal (constipation, diarrhea, vomiting, nausea, ALT/AST elevation), and cutaneous (photosensitivity, rash, pruritus, hand-foot syndrome). Toxicities of the immune checkpoint inhibitors are generally immune-mediated, can affect any organ system (including but not limited to cardiopulmonary toxicities, colitis, pancreatitis, hepatic toxicity, endocrinopathies, nephritis, cutaneous toxicities), and can occur at any time [91].

Lastly, radiation therapy may be useful in an adjuvant role in some clinical scenarios such as when negative resection margin cannot be achieved or when there is high risk of nodal basin relapse (one or more involved parotid nodes, two or more involved cervical or axillary nodes, or three or more involved inguinal nodes; presence of extranodal tumor spread; or maximum diameter of largest metastatic node $\geq$3 cm for a cervical node or $\geq$4 cm for an axillary or inguinal node) [92, 93]. Although radiating lymph node basins after surgical clearance of stage III melanoma has not improved survival, in certain situations it may be helpful for improving regional disease control [92, 93]. Adjuvant radiation therapy, particularly in the groin location, is associated with potential morbidity. It should only be considered and discussed with patients at high risk of nodal failure after lymphadenectomy by a multidisciplinary and expert team approach.

Regional Recurrences

Limited regional recurrences are generally treated with surgical excision if it can be accomplished. Surgically unresectable recurrences are discussed below (see "Management of Unresectable Stage III and Metastatic Melanoma"). Such cases can be considered for non-surgical regional therapy (e.g., talimogene laherparepvec; see below) or be referred for a clinical trial.

Management of Unresectable Stage III and Metastatic (Stage IV) Melanoma

NCCN guidelines recommend multidisciplinary tumor board consultation for patients with stage IV melanoma [4]. Patients with stage IV melanoma generally have a worse prognosis than stage I–III melanoma. Historically, the overall median survival of stage IV melanoma from the time of initial diagnosis of distant metastasis was 6–7.5 months, and the 5-year survival was less than 10%. Patients with stage IV melanoma had a 5-year survival between 19% for stage IV-M1a and 7% for stage IV-M1b [94]. However, patients with stage IV melanoma are heterogeneous, and the treatment landscape for stage IV melanoma has improved dramatically, with a subset of patients achieving durable antitumor responses and improvement in overall survival [95].

Evaluation of Patients with Suspected Metastatic Melanoma

For those with suspected unresectable or metastatic melanoma, biopsy (fine needle aspirate, core needle biopsy, incisional, or excisional) should be obtained to confirm the diagnosis. Additionally, before planning therapy, it is important to determine the metastatic burden by obtaining baseline imaging (CT, PET/CT, brain MRI) [4] (see Chap. 18).

Systemic Therapy for Unresectable Stage III and Stage IV Melanoma

The introduction of BRAF and MEK inhibitors, molecularly targeted therapies, and immune checkpoint inhibitors (anti-CTLA4 and anti-PD1 antibodies) has dramatically changed the prognosis and outlook for patients with *BRAF*-mutant unresectable stage III and stage IV melanoma. The earliest BRAF inhibitor to show efficacy in *BRAF*-mutant metastatic melanoma patients was vemurafenib [96]. Since then, improved survival has been demonstrated with BRAF/MEK inhibitor combinations (dabrafenib/trametinib, vemurafenib/cobimetinib) [18, 97–99]. In 2011, ipilimumab (anti-CTLA-4) became the first immune checkpoint inhibitor approved for the treatment of unresectable stage III and stage IV melanoma [100], although now no longer considered first-line systemic treatment for unresectable or metastatic melanoma. Anti-PD1 antibodies (pembrolizumab, nivolumab) were subsequently approved either as single agents or as nivolumab/ipilimumab combination therapy [101–103]. It cannot be overemphasized how critically important it is for clinicians to understand, discuss, and be comfortable recognizing and managing the potential complications associated with targeted therapies [4, 89] and immunotherapies [4, 90, 91], which can be permanent, severe, and life-threatening.

Metastasectomy

For select patients with stage IV melanoma (and after multidisciplinary tumor board discussion and consensus) with a limited number of lesions, palliative surgical resection might be considered [104, 105]. Patients with rapidly progressing disease will probably not benefit from metastasectomy.

Radiation Therapy

Radiation therapy can be used for palliation of symptomatic metastatic disease [106–110]. For management of central nervous system (CNS) melanoma metastases, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) techniques such as Gamma Knife and CyberKnife can be used [111–116]. For a limited number of small metastases to the brain, stereotactic radiosurgery techniques such as CyberKnife and Gamma Knife therapy potentially prolong and increase quality of life and occasionally can be curative if metastatic disease is limited to the brain. Radiation therapy, which was previously thought to be solely palliative, may have a positive impact on survival, when combined with checkpoint inhibitors, via the abscopal effect [117–120], in which localized radiation therapy results in out-of-target tumor responses. If appropriate clinical trials are available, we recommend enrolling patients to further delineate the potential benefits and limitations of this effect.

Intralesional Injection with T-VEC

Talimogene laherparepvec (T-VEC) is an intralesional injection which is composed of a genetically modified herpes simplex virus which induces tumor cell lysis and delivers localized expression of GM-CSF to injected lesions. T-VEC has been shown to produce a clinically significant and durable response in both injected and noninjected (bystander effect) lesions [121, 122] (Fig. 15.3). Common toxicities include flu-like symptoms (fatigue, chills, fevers, nausea, vomiting) as well as injection site pain.

Regional Therapy

For patients with regionally recurrent, unresectable melanoma, administration of cytotoxic chemotherapy by isolated limb perfusion (ILP) or isolated limb infusion (ILI) may be considered. ILP/ILI delivers high doses of chemotherapy to the affected limb while avoiding toxicities associated with systemic chemotherapy.

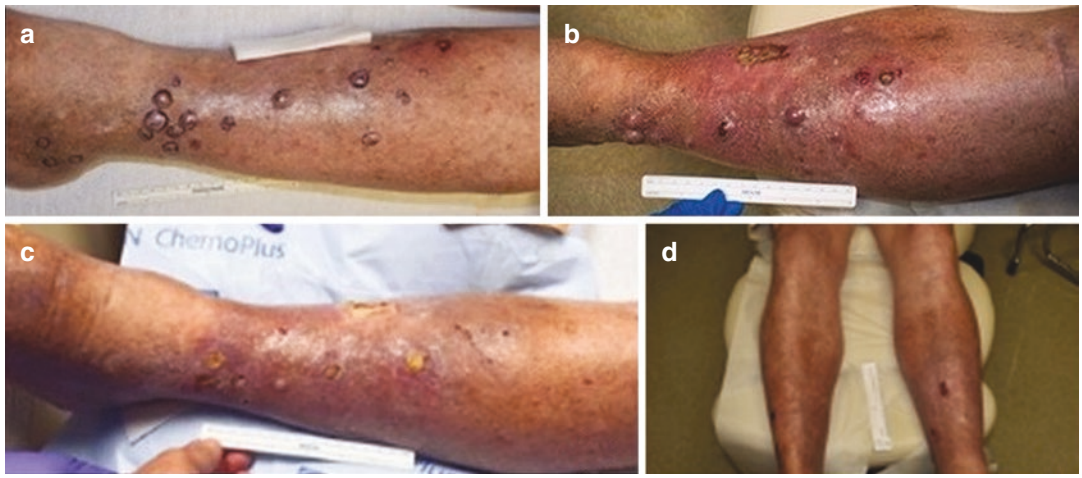

Fig. 15.3 Response to T-VEC intralesional therapy. (**a**) Patient with history of thick primary melanoma of the left medial shin with locoregional recurrence, just prior to first injection. (**b**) Response following T-VEC intralesional therapy 3 weeks after first injection, just prior to second injection. (**c**) Response following T-VEC intralesional therapy ~4 weeks after second injection. There are no remaining lesions to treat. (**d**) Response following T-VEC intralesional therapy 4.5 months after first injection. Note the slowly healing wide local excision site on the left medial shin area (still not completely healed after 10 months)

Best Supportive Care

Best supportive care should be discussed with patients with metastatic disease and with poor performance status [4].

Surveillance

Follow-up is essential due to the risk of developing a second primary in 2–10% of patients as well as the risk of locoregional or distant recurrence from the original tumor. Routine imaging is not recommended for patients with stage 0, I, or IIA melanoma [4]. Imaging can be considered at 3–12-month intervals for patients with stage IIB, III, and IV melanoma [4]. Follow-up should conform to NCCN guidelines in most cases.

Conclusion

It is truly a remarkable time for clinicians who evaluate and treat patients with cutaneous melanoma. The principles of initial patient, skin, and nodal basin assessment remain fundamental. Once a diagnosis of melanoma has been established by either incisional or excisional biopsy, WLE with adequate margin should be obtained. For patients at increased risk of nodal metastasis, regional nodal basin staging by SLNB is recommended. The role of CLND is evolving following the practice-changing results of the DeCOG-SLT and MSLT-II clinical trials. Recent advances and new systemic treatments such as targeted and immune checkpoint therapies have dramatically changed outcomes, prognosis, and survival for patients with advanced melanoma. Clinicians are learning to weigh the risks and benefits of these therapies and to recognize and treat the diverse, and at times life-threatening, potential complications associated with them. With the increasingly complex treatment options available for cutaneous melanoma, clinicians should follow NCCN guidelines and consider referral of those who fail front-line therapies for clinical trials.

Disclosures

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Chapter 16
Skin Cancer in Skin of Color

Brooke A. Jackson and Zeena Y. Nawas

Skin cancer is the most common malignancy in the United States [1–5]. While skin cancer is less common in people with skin of color [6], it is more often associated with an increased incidence of morbidity and mortality as compared to white counterparts [7–9]. This imbalance has significant public health concerns. Current skin cancer campaigns focus on Caucasian patients in high-risk groups. There is a paucity of literature on skin cancer in skin of color. Most physicians do not immediately associate skin cancer with skin of color, and little is known about the sun-protective behaviors of those with skin of color [10]. Similarly, the collection of statistics for skin cancer in skin of color is challenging as non-melanoma skin cancers (NMSCs) are not consistently reported to tumor registries, and many NMSCs in skin of color are reported as melanomas. According to the census projections, by the year 2045, 50% of the US population will be non-white [11]. This changing demographic, combined with the disparate mortality, makes it imperative that physicians become familiar with skin cancer in skin of color so that they may better educate these patients on risk factors and early detection.

Unique Features of Skin of Color

While all skin, regardless of color, contains the same number of melanocytes, the melanosomes in darkly pigmented skin are larger and more evenly dispersed throughout the entire epidermis when compared to those in white skin, which are less active and grouped together [12]. The larger, more melanized epidermal melanocytes in dark skin absorb and scatter more ultraviolet (UV) light, resulting in twice as much UVB radiation filtration by dark skin than white skin [13]. Caucasian epidermal skin transmits 24% of UVB and 55% of UVA rays, whereas black epidermal skin transmits 7.4% of UVB and 17.5% of UVA rays [13]. The intrinsic sun-protective factor (SPF) of black skin has been estimated to be 13.4, whereas light skin has an SPF of 3.4 [14]. While these unique features of ethnic skin serve to protect it against actinic damage, and UV-induced skin cancers are overall less prevalent in skin of color, the incidence of NMSC in most ethnic groups is increasing [15], suggesting that UV exposure may play less of a role in the development of certain skin cancers in skin of color. Known risk factors for non-melanoma skin cancer are listed in Table 16.1 [16].

Table 16.1 Known risk factors for NMSC [16]

UV exposure including UV light treatment
Fitzpatrick skin types I–III
Male gender
Radiation exposure
Genetic disorders (xeroderma pigmentosum, basal cell nevus syndrome)
Immunosuppression
Human papilloma virus
Chemical exposure (arsenic, coal tar products)
Chronic inflammation

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Role of the Ozone Layer

The ozone layer has decreased since the 1980s, allowing increased penetration of UV radiation to the earth's surface [17]. Increased risk of non-melanoma skin cancers has been associated with UV radiation, decreased skin pigmentation, and decreasing latitudes [2, 18]. The role that UV exposure plays in the development of NMSC in skin of color may be correlated with the differences in the anatomical distribution of various tumors. In Caucasians, non-melanoma skin cancers occur most commonly in sun-exposed areas of the body [19]. UV radiation exposure is associated with an increased incidence of skin cancer in Asians [20]. Several studies have shown that UV radiation plays a significant role in the development of basal cell carcinoma (BCC) in blacks and these tumors are seen more commonly in sun-exposed areas of the body in blacks with fair skin tones [21, 22]. Interestingly, the role of UV exposure in the development of squamous cell carcinoma (SCC) in blacks is not clear. SCC, which occurs with equal frequency in Caucasians in sun-exposed and sun-protected areas, occurs 8.5 times more frequently on sun-protected areas in blacks, indicating that UV radiation plays a much less significant role in the development of SCC in blacks [23].

Basal Cell Carcinoma

BCC is the most prevalent skin cancer found in Caucasians, Asians [24], and Hispanics and is the second most common skin malignancy in African-Americans after SCC [6, 13]. While the classic presentation of a solitary translucent papule with central ulceration may occur in skin of color, the presentation of BCC is more likely to be atypical in appearance [6] (Table 16.2; Figs. 16.1, 16.2, 16.3, and 16.4). In darkly pigmented skin, rolled pearly borders and surrounding telangiectasia may be difficult to discern. Pigmented BCCs occur more frequently in skin of color, while the morpheaform subtype is less

Table 16.2 Differential diagnosis of BCC in skin of color

Seborrheic keratosis
Nevus sebaceous
Epidermal inclusion cyst
Blue nevus
Sarcoid
Melanoma
Trauma (curling iron burn)
Lupus erythematosus

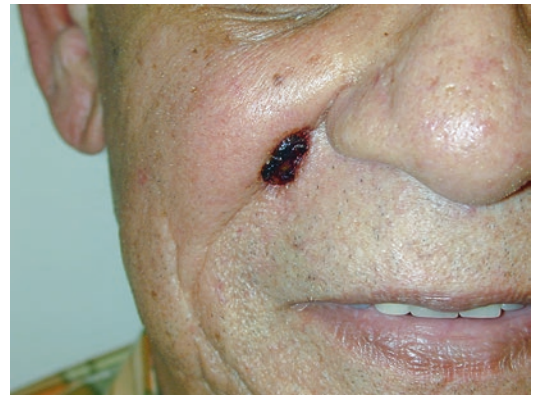

Fig. 16.1 An 80-year-old African-American man with BCC at right nasolabial fold. History of golfing

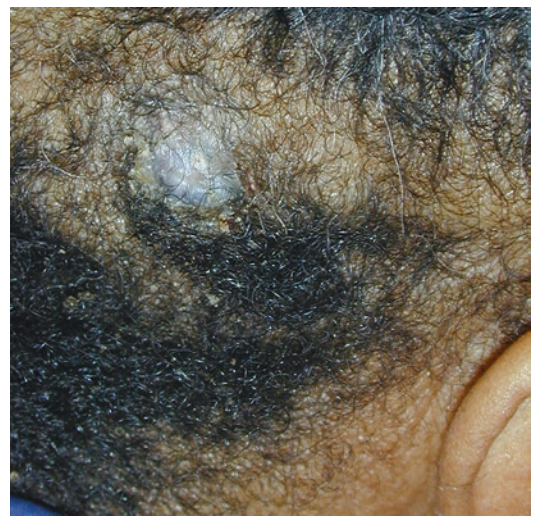

Fig. 16.2 A 75-year-old African-American woman with nodular pigmented BCC on right parietal scalp

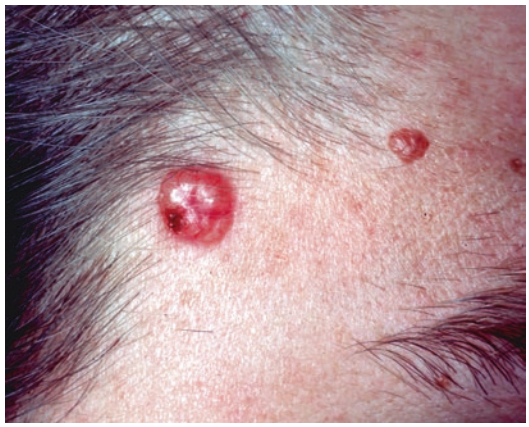

Fig. 16.3 Nodular pigmented BCC of a Hispanic female along the hairline. (Photograph courtesy of June K. Robinson, MD)

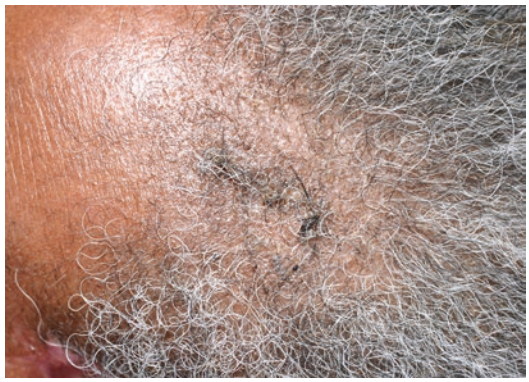

Fig. 16.4 A 70-year-old black female with multiple superficial and nodular basal cell carcinomas, each 1–2 mm in diameter in her scalp, which were initially felt to be dermatosis papula nigricans by her dermatologist

common [6, 25]. Many pigmented BCCs in skin of color have been misdiagnosed clinically as melanoma [26]. Although the majority of BCCs in skin of color do occur in sun-exposed areas, they are seen in sun-protected areas with increasing frequency [27].

Consider BCC (pigmented) in any suspicious lesion in a patient with skin of color.

As with Caucasian patients, previous studies have documented the correlation of BCC in African-Americans to UV light exposure [28]. However, those with skin of color often have a false sense of security with regard to awareness of skin cancer risk and tend not to follow general guidelines of sun protection [29] in current skin cancer campaigns. Patients with skin of color also have a higher incidence of medical conditions such as hypertension, lupus, and diabetes, which necessitate the use of photosensitizing medications [30–32]. These combined factors support the need for better patient education and counseling and perhaps a separate skin cancer campaign directed toward patients with skin of color.

Squamous Cell Carcinoma

SCC is the most common cutaneous malignancy in African-Americans and the second most common cutaneous malignancy in Hispanics, East Asians (including Japanese and Chinese patients), and Caucasians [6, 13, 20]. Of interest, actinic keratoses, the precursor lesion to SCC, tend not to occur in African-Americans [33], but are common in Japanese [34] (Figs. 16.5, 16.6, and 16.7). While most SCCs in Caucasians occur in sun-exposed areas of the head and neck, SCCs in African-Americans are found primarily in sun-protected areas [21, 35, 36], such as the lower extremity and anogenital areas, suggesting that UV radiation plays less of a role in the development of SCCs in African-Americans. The mortality rate of African-Americans with SCC has been reported to range from 18.4% to 29% [37,

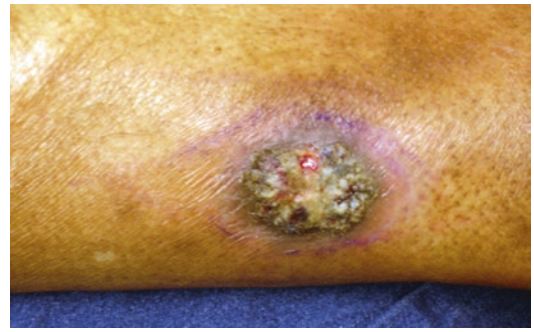

Fig. 16.5 An African-American female with SCC on her lower extremity, with a history of thermal burn to the area as a child

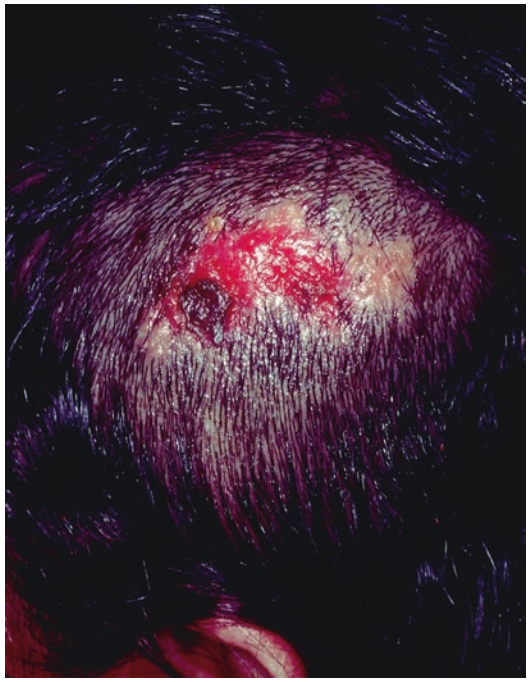

Fig. 16.6 An Indian female with SCC in nevus sebaceous of scalp. (Photograph courtesy of June K. Robinson, MD)

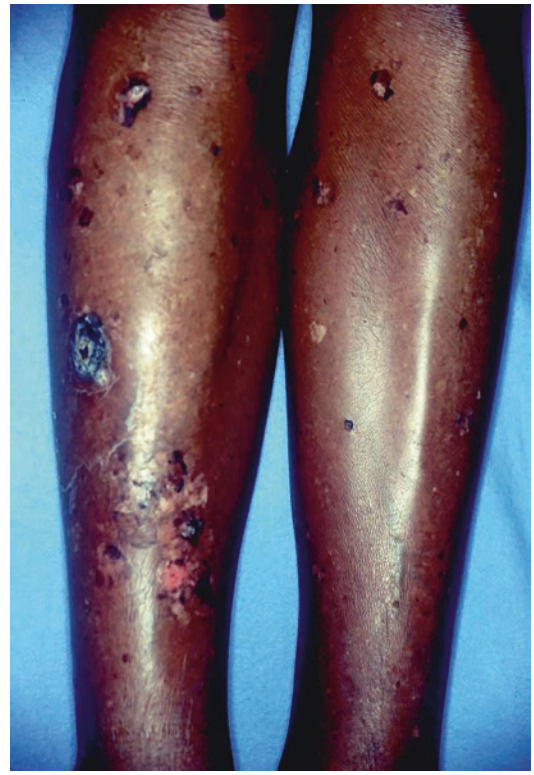

Fig. 16.7 An African-American female with SCC and arsenical keratoses on her lower extremities. History of well water ingestion. (Photograph courtesy of June K. Robinson, MD)

38] and is particularly high with anogenital lesions. Increased mortality may be related to both delayed diagnosis and the potentially more biologically aggressive nature of tumors in sun-protected areas [38].

Bowen's disease (SCC in situ) is uncommon in African-Americans. When it does occur, it presents as a non-specific hyperkeratotic, often pigmented plaque on the lower extremity [39, 40].

Risk factors associated with the development of SCC in skin of color include chronic scarring and inflammatory processes [41–45] (Figs. 16.6 and 16.7), as well as other disease states, listed in Table 16.3. It is also imperative that these patients be counseled and followed up routinely for full skin examination.

Table 16.3 Risk factors for SCC in skin of color [41–45]

Lupus vulgaris
Scars from burn or trauma
Hidradenitis suppurativa
DLE/LE
Granuloma inguinale
Radiation sites
HPV
Immunosuppression
Albinism
Chemical exposure (tar, arsenic)
Chronic leg ulcers

Because of the increased mortality rate with African-Americans, surveillance of sun-protected areas with biopsy of any non-healing ulcer associated with areas of chronic inflammation or scarring is warranted.

Malignant Melanoma

The incidence of melanoma of the skin has risen rapidly over the past 30 years, although current trends differ by age. From 2006 to 2015, the rate

increased by 3% per year among men and women ages 50 and older, but was stable among those younger than age 50 [5].

Although age-adjusted incidence rates (per 100,000) for melanoma are lower among Hispanics and blacks (4.3 and 1.0, respectively) compared to whites (20.8) [46], melanomas among darker-skinned populations are more likely to occur in sun-protected acral and mucosal areas, to metastasize, and to have poorer outcomes than among whites [47, 48] (Fig. 16.8).

While family history and UV radiation exposure are risk factors for the development of malignant melanoma in Caucasians, these factors do not appear to play as significant a role in the development of MM in skin of color (Table 16.4). The etiology of melanoma in non-whites, however, is still to be elucidated.

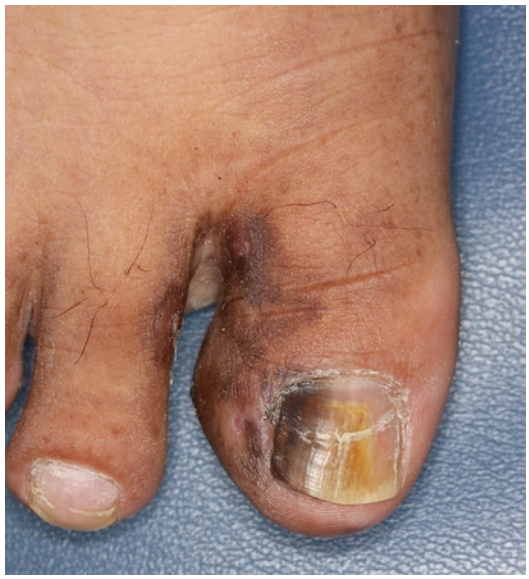

Fig. 16.8 A 43-year-old Hispanic male with a 2-year history of discoloration of right great toe and toe nail, which he treated with antifungal medication. Biopsy confirmed a melanoma

Table 16.4 Differential diagnosis for malignant melanoma in skin of color

Pigmented BCC	Tinea unguium
Seborrheic keratosis	Trauma (subungual hematoma)
Nevus	Verruca

The overall survival for melanoma in skin of color is significantly lower when compared to Caucasians [8, 49, 50]. Because survival rates are directly correlated with Clark's level staging at diagnosis, early detection is critical for increased survival.

Mycosis Fungoides

Mycosis fungoides (MF), a variant of cutaneous T-cell lymphoma, classically presents as scaling plaques, nodules, tumors, or erythroderma [15, 51] and occurs almost twice as often in African-Americans than in Caucasians, regardless of sex or age [51–54]. Hypopigmented MF is a variant of MF occurring almost exclusively in younger patients with skin of color (Fig. 16.9) and presents as ill-defined, hypopigmented patches [51]. Because these patients often have a history

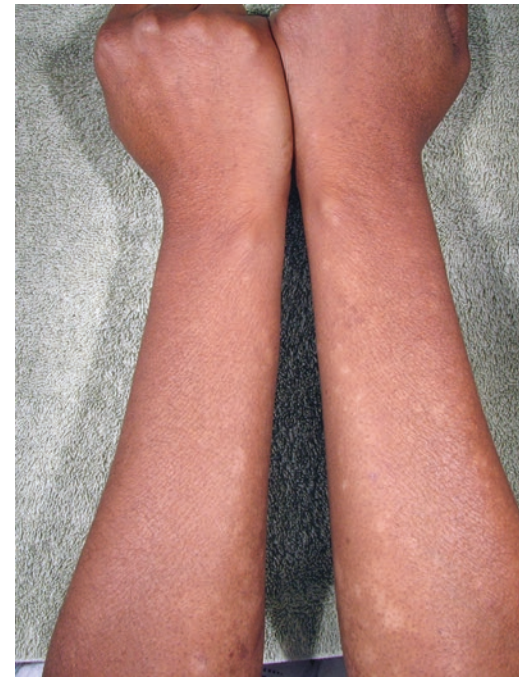

Fig. 16.9 A 37-year-old Filipino male who presented with a 2-year history of rash and was found to have hypopigmented MF. (Photograph courtesy of the Section of Dermatology, Research Institute for Tropical Dermatology, Philippines, Evangeline B. Handog, MD)

Table 16.5 Differential diagnosis for hypopigmented mycosis fungoides in skin of color

Pityriasis alba	Post-inflammatory hypopigmentation
Vitiligo	Sarcoid
Tinea versicolor	

of eczema and these lesions may look similar (Table 16.5), diagnosis may be delayed from 7 months to 10 years from disease onset to histologic diagnosis [55].

> Biopsy should be considered in those patients with skin of color whose eczema is unresponsive to standard therapies or who have an unexplained exacerbation of disease. Serial biopsies may be necessary.

Treatment Options and Operative Considerations

Treatment options for skin cancer in skin of color patients do not differ from those used in Caucasian patients and are addressed more fully in other chapters of this text.

> When treating pre-cancerous lesions, this author avoids use of liquid nitrogen in skin of color in favor of imiquimod in an effort to avoid posttreatment loss of pigment.

Keloid formation can occur in any race; however, the rate in skin of color has been reported to be from 5 to 15 times higher than that of the white population [56, 57]. In Hawaii, keloids are found three times more commonly in the Japanese population and five times more commonly in the Chinese population than in white populations [58]. Because of this increased risk, care must be taken to minimize tension with wound closures. Patients should be counseled on the potential for hypertrophic scar and keloid formation, both of which may be treated with standard therapies of intralesional triamcinolone, intralesional fluorouracil, and pressure therapy. Silicone dressings have also been shown to be an effective treatment for abnormal scarring; and due to the ease of use, this author prefers the use of Stratamed, a liquid silicone dressing. Postoperative hypertrophic scars in Caucasians and lightly complected patients of color (skin types I–IV) may be treated with the pulsed dye laser.

Several lasers may be used to improve the appearance of an erythematous scar in ethnic skin. In skin types III–IV, consider using the PDL laser with 10-mm spot, 0.5 ms, 2–3 joules, and treat every 3–4 weeks. There are multiple modalities for scar improvement and collagen remodeling which include fractionated 1550, microneedling devices [59], intralesional injections, and topicals including tacrolimus. Combination therapies are often needed to achieve the most improvement.

Summary

Although less common than in Caucasians, skin cancer does occur in skin of color, and these patients are more likely to have higher morbidity and mortality due to their disease. This disparity is due to both delayed diagnosis and the more aggressive biologic nature of these tumors in skin of color. BCC is the most prevalent skin cancer found in Caucasians, Asians, and Hispanics and is the second most common skin malignancy in African-Americans after SCC. Pigmented BCCs are found more commonly in skin of color than in Caucasians. Although malignant melanoma occurs less frequently in skin of color, the aggressive acrolentiginous form accounts for poor prognosis in these patients. While sun exposure appears to play a role in the development of BCC in skin of color, there is less of a correlation with SCC and MM due to the propensity of these skin cancers to occur in sun-protected locations.

Little is known about the skin cancer awareness of patients with skin of color [31]. Current skin cancer campaigns have focused on Caucasians in high-risk groups. Skin of color patients who do not perceive themselves as being at high risk for skin cancer development are likely to ignore early warning signs. In turn, those physicians who do

not associate skin cancer with skin of color may be less likely to consider it in a differential diagnosis or to counsel patients appropriately on risk prevention, surveillance, and follow-up. A greater effort to increase public awareness must be instituted in ethnic communities. The combined efforts of physicians and an improvement in public education will result in earlier diagnosis and a better prognosis for skin of color patients with skin cancer.

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Chapter 17
Management of Skin Cancers in Solid Organ Transplant Recipients

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The number of organ transplants performed in the United States continues to rise, with 34,770 organ transplant procedures performed in 2017, representing a 3.4 percent increase from 2016 [1]. Survival after solid organ transplantation has also increased, with recipients living on average 4.3 years longer [2]; however, with the immunosuppression necessitated to prevent allograft failure, these patients are at an elevated risk of developing skin cancer [3–5], with more than 50% of these patients ultimately diagnosed with at least one skin cancer [4, 6].

Increased posttransplant survival may be attributed to improvements in surgical technique as well as optimization of immunosuppressive therapy [7]. However, skin cancer remains an unfavorable complication in organ transplant recipients that may account for a significant source of morbidity and mortality Therefore, the prompt diagnosis and management of skin cancer in organ transplant recipients is of utmost importance.

The following chapter will discuss the epidemiology and pathogenesis of skin cancer in solid organ transplant patients and then provide some practical suggestions for the management of this challenging population.

Epidemiology

Keratinocyte Carcinoma Following Organ Transplantation

In the organ transplant population, the risk of skin cancer is much greater than in the general population. Keratinocyte carcinoma (BCC and cSCC) accounts for the majority of skin cancer diagnosed in this population [8–11]. Cutaneous squamous cell carcinoma (cSCC) is the most common type of skin cancer diagnosed in solid organ transplant recipients (SOTRs) and remains a significant cause of morbidity and mortality in these patients [4, 6]. Compared to the general population, the risk of developing cSCC is increased by 65- to 250-fold [4, 7, 10, 12], while the risk of development of BCC is increased by 10-fold [4].

While among the general population, the ratio of cutaneous squamous to basal cell carcinoma is 1:4, in the transplant population, this ratio is reversed, with cSCC being the more common [6, 7, 12]. A review of 2561 transplant recipients over a 30-year period found the incidence of cSCC to be increased by 65-fold [10]. In a Swedish cohort of 5356 transplant recipients followed between 1970

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and 1994, the relative risk of "non-melanoma skin cancer," excluding basal cell carcinoma, was 108.6 for men and 92.8 for women [13].

Risk factors for the development of skin cancer after organ transplantation are multiple. Time posttransplant and amount of immunosuppression are both associated with increased risk of cSCC [3, 12]. A recent retrospective cohort study analyzed incident skin cancer in adult recipients of a primary transplant at 26 centers across the United States [3]. The authors found a statistically significant elevated risk for skin cancer in patients of male sex, white race, and age of at least 50 years at the time of transplantation and with history of pretransplant skin cancer. Thus, it makes sense that heart and lung transplant patients are of greatest risk of development of cSCC, in light of their increased immunosuppression and older age at transplantation [3]. Additionally, the presence of keratotic skin lesions, such as actinic keratoses, seborrheic keratoses/warts, and hyperkeratotic papillomas, is associated with increased risk of both cSCC and BCC in organ transplant recipients compared to those organ transplant recipients who do not have these keratotic lesions [14].

One retrospective case-control study compared the histopathology of skin cancers in immunosuppressed organ transplant recipients to immunocompetent individuals [15]. Transplant patients were younger at the time of skin cancer diagnosis, and those who were diagnosed with cSCC had a worse prognosis than those diagnosed with basal cell carcinoma (BCC). Spindle cell morphology, which is characterized largely by atypical spindle cells, can be clinically aggressive and was found to be more common in transplant patients. Additionally, histological features of human papilloma virus (HPV) infection were overrepresented in transplant-related SCC.

Other rarer non-melanoma skin cancers, such as Merkel cell carcinoma and Kaposi sarcoma, also have elevated incidence in this population, up to 24-fold and 84- to 500-fold, respectively [3, 6, 10, 12, 16, 17]; due to space limitations, these will not be addressed in this chapter.

Melanoma Following Organ Transplantation

Malignant melanoma (MM) was initially thought to be associated with greater morbidity and mortality in organ transplant recipients based on decreased 1-, 3-, and 5-year survival rates reported in an early study from the Penn transplant registry [18]. In that study, the average Breslow depth of MM was 1.51 mm. More recent data indicates that MM is overrepresented in transplant patients with a 2.2- to 8-fold increase compared with the general population [10, 19, 20]. A recent retrospective cohort study [3] demonstrated that the incidence of posttransplant MM was 125 per 100,000 person years, representing a rate increase of 7- to 14-fold in comparison with the general population [21, 22]. However, the prognosis does not seem to significantly differ in this cohort. A study of 48 MM patients from the Mayo transplant registry revealed no difference in the development of metastases or overall survival between transplant recipients with MM and otherwise prognostically matched immunocompetent patients [23].

Pathogenesis

Although the pathogenesis of skin cancer in organ transplant recipients is complex, chronic sun exposure remains one of the most important risk factors in developing cSCC [6, 24]. Ultraviolet radiation (UVR) in the UVB range (290–320 nm) is a carcinogen, triggering mutations in the p53 tumor suppressor gene within

keratinocytes, thus preventing apoptosis of mutated cells [25]. Unchecked proliferation of mutated keratinocytes drives the transition from actinic keratosis to SCC in situ and, ultimately, to invasive SCC.

This immunosuppressed transplant recipient population has a greater susceptibility for the development of virally induced benign and malignant neoplasms [26]. HPV-induced warts are common in organ transplant recipients. Epidermodysplasia verruciformis HPV types are prevalent in benign and malignant skin lesions in transplant recipients. cSCC in transplant recipients has a higher rate of HPV compared with normal skin (90% versus 11–32%, respectively) [27]. Additionally, after cessation or tapering of immunosuppression, skin cancers associated with HPV recede [26]. It is plausible that HPV-infected transplant recipients may be at elevated risk of developing actinic keratosis (AK) or cSCC due to suppression of p53 apoptotic response, mediated by HPV-derived protein E6 [28].

Ras signaling and NF-kB activation are key mediators of cell signal transduction pathways, differentiation, and apoptosis [29]. In one study, Ras signal transduction pathway in association with NF-kB inhibition was sufficient to induce normal human epidermis to transform into tumoral tissue that retained fundamental features of SCC [30].

Haider et al. [31] established that there is a unique gene expression signature of cSCC in comparison to benign epithelial hyperplasia. Specifically, cSCC is characterized by an increase in the WNT receptor frizzled homolog 6 (FZD6) and prostaglandin-metabolizing enzyme hydroxyprostaglandin dehydrogenase, as well as an upregulation of matrix metalloproteinases 1, 10, and 13 (MMP1, MMP10, MMP13), cathepsin, and cystatin. IL-24 drives expression of MMP-7 at the leading edge of SCC which may contribute to its ability to invade [32]. Interleukin 22 and its receptor drive catastrophic behavior in transplant-associated SCC. Blocking IL-22 directly or downstream via JAK inhibitor leads to decreased tumor burden in model systems. The lack of potential deleterious effects on allografts supports consideration of JAK inhibitors as a potential therapeutic modality for catastrophic SCC in transplant recipients [33–35]. Recently, it has been established that MAGEA3 gene may be a useful biomarker in aggressive cSCC, portending high risk and poor prognosis, and may serve as a successful target for future immunotherapy [36].

Notch pathway signaling regulates cell survival, differentiation, and proliferation in development [37]. The transmembrane receptor Notch1 functions as a tumor suppressor in keratinocytes [38]. In mice, deletion of the Notch1 gene results in extensive epidermal hyperplasia and spontaneous development of BCC. Additionally, pan-inhibition of Notch signaling in the epidermis leads to the spontaneous development of both SCC and actinic keratosis [39].

Catastrophic cutaneous carcinomatosis has been defined as the development of greater than ten distinct non-melanoma skin cancers among organ transplant recipients in 1 year [4]. This likely represents a “perfect storm” phenomenon whereby long-term actinic damage provides initial “hits” of DNA damage, compounded by HPV infection and further ultraviolet exposure, leading to extensive field disease with innumerable lesions in many immunosuppressed patients. Atypical cells avoid apoptosis by means of HPV E6-mediated inhibition of p53. Malignant transformation may be driven in part by RAS and extensive proliferation via the Notch signaling pathway. Finally, the matrix metalloproteinase expression profile suggests facilitated passage through an already weakened basement membrane. A crucial direct carcinogenic hit is likely provided by the otherwise lifesaving and organ-sparing immunosuppressive agents [4], discussed in the following section.

Immunosuppression and Skin Cancer

The mainstay in the prevention of organ transplant rejection are immunosuppressive medications. Unfortunately, however, these immunosuppressive regimens are thought to have a large impact on both the increased incidence and aggressive nature of skin cancer in this population [26]. In addition to direct carcinogenic effects, these immunosuppressive drugs are thought to impair immune surveillance, leading to failure to recognize and destroy precancerous cells [26]. We will briefly review the mechanism of action of some classic immunosuppressive drugs and describe their potential role in the development of skin cancer.

Azathioprine

Azathioprine is a purine synthesis inhibitor, metabolized in the blood to 6-mercaptopurine, which is then converted to 6-thioguanine by hypoxanthine-guanosine phosphoribosyltransferase (HGPRT). These thioguanines have been found in elevated concentrations in erythrocytes of renal transplant recipients with skin cancer, which supports the association of increased incidence of skin cancer with higher doses of azathioprine [40, 41]. Additionally, azathioprine and UVA light have demonstrated synergism in the promotion of oxidative DNA damage and mutagenesis [42]. This conglomerate of data suggests that patients with extensive actinic damage on azathioprine may be at elevated risk for skin cancer, principally cSCC.

Cyclosporine

Cyclosporine (CsA) is an inhibitor of calcineurin, a phosphatase enzyme critical for the production of interleukin-2 (IL-2) in T lymphocytes [43]. CsA has demonstrated resistance to photo-induced apoptosis in human keratinocytes and additionally promotes the production of TGF-beta, a key growth factor furthering tumor growth and invasion [44–46]. Recent studies suggest that CsA use is associated with catastrophic SCC [34]. CsA enhances expression of IL-22R by SCC, and treatment with JAK inhibitor ruxolitinib decreased growth of CsA-induced tumors in nude mice [35].

Sirolimus

Sirolimus, also known as "rapamycin," inhibits the mammalian target of rapamycin complex 1 or mTORC1. While other immunosuppressive medication may promote skin cancer, studies have demonstrated that conversion to sirolimus reduces the risk of skin cancer [46–51]. Reduction of immunosuppression and conversion to sirolimus are further discussed in the management section below.

Voriconazole

Voriconazole is an agent commonly used to supplement the immunosuppressive regimen of organ transplant recipients in the prophylaxis or treatment of invasive fungal infection. In lung transplant recipients, it has been established that voriconazole serves as an independent risk factor for skin cancer, although the mechanism by which this occurs is unknown [52]. As such, in 2010, the product label was altered to recommend voriconazole be discontinued upon development of cSCC or melanoma [52].

Presentation and Natural History

Primary cSCC in Organ Transplant Patients

Primary cSCC commonly presents as a red, scaly patch or plaque (Fig. 17.1). The differential diagnosis can include benign inflammatory dermatoses, such as eczema or psoriasis, as well as benign neoplasms, such as irritated

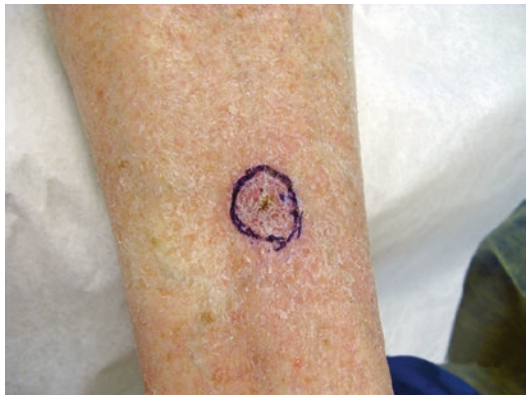

Fig. 17.1 Primary cutaneous SCC presenting as a scaly plaque

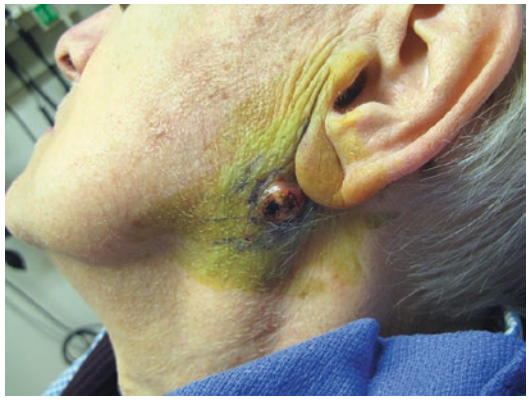

Fig. 17.2 Keratoacanthoma-like SCC presenting as a rapidly growing nodule in a transplant recipient

seborrheic keratoses or traumatized warts. Differentiation from precancerous actinic keratosis may be clinically challenging. Nodular appearing, KA-like cSCC (Fig. 17.2) may resemble a subcutaneous abscess early in its course; however, a lack of fluctuance, drainage, and punctum will help to distinguish these entities, and failure to resolve should prompt biopsy for diagnosis. In transplant patients, SCC is more often part of an overall cutaneous dysplasia (Fig. 17.3) than an isolated lesion. Although SOTRs can have discrete lesions they often develop SCC on a background of extensive can have field disease.

Full body exam is a must for the initial evaluation of all transplant recipients.

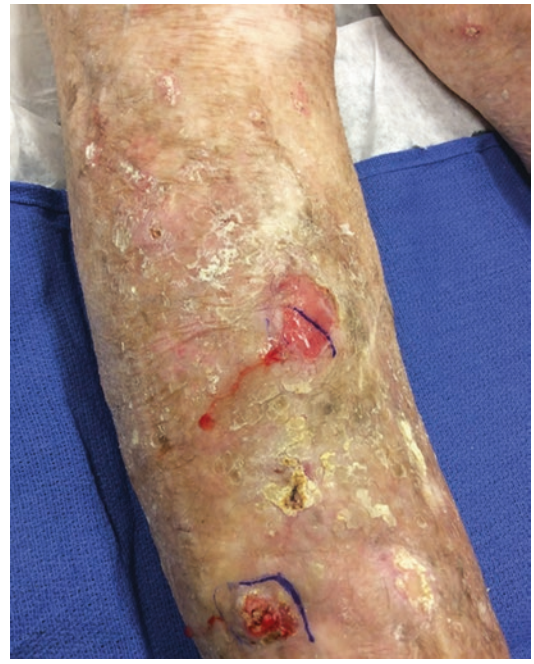

Fig. 17.3 *Cutaneous* dysplasia in a transplant recipient

Cutaneous squamous cell carcinoma tends to behave more aggressively in transplant recipients, with risk of local recurrence of 13.4% and risk of metastasis of up to 8% [6, 10, 53–55]. A recent retrospective review of 51 patients who underwent solid organ transplantation evaluated the risk factors associated with "aggressive squamous cell carcinoma" in this population, as defined by nodal or distant metastasis or death [56]. Although limited in subject number and significance statistics not performed, this study found certain tumoral characteristics at elevated levels in organ transplant patients who had "aggressive" cSCC, including preferential localization on the face (67%), poor differentiation (41%), median tumor diameter of 18 mm, median tumor depth of 6.2 mm, and perineural invasion (39%) [56]. Patients with "aggressive" cSCC in this population have a poor prognosis, with estimated 5-year overall survival rate of 23–35% and disease-specific survival rate of 30.5–50% [56, 57].

Risk stratification of individual cSCCs is paramount when managing patients with a multitude of lesions. A risk stratification algorithm was developed by the International Transplant

Skin Cancer Collaborative [58]. Characteristics of cSCC at highest risk for local invasion, metastasis, or recurrence include the following: multiple cSCCs; size; indistinct borders clinically; rapid growth; ulceration; location on the head and neck (especially the ear and lip) or within a scar, chronically inflamed area, or at the site of prior radiation therapy; recurrent after seemingly adequate treatment; presence of satellite lesions; and certain high-risk histologic features (Table 17.1). Perineurally invasive cSCC on the ear of liver transplant recipient is shown in Fig. 17.4. Lower-risk lesions include actinic keratoses and SCC in situ located on the trunk and extremities.

Table 17.1 Characteristics of high-risk cSCC in solid organ transplant recipients [55, 58, 59]

Characteristic	
Multiple cSCCs	
Size	> 0.6 cm ("mask" areas of face, genitalia, hands, feet) > 1.0 cm (scalp, forehead, cheeks, neck) > 2.0 cm (trunk and extremities)
Indistinct borders clinically	
Rapid growth	
Ulceration	
Location	Ear, lip, scalp, midface, genitalia, or digits Within prior scar, chronically inflamed area, or the site of previous radiation therapy
Recurrent after seemingly adequate treatment	
Presence of satellite lesions	
High-risk histologic features	Extension to subcutaneous fat Perineural invasion Perivascular invasion Poor differentiation

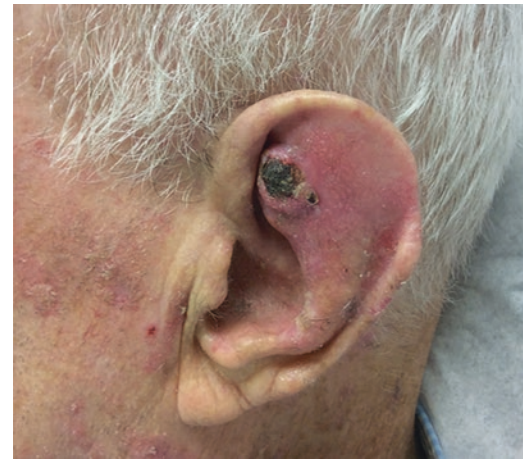

Fig. 17.4 Perineurally invasive SCC in a high-risk location

Field Cancerization

Field cancerization, or extensive areas of actinic damage with numerous keratotic lesions including actinic keratoses, represents a field of tissue with malignant potential when exposed to persistent carcinogenic insult and at high risk for the development of cutaneous malignancy [60–62]. Extensive field disease is common in transplant recipients with fair skin and history of chronic sun exposure. Oftentimes, it is difficult to determine where one lesion ends and the next begins in the background of keratinocyte dysplasia [63]. The authors have observed this phenomenon on the head, neck, trunk, and extremities (Fig. 17.5). Patients with severe field disease require frequent total body skin examination and multimodal therapy with topical agents, destruction, excision, and photodynamic therapy (PDT); additionally, a suppressive regimen should be considered with topical and or oral retinoids, discussed below [64].

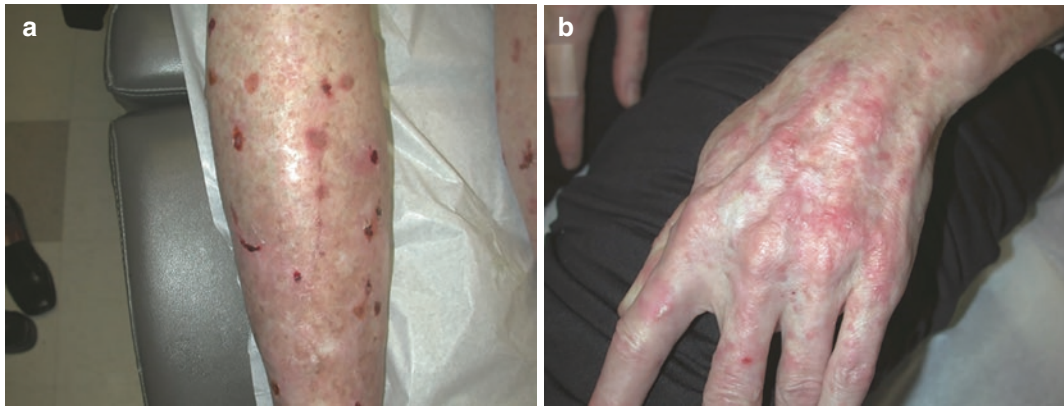

Fig. 17.5 (**a**) Cutaneous dysplasia in a transplant recipient. (**b**) Cutaneous dysplasia in a transplant recipient manifesting as "transplant hand"

In-transit Metastasis

In-transit metastasis has been previously defined in the literature as the occurrence of cSCC within the dermis or subcutaneous tissue at a location between, and clinically distinct from, the site of primary tumor and the local nodal basin [54, 65, 66]. Clinically, these present as subcutaneous or dermal papules, usually lacking an epidermal component, which are not contiguous to the site of the primary or recurrent tumor (Fig. 17.6). Ma et al. have proposed diagnostic criteria for in-transit metastasis requiring clinicopathological correlation in order to differentiate from local recurrence or perineural spread [66]. Clinically, the in-transit metastasis should be distinct from scars of previous treatment, occurring as a foci between the initial tumor and potential draining lymph nodes [66]. Histologically, the tumor should not be of epidermal origin nor should it lie entirely in perineural locations, it should be distinct from scars of previous treatment, and it should at least focally resemble the primary tumor histologically [66].

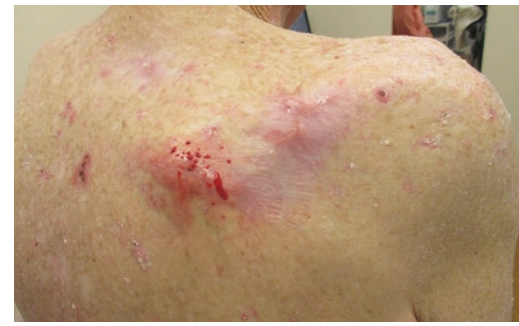

Fig. 17.6 In-transit metastatic SCC presenting as a nodule without epidermal change distal to a previously treated site and anesthetized prior to biopsy

The initial case series to date of in-transit metastasis in organ transplant recipients found in-transit metastases to have increased morbidity and mortality in this population [65]. At a mean follow-up of 2 years, 33% of transplant recipients with in-transit metastasis (5/15) had no evidence of disease, compared with 80% of non-transplant patients (4/5) [65]. In-transit metastases, whether occurring in organ transplant recipients or immunocompetent individuals, appear to arise from higher-risk primary tumors [65, 66].

Nodal Metastasis

Among all-comers, nodal metastases occur in as many as 2–4% of cutaneous SCC and present as palpable lymph nodes [67–70]. Risk factors for nodal and distant metastases in organ transplant recipients include large size, perineural invasion, location on the non-glabrous lip or ear, poor differentiation, and invasion to subcutaneous fat, as per Rowe et al. [55]. Additionally, immunosuppression following solid organ transplantation is a crucial risk factor for metastasis of cutaneous SCC in this population. History of in-transit metastasis is associated with increased nodal metastases [65]. Interestingly, lymph node metastases are more common than distant metastases from cSCC. Lymph node metastases are more frequent cause of death from SCC.

Distant Metastasis

Distant metastasis of cSCC occurs by hematogenous spread to the bone, brain, lung, and liver. Organ transplant recipients with distant metastasis have a poor prognosis. A retrospective review of 68 organ transplant recipients for the International Transplant Skin Cancer Collaborative found the incidence of relapse to be 29% at 1 year after metastasis, and the 3-year disease-specific survival rate was 56% [54].

Basal Cell Carcinoma

The clinical presentation of BCC in both immunosuppressed and immunocompetent patients is similar. BCC typically presents as a shiny, pearly papule that is often ulcerated (nodular BCC) and may have pigmentation (pigmented BCC), scar-like plaque (morpheaform BCC), or most commonly a well-circumscribed erythematous patch or thin plaque on the trunk or extremities (superficial BCC) (Fig. 17.7). Fair-skinned patients, or those of Fitzpatrick skin types I–III, have increased incidence of BCCs. BCCs in organ transplant patients, unlike SCC, have not demonstrated a more aggressive nature than those seen in immunocompetent patients [71]. The authors recommend a low threshold for biopsy for potential basal cell carcinomas in these immunosuppressed patients.

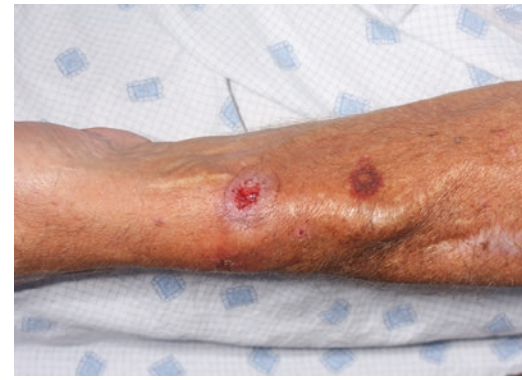

Fig. 17.7 Basal cell carcinoma over an AV fistula in the arm of a kidney transplant recipient. Photograph courtesy of Deborah F. MacFarlane, M.D.

Melanoma

Although there is only moderate increase in incidence in melanoma among organ transplant recipients compared to the general population, mortality is much greater [72]. The lesion clinically presents similarly, as an irregularly pigmented macule, patch, or papule. The appearance of pigmented lesions or change in a previously existing pigmented lesion may signal early melanoma. The authors maintain a low threshold for biopsy of new or changing pigmented lesions in transplant recipients.

Management of Cutaneous Squamous Cell Carcinoma

The management of cSCC in transplant recipients should be based on risk stratification, as discussed in the previous section.

Actinic Keratosis and Squamous Cell Carcinoma In Situ

Lower-risk AKs should be treated with topical agents, such as 5-fluorouracil (5-FU), imiquimod, diclofenac, and ingenol mebutate as discussed below, or by destructive methods most commonly liquid nitrogen cryotherapy. AKs should be treated early on, given the increased risk of swift progression to cSCC in this population [73, 74]. SCCIS should be treated with electrodesiccation and curettage (ED&C), surgical excision with postoperative margin assessment, or Mohs micrographic surgery (based on size and location) [75]. The off-label usage of 5-FU may also be considered in the treatment of SCCIS.

Management of Field Cancerization

As previously discussed, extensive field disease is common in organ transplant recipients with fair skin and history of significant UV exposure. Patients with severe field disease require frequent total body skin examination and multimodal therapy. Topical therapy in addition to destructive measures may be employed initially. In cases of extensive field disease unresponsive to topicals, or in the case of multiple, eruptive, invasive cancers, photodynamic therapy (PDT) may be effective. Additionally, in this population, chemoprophylaxis with oral retinoids, capecitabine, and nicotinamide, as well as reduction or change of immunosuppressive regimen, should be considered. A recent survey of the International Transplant Skin Cancer Center Collaborative found that the most common prophylactic therapy prescribed in this population was 5-FU, followed by PDT, acitretin, and imiquimod, with 27% of transplant recipients receiving more than one intervention [76].

The treatment modalities used in combination for extensive field disease are discussed in detail below.

Topical 5-Fluorouracil (5-FU)

5-FU is a competitive inhibitor of thymidylate synthase, a critical enzyme in the biosynthetic pathway of pyrimidines in DNA. Uptake of 5-FU in proliferating keratinocytes causes termination of DNA synthesis resulting in cell death. Topical 5-FU is considered to be a safe and effective treatment for AKs. A small case series of eight kidney transplant recipients in Australia found that when 5-FU 5% cream was applied twice daily to AKs on the face for 3 weeks, there was a mean AK clearance rate of 98% at 8 weeks and 79% at 12 months, with minimal adverse events including local erythema, itch, and flaking [77].

In the non-transplant literature, there is evidence for the use of a shorter regimen of combination therapy of topical 5-FU with calcipotriol, a vitamin D analog that when used topically induces thymic stromal lymphopoietin, an epithelium-derived cytokine thought to contribute to antitumor immunity in the skin with defective barrier [78]. A recent randomized, double-blind trial performed in 131 patients with actinic keratoses compared a 4-day regimen of twice daily application of topical 5-FU plus calcipotriol (5-FU 5% cream was mixed with 0.005% calcipotriol ointment in a 1:1 weight ratio) to 5-FU plus vehicle (Vaseline) [78]. They found that by week 8, there had been a mean reduction in facial AKs of 87.8% in the test group versus 26.3% among controls ($P < 0.0001$) [78]. The authors concluded that there is a synergistic effect of this combination therapy in the treatment of AKs via activation of CD4+ T-cell-mediated immunity.

Imiquimod

Imiquimod is an immune response modifier, approved by the Food and Drug Administration (FDA) for the treatment of actinic keratoses, as well as superficial basal cell carcinomas and genital warts. It binds to toll-like receptors (TLRs) TLR7 and TLR8 and may enhance release of interferon-α (IFN-α) [79].

The safety of imiquimod has previously been questioned due to theoretical risk of immune stimulation; however multiple studies report the use of topical imiquimod in the setting of organ transplant recipients receiving immunosuppressive drugs with no evidence of associated graft rejection [80].

A multicenter, randomized, placebo-controlled study of 43 transplant recipients randomized to either 5% imiquimod cream or placebo cream for 16 weeks demonstrated complete clearance of AKs in 62.1% (18/29) of the treatment group versus 0% (0/14) for vehicle alone [81]. This was achieved without impact on graft function. Common adverse effects include local erythema, itch, and erosion, while rare effects include flu-like symptoms and headache [82]. There was one case report of biopsy-confirmed acute tubular necrosis in a renal transplant recipient after the use of topical imiquimod [82]. Caution should be taken when applied to large areas due to cytokine release; therefore 5-FU is preferable for the treatment of field disease in this population [83].

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase-2 (COX-2). A case series of six transplant patients with numerous actinic keratoses treated with 3% diclofenac cream twice daily for 16 weeks found complete clearance of AKs in 50% (3/6) at the completion of 16 weeks of treatment [84]. Two patients demonstrated 75% reduction in AKs, and one patient demonstrated 30% reduction in AKs.

Photodynamic Therapy (PDT)

In PDT treatment, a photosensitizer such as 5-aminolevulinate (5-ALA) or methyl 5-aminolevulinate (MAL) is first applied topically to the lesion. Subsequent photoactivation by a red or blue light source results in the formation of reactive oxygen species culminating in cell death (Chap. 4). In one study, eight organ transplant recipients with actinic keratoses were randomized to treatment with topical 5-FU cream applied twice daily for 3 weeks or two cycles of MAL PDT 1 week apart [85]. PDT was found to be more effective than 5-FU in achieving complete resolution at 1, 3, and 6 months, with a mean lesional area reduction of 100% in PDT versus 79% in 5-FU-treated lesions. In another study, PDT was successfully used to treat AKs in kidney transplant recipients that had been previously unresponsive to conventional therapy, with a complete response of 71% after two treatment sessions [86]. Additionally, preliminary data in renal transplant patients demonstrate that PDT may be beneficial as a preventative measure in delaying the development of AKs — at 3-year follow-up, AKs were observed in 28% of patients in areas treated with PDT compared with 63% of patients in untreated areas [87]. Pulsed dye laser (PDL, 585–600 nm) is absorbed by 5-aminolevulinate and may provide an alternate source for treating individual lesions. Curettage can be performed with local anesthesia for thicker hyperkeratotic lesions prior to PDT.

Oral Retinoids

Retinoids are vitamin A analogues that have demonstrated utility in chemoprophylaxis [88]. Studies of low-dose acitretin usage in solid organ transplant patients have revealed reduction in the incidence of squamous cell carcinoma [89–91].

A 16-year retrospective study found that the usage of low-dose acitretin in organ transplant recipients significantly reduced the development of cSCC in the first 3 years of treatment, and this effect may be sustained for at least 8 years [91]. Side effects are generally well tolerated and commonly include xerosis, dry eyes and lips, and hair loss. The authors recommend discussing oral retinoid use with the primary transplant team prior to starting therapy. Oral retinoids are contraindicated in pregnancy. Baseline laboratory evalua-

tion and routine monitoring, including complete blood count, liver function tests, lipid panel, and creatinine, are indicated (see Chap. 21).

Thus, the authors prescribe acitretin for transplant recipients with extensive field disease, elevated incidence of primary cSCC (>5 annually), or metastatic disease. Multiple studies have found an increased frequency of cSCC after discontinuation; therefore, the authors recommend that this should be considered a lifelong therapy.

Capecitabine

Capecitabine is a carbamate derivative of 5-FU that is converted to its active form within tumor cells. Capecitabine has been used in SOTRs both in the setting of field cancerization [92] and in the treatment of advanced cSCC concomitantly with IFN-α [93]. A retrospective case series of 15 SOTRs with recurrent cSCC or BCC who were treated with low-dose oral capecitabine found decreased incidence rates of recurrent cSCC, BCC, and AKs, with tolerable adverse events [94]. A prospective cohort study of ten SOTRs who were treated with low-dose oral capecitabine found a significant decline in the incidence of cSCC during the first 12 months of treatment, as well as a reduction in AKs [92].

IFN-α enhances the uptake of capecitabine into tumor cells. A report of four patients with advanced cSCC treated with oral capecitabine and subcutaneous IFN-α saw complete remission in two patients and partial response in two patients [93]. Although highly rare, severe toxicity and even death may result if administered to patients with dihydropyrimidine dehydrogenase enzyme deficiency [94]. Fatal bone marrow suppression has been reported when administered with brivudine, a drug utilized in the treatment of herpes zoster [95]. Further studies of larger caliber are warranted to evaluate its potential safety and efficacy in the treatment of severe field disease in transplant patients. The authors recommend discussing the use of capecitabine with the primary transplant team and medical oncology team managing the patient.

Nicotinamide

Nicotinamide is an amide form of vitamin B_3 that contributes to repair of photodamaged DNA, currently undergoing studies for chemoprevention. Oral nicotinamide has demonstrated efficacy in the prevention of keratinocyte carcinoma in a phase III randomized trial of immunocompetent patients [96]. A smaller-scale phase II randomized trial failed to demonstrate significant results [97]. A case-control study of 38 transplant patients found a statistically significant reduction in both size of AKs and development of new AKs in the case group on oral nicotinamide [98]. The drug is well tolerated; however there are reports of liver failure at elevated doses above 3 g/day [99]. A phase III trial in transplant patients is warranted. Recommended dose is 500 mg twice daily.

Primary Invasive Cutaneous SCC

As in the immunocompetent patient, high-risk lesions are best treated with Mohs micrographic surgery (MMS). MMS offers the highest cure rates with maximal tissue conservation. In SOTR, if MMS or excision with intraoperative frozen section control is not possible, then excision with margins of at least 6–10 millimeters with postoperative margin assessment is recommended [58]. For those patients who are unable to tolerate surgical excision or if the tumor itself is inoperable, radiation therapy is the next best option for primary management [54, 58]. In the case of considerable perineural invasion or inability to achieve clear surgical margins, adjuvant radiation therapy should be considered [58]. Moderate-risk lesions, which include well-differentiated, smaller cSCCs, may be treated with standard excision with postoperative margin confirmation.

One strategy for patients with multiple primary, lower-risk SCCs is treatment by shave excision followed by electrodesiccation and curettage (ED&C). In this manner, multiple lesions can be treated in a single session under local anesthesia. Histological analysis of the

tangential excision specimen will help to determine whether additional treatment is necessary [58]. We tend to use Mohs surgery for higher-risk lesions and cycle various field therapies in attempt to achieve control of widespread cutaneous disease.

Metastatic Cutaneous SCC

Organ transplant recipients are predisposed to relapse via local recurrence or metastasis. In light of increased risk of metastasis in the organ transplant population, clinical follow-up is of paramount importance, including palpation of the draining lymph nodes in any such patient with a history of cutaneous SCC.

Palpation of previously treated areas is crucial for evaluation for in-transit metastases from primary cutaneous SCC since these may present as subcutaneous papules with little or no epidermal change.

Consider wide-field irradiation (3–5 cm) following removal with clear margins of in-transit metastases or deep marginal recurrences from SCC by Mohs surgery or standard excision. Uncomplicated peripheral marginal recurrence is best managed by Mohs surgery. Patients with palpable lymphadenopathy should be further evaluated with magnetic resonance imaging (MRI) to assess the extent of involvement, a positron emission tomography (PET) scan or PET-computed tomography (PET-CT) scan to assess for distant metastasis, and fine needle aspiration (FNA) for pathologic confirmation. Imaging of the primary tumor as well as draining nodal basins may also be considered in tumors of high risk without palpable lymphadenopathy, based on staging (Brigham and Women's Hospital (BWH) T2b and T3) [100]. At this time, there are no consensus guidelines for the use of sentinel lymph node biopsy (SLNB) for the routine evaluation of nodal metastasis in either the organ transplant or general population with need for further studies. It has been suggested that SLNB may be indicated in patients with tumors meeting certain staging criteria, namely, BWH Stage T2b or American Joint Committee on Cancer (AJCC) T2 tumors greater than 2 cm diameter [101]. When distant organ involvement is suspected, patients should be evaluated by appropriate screening and imaging studies, including PET-CT, MRI, and CT scan.

Patients with in-transit metastases are best served by surgical removal followed by radiation. We have successfully treated in-transit metastatic SCC with the combination of Mohs surgery and RT. Following definitive therapy, patients can be considered for oral retinoids and evaluated for reduction of immunosuppression or replacement with sirolimus. Patients with nodal metastases should be evaluated for neck dissection followed by XRT. Patients with distant metastases should be referred to an oncologist for evaluation for systemic chemotherapy. Platinum-based chemotherapy as monotherapy or in combination with 5-FU has been used in patients with cSCC [102, 103] and may be considered for transplant recipients with distant metastases. For locally advanced cSCC as well as distant metastatic disease, targeted therapy (i.e., cetuximab) and immune modulators (i.e., checkpoint inhibitors) have demonstrated promising results in the general population, discussed in detail below [83]. We were successful in treating AJCC T 3 SCC in an immune-competent patient with pembrolizumab [104]. In organ transplant recipients, data regarding the usage of these agents is limited, and caution is advised.

Modification of Immunosuppression

In the case of high-risk skin cancer, multiple skin cancers, or metastatic disease, one may consider either reduction of immunosuppressive dose or alterations in immunosuppressive regimens. An expert consensus panel

organized by the International Transplant Skin Cancer Collaborative and Skin Care for Organ Transplant Patients Europe Reduction of Immunosuppression Task Force developed guidelines for the consideration of reduction of immunosuppression for SOTR with skin cancer [105]. For patients developing multiple skin cancers annually or with individual skin cancers of high risk, mild reduction of immunosuppression was recommended. For patients with more than 25 skin cancers annually or with skin cancers with a 3-year mortality risk of 10%, moderate reduction of immunosuppression was recommended. In the case of life-threatening skin cancer, severe reduction is reasonable.

Switching agents from calcineurin inhibitors to sirolimus, a mammalian target of rapamycin (mTOR) inhibitor with antiproliferative effects, has been associated with decreased frequency and severity of cSCC [106]. Randomized controlled trials of renal transplant recipients have demonstrated a statistically significant reduction in skin cancer upon conversion to sirolimus [48, 107], as well as when sirolimus is used as first-time treatment [108]. One study found that patients who had been switched from calcineurin inhibitor to sirolimus had a statistically significantly longer time to development of cSCC than the group that was maintained on a calcineurin inhibitor, with new cSCC developing in 22% on sirolimus (median onset 15 months) vs 39% on calcineurin inhibitor (median onset 7 months) [48]. One retrospective cohort study of 329 organ transplant recipients demonstrated that conversion to sirolimus after initial posttransplant skin cancer leads to significant reduction in the risk of subsequent skin cancer among renal transplant recipients [50]. This reduction of subsequent skin cancer was also observed in nonrenal organ transplant recipients, albeit without statistical significance [50].

However, adverse events have been reported in the majority of sirolimus-treated organ transplant patients. One study found that 94% of renal transplant patients receiving sirolimus developed adverse events, with the most common being edema, acne-like lesions, aphthous ulcers, proteinuria, diarrhea, dyslipidemia, pneumonitis, anemia, cough, and arthralgia (listed in order of frequency) [48]. The most commonly reported serious adverse event was pneumonitis [48]. Gradual change to sirolimus and lower doses have been reported to have fewer adverse events.

Reduced immunosuppression carries the risk of graft rejection, and conversion of therapy to sirolimus is associated with increased adverse events; therefore, decisions regarding alteration of therapy should be made with a multidisciplinary team of transplant physicians and dermatologists.

Cetuximab

Cetuximab is an epidermal growth factor receptor (EGFR) antagonist that is FDA approved for the treatment of squamous cell carcinoma of the head and neck and colorectal carcinoma. However, it has also been used off-label for cSCC. Cetuximab has demonstrated response as a first-line single-agent therapy for unresectable cSCC in a phase II trial of 36 patients, with a 69% disease control rate at 6 weeks [109]. More recently, a pilot study was performed in 20 patients with inoperable cSCC using cetuximab monotherapy or cetuximab plus chemotherapy or radiation therapy [110]. Four of the 20 patients were recipients of solid organ transplantation. Among the entire cohort, there was a 47% disease response rate at 2 months (80% for cetuximab plus radiation therapy, 37.5% for cetuximab plus carboplatin, 33% for cetuximab single-agent therapy). However, remission is infrequently sustained [83]. Cetuximab is generally well tolerated, although it should be used with extreme caution in lung transplant patients in light of case reports of fatal diffuse alveolar damage [111].

Immune Checkpoint Inhibitors

The immune checkpoint inhibitors are agents that inhibit programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 (CTLA-4). This

inhibition promotes activation of T cells, thus stimulating an antitumoral response. However, these activated T cells are not limited in their activation against tumor cells but also are stimulated against the foreign donor allograft antigens [112]. Additionally, a host of autoimmune-related adverse effects may occur secondary to removal of self-protective T-cell inhibition [113, 114]. PD-1 inhibitor therapy has been associated with acute graft rejection in the setting of renal transplantation [115–117], although CTLA-4 inhibitors have been used in renal transplant patients without rejection [118]. However, one case report demonstrated that the combination of glucocorticoid and sirolimus administered preemptively to PD-1 inhibitor therapy may have prevented the renal transplant rejection [119].

The PD-1/PD-L1 blockade has demonstrated utility in the treatment of high-risk and metastatic cSCC. One study of 38 cSCC biopsy specimens found increased expression of PD-1 and its ligands (PD-L1 and PD-L2), especially so in cSCC with perineural invasion, BWH Stage T2B and T3, and organ transplant-associated cSCC [104]. A retrospective review of 40 primary and 5 metastatic cSCCs found the expression of PD-L1 to be positively correlated with larger diameter, increased thickness, higher histological grade of tumor, and elevated risk of metastatic disease [120]. In a recent phase I study of expansion cohorts of patients with locally advanced or metastatic cSCC as well as phase II metastatic disease cohort, the PD-1 inhibitor cemiplimab demonstrated a response rate in roughly half of the patients [121]. Then in September 2018, cemiplimab was approved by the FDA for the treatment of metastatic or locally advanced cSCC in patients who are ineligible for treatment with either surgery or radiation therapy [53]. Although there is great anticipation surrounding the use of the immune therapy in advanced cSCC, this should be administered with caution in the transplant population due to the delicate balance of immune system activation, both antitumoral and anti-graft. In most cases, one would expect the possibility of graft loss. Therefore, consideration should be reserved for life-threatening cancers, and use should be approached with extreme caution.

Management of Basal Cell Cancer in Transplant Recipients

The management of BCC in organ transplant patients parallels management in the immunocompetent. Superficial lesions on the trunk may be treated by ED&C; this is especially useful for patients with multiple lesions. Mohs surgery should be considered for SOTR with primary superficial BCC in medium- or high-risk location, primary nodular BCC in medium- or high-risk location, recurrent BCC, or BCC with aggressive histology [75]. Of note, high-risk locations include mask areas of face, genitalia, hands, feet, nail units, ankles, and nipples/areolae [75]. Medium-risk locations include cheeks, forehead, scalp, neck, jawline, and pretibial skin [75].

Vismodegib

In patients with locally advanced BCC who are not candidates for surgery or radiation therapy, or in patients with metastatic BCC, vismodegib, a hedgehog pathway inhibitor, may be considered. Cusack et al, report a case of a heart transplant patieny with metatstaic BCC who was sucessfully treated with vismodegob without graft failure [122].

Management of Melanoma in Transplant Recipients

Management of melanoma in organ transplant recipients is similar to management in immunocompetent patients. Excision with appropriate clear margins based on NCCN guidelines is the treatment of choice for melanoma in transplant recipients (Chap. 15). The 2016 NCCN guidelines recommend that SLNB should be offered to patients with MM of Breslow depth >1 mm with clinically negative lymphadenopathy, as well as for high-risk thin melanomas of Breslow depth 0.8 to 1 mm with either ulceration or mitoses [123]. SLNB should be consid-

ered in thin melanomas of Breslow depth 0.8 to 1 mm. Mohs surgery or staged excision may be helpful for lentigo maligna lesions on the head and neck located on a background of extensive actinic damage (Chap. 11). As with cSCC, reduction in immunosuppression or conversion to sirolimus may be considered, and it should be managed in concert with the transplant team [105, 124].

Dermatologic Screening, Prevention, and Follow-up in Transplant Recipients

Skin cancer is a clearly established significant cause of morbidity and mortality in solid organ transplant patients. With the increasing number of organ transplant recipients annually, skin cancer screening remains crucial. Regular total body skin examination by dermatologists, along with enhanced patient education, is vital in the reduction of morbidity and even mortality in these patients. Christenson et al. advocate the use of an organized, established clinic model to provide ongoing educational and preventive dermatologic care for organ transplant recipients [125]. Clowers-Webb et al. demonstrated that intensive education regarding skin cancer after organ transplantation has the ability to enhance compliance with sun-protective behavior [126].

Sun protective behavior and regular usage of sunscreen may prevent the development of additional AKs, invasive cSCC, and to a lesser degree BCC in organ transplant recipients [127]. Preventative measures including topical therapy, PDT, and oral chemoprevention should be individually assessed with every patient's case. High-risk patients often require long-term follow-up and treatment for their skin cancers by a multidisciplinary team that includes the dermatologist, Mohs surgeon, transplant physician, medical oncologist, and oncologic surgeon.

Summary

The increasing number of successful solid organ transplants, coupled with the ever-rising incidence of skin cancer in the United States, has set the stage for a dramatic increase in skin cancer incidence, particularly cSCC, in immunosuppressed organ transplant recipients. As organ transplant recipients have increased susceptibility to, morbidity from, and mortality from skin cancer, we recommend heightened efforts to educate these patients on photoprotection, chemoprevention, and early detection strategies. It is imperative that these patients are evaluated by dermatologists at the earliest point in their course, preferably prior to transplant surgery, and with routine follow-up afterward.

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Chapter 18
Imaging of Head and Neck Skin Cancer

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It is important for clinicians to understand and to take advantage of imaging techniques available for the management of skin cancers. There is little written in either skin cancer or radiology texts on the topic of imaging in head and neck skin cancers. This chapter is an attempt to find a common ground between the disciplines of surgery and radiology so that each may communicate more effectively with the other, thereby benefiting patient care and health-care costs.

We begin with an overview of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and positron-emission tomography/CT (PET/CT) in order to clarify their specific strengths and limitations. Our next objective is to provide guidance on the indications for pre- and postoperative imaging of skin cancer and on choosing the best modality for specific clinical indications. Figures will illustrate the imaging characteristics of certain skin cancers, and this will be accompanied by a review of the relevant literature. Discussion of high-resolution MRI and US imaging for diagnosis of skin cancers is beyond the scope of this chapter. For further discussion of the role of imaging in the management of nonmelanoma skin cancer and additional case series, the reader may consult supplementary literature by the authors [1, 2].

Anatomic Planes

In order to understand imaging modalities, one must first understand the anatomic planes involved. The axial plane is the plane parallel to the floor if the patient is standing up. By convention, the patient's left side is the right side of the image. If the patient were standing in front of a window, looking out, the coronal plane could be defined as parallel to the window. Sagittal planes are parallel to the plane that would divide the body into symmetric halves, as seen in Fig. 18.1.

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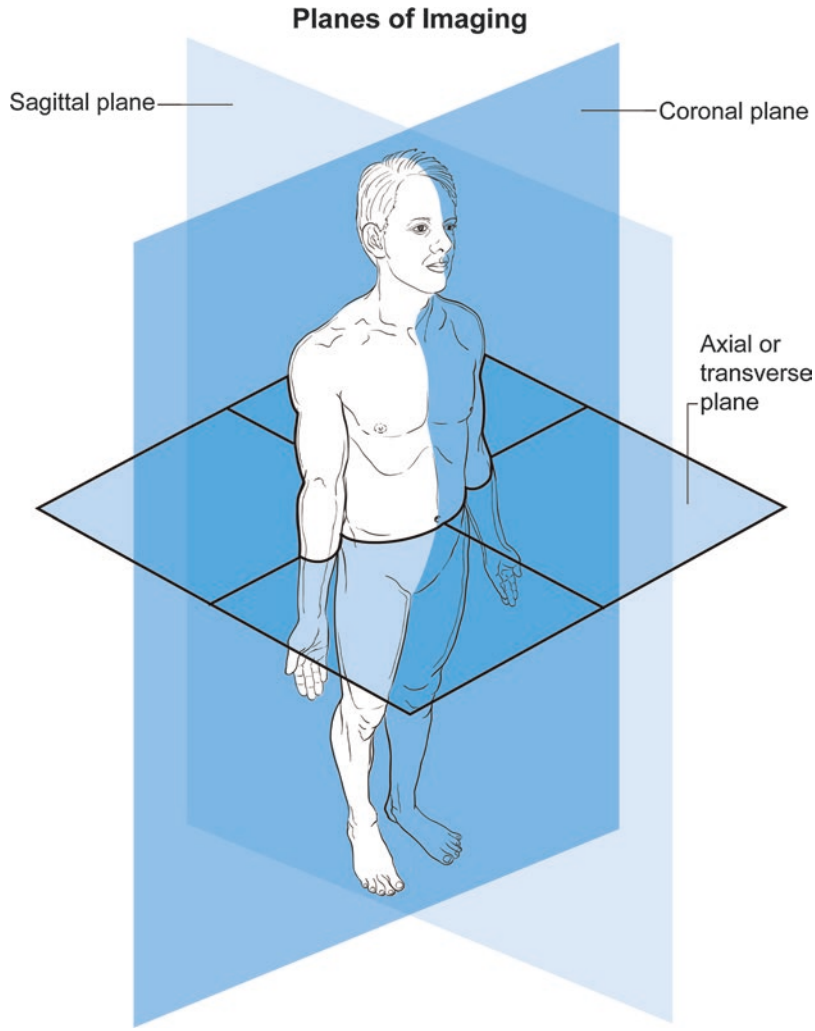

Fig. 18.1 Body planes (Illustration by Alice Y. Chen)

Imaging Techniques

Computerized Tomography

Computerized tomography (CT) is the workhorse of our imaging evaluation of skin cancers at MD Anderson Cancer Center (MDACC) because it delivers the best spatial resolution, and is also fast and relatively economical. This modality uses ionizing radiation (X-rays) to produce axial images. By convention, axial images are always shown as if the feet of the supine patient were closest to us—so the patient's left is on the right side of the image. The rotating gantry within a CT scanner houses the source of a beam of ionizing radiation, as well as multiple detectors that register the attenuation of the beam after it passes through the body. The beam is attenuated as it passes through tissue, proportional to the density of the tissue, resulting in relative values similar to that of X-ray images. For example, bone is the most attenuating (or white), water is next, then fat, and lastly air is the least attenuating (and appears black). The unit of attenuation is the Hounsfield unit (HU). Water is arbitrarily set at 0 HU; soft tissue measures 10–50 HU, and bone measures >1000 HU. Intravenous contrast enhancement increases the X-ray attenuation of blood, making vessels appear "whiter" and giving many types of

pathology a characteristic enhancement pattern. For CT examinations, iodinated contrast agents are used. Unless the scan is obtained specifically to evaluate bone, administration of intravenous contrast will always provide more information than a noncontrast scan.

The first human CT scan was a brain CT performed in 1971. Each scan resulted in two contiguous slices and each scan took 4.5–20 min to acquire and 20 min to process [3]. The technical advances of helical scanning and multiple detectors have since greatly increased the rapidity of CT studies and decreased the possible slice thickness. For example, high quality CT images at 1.25-mm slice thickness, from aortic arch to the vertex, may be obtained in 30 s. At this slice thickness, exquisite multi-planar reconstructions may be obtained.

Contraindications

Renal insufficiency and severe hypersensitivity are contraindications to iodinated contrast administration. Iodinated contrast can exacerbate renal insufficiency [4]. Mild hypersensitivity reactions can be avoided by pretreatment with anti-histamine and/or steroids. Consultation with the imaging facility is recommended.

During pregnancy, because of the risk of ionizing radiation to the development of the fetus, it is important to perform a thorough risk-benefit analysis when deciding whether to perform a CT study. The same is true for children generally, especially when the orbits or thyroid gland would be included in the scan range, as these tissues are especially radiosensitive. Ultrasound or MRI would generally be a safer choice.

Strengths and Limitations

CT provides excellent spatial resolution and excellent visualization of osseous structures. For example, the question of whether a scalp mass is eroding the adjacent bone is best answered by CT. CT is also a good modality for screening lymph nodes. Because of its spatial resolution, CT is a very good tool for surgical planning. The quality of the multi-planar reconstructions obtained depends on how thin the axial slices are. The new multi-detector CT scanners easily obtain 1.25-mm images, which result in exquisite reconstructions. From a cost viewpoint, CT is considerably faster than MRI and is also much less expensive.

Artifact from dental amalgam and metal, which is a problem with both CT and MRI, can be circumvented to some extent on CT by obtaining angled images. This is routinely done for patients with dental fillings, as seen in Fig. 18.2. CT can be less sensitive than MRI for bone metastases that are limited to the marrow, and is definitely less sensitive for perineural involvement or small brain metastases.

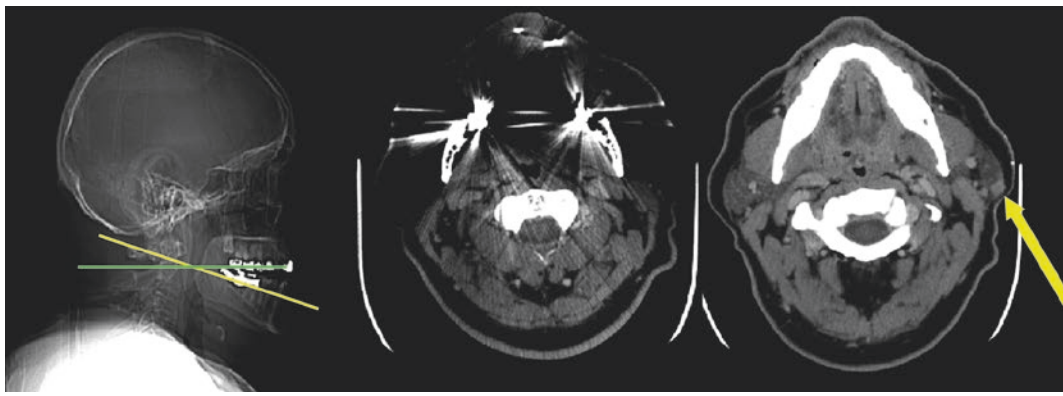

Fig. 18.2 This 70-year-old man had undergone Mohs surgery for a left preauricular squamous cell carcinoma 4 months prior to this CT. *Left*: The lateral scout image shows the planes of the axial images. *Middle*: The left parotid gland is completely obscured by streak artifact from dental fillings. *Right*: Angled image revealing a left intra-parotid nodal metastasis

Magnetic Resonance Imaging

In contrast to CT, magnetic resonance imaging uses no ionizing radiation. The first requirement for MRI is a strong standing magnetic field, typically 1.0–4.0 Tesla for diagnostic medical imaging. This magnetic field aligns the spins of hydrogen protons in tissue. A radiofrequency stimulator and antenna system are used to generate a radiofrequency gradient and superimposed radiofrequency pulses, causing a change in alignment. The prescribed set of pulses and signal acquisitions is described as a pulse sequence. The signal acquired from the re-alignment of the protons is processed using Fourier transformation into the MR image.

A large, and expanding, repertoire of pulse sequences allows excellent contrast resolution between different types of tissue, for example, skin and subcutaneous fat or gray matter and white matter in the brain. The pulse sequences we use most commonly for skin cancers are T1-weighted, T2-weighted, and T1-weighted with contrast and fat saturation. On T1-weighted images, materials such as fat, some blood products, some types of calcification, and the gadolinium-based contrast agents are bright. Gray matter and muscle are of intermediate signal intensity. Fluid has low signal intensity. Dense calcification, as seen in cortical bone, and blood vessels running perpendicular to the plane of the image generate very low or no signal. On T2-weighted images, water demonstrates the highest signal intensity, so cerebrospinal fluid and vitreous humor are very bright. In the case of fat suppression, a radiofrequency pulse is applied at exactly the right time to null the signal that would have been generated by fat. Fat suppression can be used with both T1 and T2 weighting. It is almost always used when gadolinium-based contrast is administered, so that enhancement can be distinguished from fat. Fat suppression is required for contrast-enhanced imaging of the orbits, as the orbital contents are surrounded by fat. See Fig. 18.3 for examples of T2-weighted; T1-weighted; and T1 gadolinium-enhanced, fat-suppressed images of the neck.

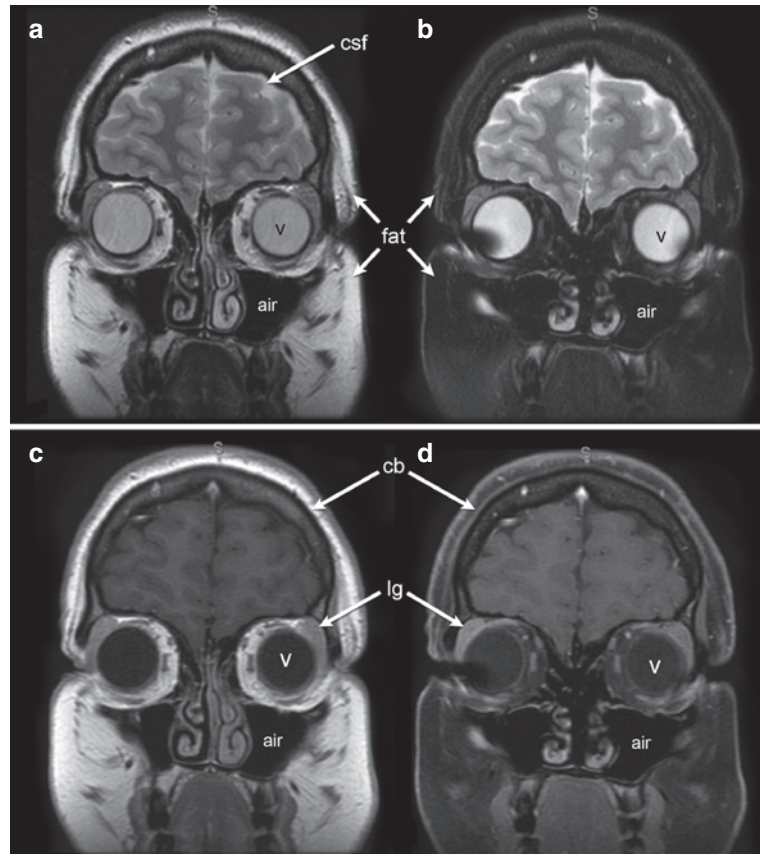

Fig. 18.3 Coronal MR sequences of the orbits illustrating varying signal intensity of fluid and tissues according to MR sequence. (**a**) noncontrast T2, (**a**) noncontrast T2 with fat saturation, (**a**) noncontrast T1, (**a**) gadolinium-enhanced T1 with fat saturation. Cerebrospinal fluid (csf) and vitreous humor (v) demonstrate high signal intensity on T2 (**a, b**) and dark on T1 (**c, d**). Fat has high signal intensity on both T2 (**a**) and T1 (**c**), but the signal intensity becomes low when fat saturation is applied (**b, d**). Air and cortical bones (cb) demonstrate no signal on all sequences. The lacrimal gland (lg) shows intermediate signal on T1 (**c**) and is moderately enhancing (slightly increased signal on (**d**) compared to (**c**)). The lacrimal gland is more easily distinguished from orbital fat when fat saturation is applied

Intravenous contrast administration is always preferred in cases of malignancy, as most neoplasms and nodal metastases will enhance. Most neoplasms will also demonstrate bright signal on T2-weighted images, due to their increased water content.

Contraindications

The use of certain Gd-based contrast agents (GBCA) is contraindicated in cases of severe renal insufficiency or acute renal failure, due to the risk of nephrogenic systemic fibrosis (NSF) [5]. NSF, originally called nephrogenic fibrosing dermopathy, consists of thickening and tightening of the skin, most often the lower extremities and occasionally the trunk. Fibrosis of other organs can include the heart, lungs, bone, and skeletal muscle. In 2019, a systematic review of the literature found 639 cases of biopsy proven, published reports of NSF; only 7 occurred after 2008 [6]. This is attributed to decreased use of the gadolinium-based contrast agents (GBCA) that were most associated with risk of NSF (linear or Class I agents), and increased use of agents that have a stronger molecular bond to gadolinium (macrocyclic or Class II agents). Consultation with the imaging facility is recommended in cases of impaired renal or hepatorenal function.

In 2017, the FDA issued a safety announcement to the effect that brain retention of gadolinium is known to occur, but no harmful effects have been associated with this retention. Retention or deposition of gadolinium is more closely associated with linear agents than macrocyclic agents and increases with number of GBCA administrations [7]. Consultation with the radiologist is helpful in identifying instances where contrast administration will be unnecessary. Generally, for evaluation of malignancy, contrast is indicated.

It is rare, but up to 0.7% of patients will have an allergic-type reaction to GBCA [4]. In severe cases, contrast should not be administered again, but many patients with a mild reaction can be switched to a different contrast agent. GBCA are known to cross the maternal blood–placenta barrier; however, no adverse effects have been identified in studies to date [4]. A careful risk-benefit analysis is warranted when considering MRI in pregnancy. Continuing to breastfeed after GBCA administration is considered safe [4].

Other contraindications to MRI include the presence of ferromagnetic foreign bodies and implants, and functioning stimulators such as pacemakers and defibrillators, transcutaneous electrical nerve stimulator (TENS) devices, and cochlear implants [8]. These can be dislodged or may malfunction in the presence of the strong magnetic field. Many patients with pacemakers and defibrillators may safely undergo MR scanning at 1.5T or lower field strength, after evaluation [9–11]. Many aneurysm clips and stents placed within the body are nonferromagnetic and considered safe. If a patient has a history of cerebral aneurysm clipping, this potential contraindication can be addressed in advance. The MR center may request, upon the patient's medical information release, detailed information from the operative note or neurosurgeon regarding the exact type of aneurysm clip and its compatibility with a strong magnetic field. Other medical devices are only safe after a certain time period following implantation such as 6 weeks for certain types of carotid stents.

Strengths and Limitations

The major strength of MRI is the excellent tissue contrast. GBCA enhancement of the nervous system, especially cranial and peripheral nerves and brain parenchymal masses, remains far superior to iodinated contrast enhancement as seen by CT. MRI incurs none of the potential risks of ionizing radiation. MRI is much more sensitive in diagnosis of perineural involvement than is CT [12]. Although CT is better for cortical bone, MRI is better for bone metastases because they involve the marrow before they involve the cortex.

However, MRI does have diagnostic limitations and is not always superior to CT, despite the more-than-double cost. MRI is not as sensitive to subtle changes in cortical bone, which may signal involvement by, for example, a scalp tumor. Lymph nodes are difficult to evaluate by MRI, mainly because their size is quite small with respect to MRI slice thickness, and size is the main criterion by which they can be evaluated using MRI. Spatial resolution is not as good as with CT. Despite using axial T2-weighted images with fat saturation techniques through the neck, the detection of cervical adenopathy is not as good as CT or US [13]. However, at

our institution, when the primary site is best evaluated by one modality, that same modality is used to screen for lymphadenopathy.

The long scan times, generally at least 30 min if contrast-enhanced sequences are performed, may result in enough patient motion to significantly degrade the images. Children may require sedation or even general anesthesia.

Ultrasound

Ultrasound (US), like MR, does not expose the patient to ionizing radiation. Frequencies higher than those we can hear are transmitted, and the time at which the reflection of the wave is received back is used to infer the location of the material that reflected the wave. The first diagnostic use of US was to distinguish solid tumors from benign cysts. This remains a primary function of ultrasound. Cysts are completely anechoic or "black" because the ultrasound waves are fully transmitted through the cyst without being reflected back to the probe. Solid tissue will reflect some or all of the waves back to the probe. As more waves are reflected, fewer waves are available to be transmitted to structures at a greater depth. Also, higher frequency waves have a decreased penetration but generate a higher resolution image. Thus, with ultrasound there is an inverse relationship between the penetration, or the depth of tissue that can be imaged, and the resolution of the images produced. Doppler ultrasound imaging is an ultrasound technique that allows characterization of vascular flow. The physical principle of Doppler shift of a waveform reflected by a moving target is used to analyze the velocity and direction of flowing blood or to detect small amounts of flowing blood.

Many tissues have a characteristic "echotexture" or pattern generated by ultrasound. For example, fat has small septations and is "echogenic" or bright. Muscle has many echogenic lines within it. Skin is typically hyperechoic. As mentioned previously, fluid-containing structures, including blood vessels, are black or anechoic. Calcified structures will also appear anechoic because all of the ultrasound waves will be reflected back to the probe. However, the edge of the calcification, where the ultrasound waves were reflected, will appear echogenic. By convention, images obtained with the probe perpendicular to the long axis of the body are labeled transverse, and those obtained with the probe parallel are labeled longitudinal. The patient's right will be on the right side of the image, as with CT.

Ultrasound is a very good choice for detection and biopsy of abnormal lymph nodes. Probably more nodal characteristics can be evaluated by ultrasound than by any other modality. A benign node typically is oval in shape, has an echogenic hilum, and demonstrates hilar blood flow, as seen in Figs. 18.4 and 18.5.

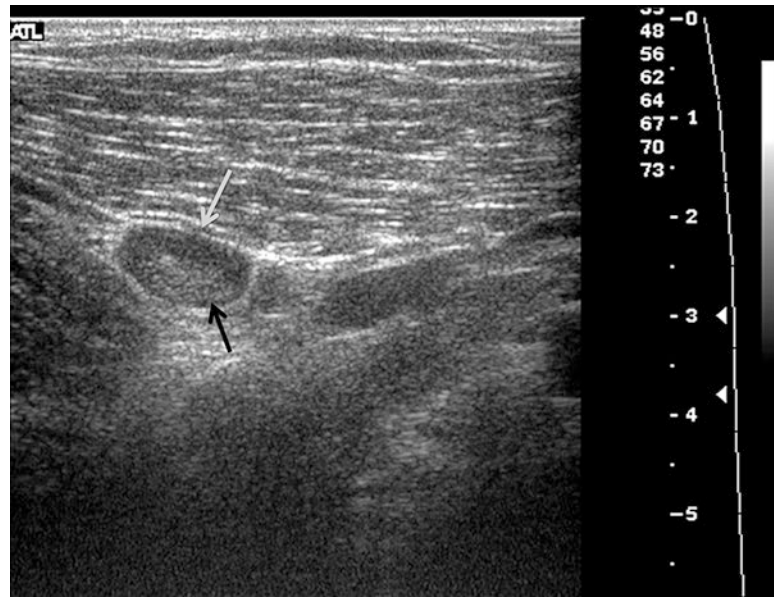

Fig. 18.4 Transverse ultrasound image of the axilla. The *top edge* shows the echogenic line of the dermis. Below this is subcutaneous fat, then the striations of muscle. The oval structure indicated by the white arrow is a normal lymph node seen in transverse (roughly axial) orientation. The *black arrow* demonstrates the echogenic hilum

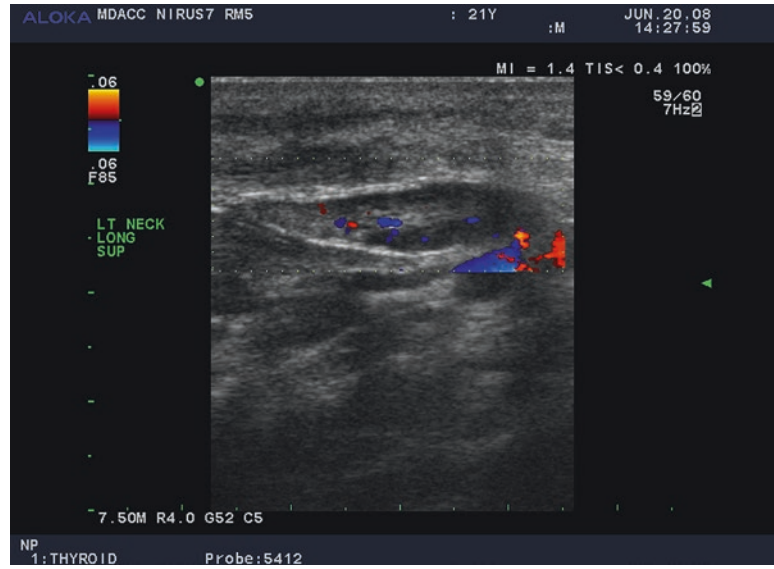

Fig. 18.5 Doppler ultrasound imaging of a normal cervical lymph node. The echogenic line at the *top* of the image represents the dermis. The lymph node demonstrates normal cortex with relatively decreased echogenicity compared to the hilum. The *red* and *blue* colors indicate normal blood flow in opposite directions, contained within the hilum

Size has traditionally been regarded as the most important nodal characteristic in CT and MRI. With ultrasound, measurements in three dimensions can be obtained very accurately, and an increase in node size over time is relatively straightforward to detect.

A rounded rather than oval shape, decreased echogenicity or increased "reticulated" echogenicity, the presence of necrosis, calcification, clustering, and extra-capsular spread can all be seen or assessed using grayscale ultrasound of suspicious lymph nodes (Figs. 18.6 and 18.7). Color or power Doppler ultrasound can further contribute to the detection of suspicious lymph nodes by identifying peripheral rather than normal hilar blood flow. Diffusely increased vascularity may also be suspicious. While no single ultrasound criterion for malignancy may be specific, the combination of a rounded hypoechoic lymph node with peripheral flow outside of the hilum would be highly suspicious for a nodal metastasis.

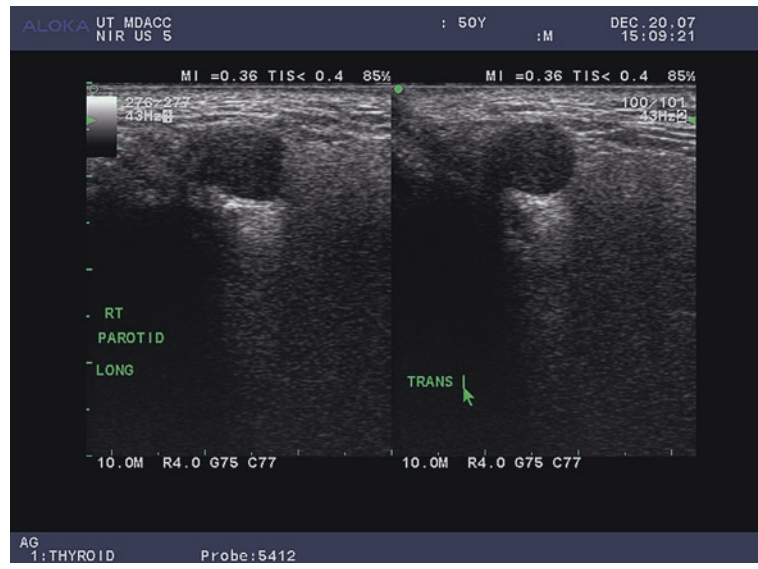

Fig. 18.6 A 50-year-old man was referred to MD Anderson Cancer Center after excision of a forehead Merkel cell carcinoma with positive deep margins. These transverse and longitudinal ultrasound images of the parotid gland were obtained as part of a staging evaluation. A 1 cm, round, hypoechoic intra-parotid lymph node is identified. Fine needle aspiration demonstrated metastatic Merkel cell carcinoma

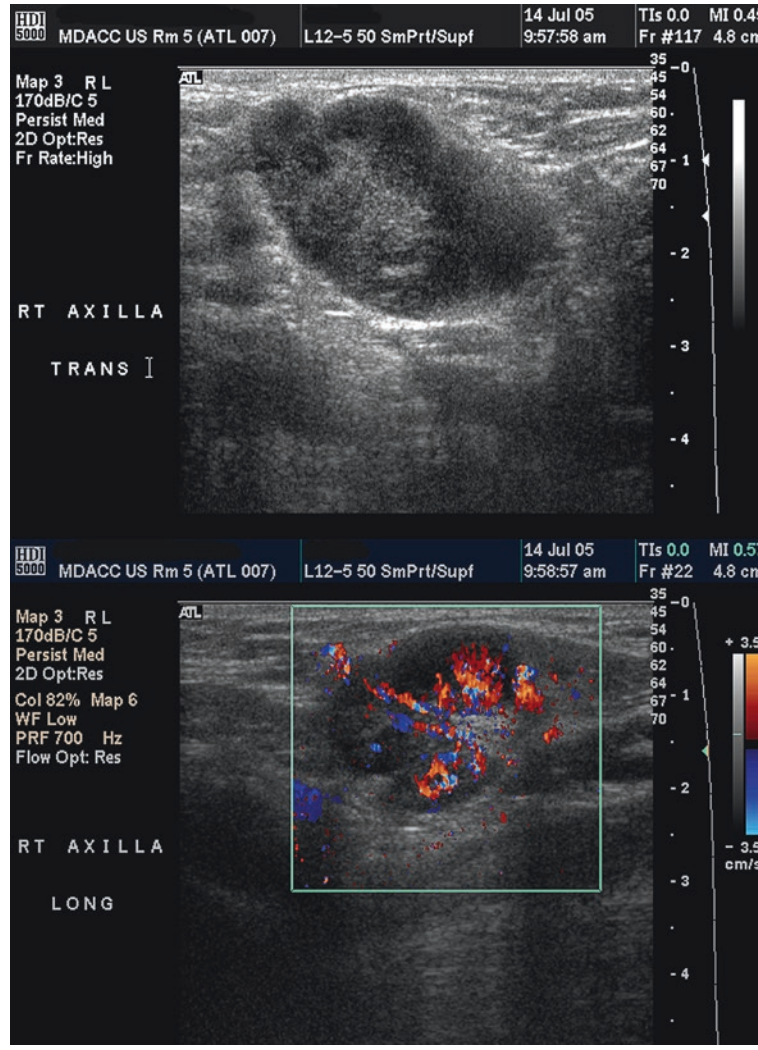

Fig. 18.7 This 68-year-old man with a history of chronic lymphocytic leukemia as well as multiple squamous cell skin cancers presented with a biopsy-proven left axillary metastasis. During chemotherapy, he developed new right axillary adenopathy. Prior to surgery to excise the metastasis, evaluation of the right axillary node was requested. Grayscale (*top*) and color Doppler (*bottom*) ultrasound images of an axillary lymph node are shown. On grayscale, the node is enlarged but retains its lobulated shape and echogenic hilum. The cortex demonstrates mildly increased echogenicity with a regular, reticular echotexture. Color Doppler does show increased flow, but the flow remains centered at the hilum. The imaging findings suggested leukemic involvement rather than nodal metastasis from the skin cancer, and this was confirmed by biopsy

Strengths and Limitations

An important advantage of US is that biopsy can be performed at the time of the study. Other technical advantages include mobility of the probe and machine, and the ability to scan in any plane. Patients who are unable to lie flat can be accommodated for scanning and biopsy.

As discussed above, lymph node evaluation is a strong advantage of ultrasound. While the normal neck may contain up to 300 lymph nodes, typically only 5–20 of the largest and/or most superficial nodes will be detected by ultrasound. The detection of abnormal lymph nodes is also significantly operator dependent and requires experience and care. Ultrasound images can be difficult to use for surgical planning, unless they have been helpfully annotated. Often, an additional CT and/or intraoperative ultrasound will be useful for the surgeon.

Dressings, wounds, and sutures may interfere with the ability to place the probe and coupling gel in the appropriate area. Poor

quality images may be obtained on obese patients, or if recent postoperative or postradiation changes are present.

Positron-Emission Tomography

Both positron-emission tomography (PET) and lymphoscintigraphy (discussed later) are considered nuclear medicine procedures. The strength of nuclear medicine is imaging structure *and* function. This is achieved by attaching a radionuclide, which can be imaged, to a molecule that can participate in a targeted physiologic process.

PET images begin with the intravenous administration of 18-fluoro-deoxyglucose (18-FDG), a molecule similar to glucose, which can be incorporated into the same metabolic pathways as glucose, and contains 18-Fluorine, a positron emitter that can be imaged. Malignancies that have a higher rate of cellular turnover will have increased 18-FDG activity on PET scans. Modern PET scanners are often combined with CT scanners in the same housing. This allows for the accurate fusion of CT images with PET images. In this way, both function and structure can be imaged. The fusion of PET to CT images has greatly improved the anatomic localization of 18-FDG avid foci [14].

The patient must fast for 4–6 h prior to an oncologic PET/CT. Plasma glucose levels are checked prior to scanning and must be within normal limits. After injection of 18-FDG, the patient must rest quietly for 1 h to allow distribution of the radiotracer. The scanning itself usually takes less than 30 min. Typically, scans are obtained from the base of the skull to the proximal thighs. For patients with, for example, melanoma of the toe, the entire lower extremity will also be scanned.

PET/CT has supplanted PET alone. With this technique, a CT scan is obtained at the same time at the PET scan, using the same equipment. Often, the CT component will be performed using a technique that results in less radiation dose but also slightly decreased spatial resolution compared to a routine CT scan, and usually will not include iodinated contrast administration. The information obtained by CT is used to process the PET information in order to display it to best advantage. This is called "attenuation correction." In addition, the CT images are fused to the PET images, allowing significantly improved localization of anatomic structures.

Benefits of PET/CT include accurate localization and staging, monitoring tumor response to therapy, and early detection of recurrence. Substantial research on PET/CT scanning in the staging of malignant melanoma and in predicting the response to treatment has found a significant benefit with the use of this modality [15].

A disadvantage is that locoregional nodal metastases can be difficult to visualize in comparison to the highly avid uptake at a primary site. Technically, lung metastases less than 1 cm are difficult to detect due to respiratory motion. Brain metastases can be difficult to detect due to the inherent FDG avidity of gray matter [15]. Infectious and inflammatory false positives are very common; for example, acne can be mistaken for a primary skin cancer.

Lymphoscintigraphy

In this nuclear medicine study, the ability of lymph nodes to trap colloidal particles is exploited. A colloidal material, for example, ultra-filtered sulfur colloid, is labeled with a radioisotope that can be imaged, such as Technetium-99m. When the 99m-Tc-sulfur colloid is injected adjacent to a primary site of tumor, the material is collected by the lymphatic system and follows the same drainage pattern as would the tumor cells. For skin cancers, the material is injected intradermally at the primary site. The 99m-Tc allows imaging of this drainage pattern, and also can be detected by gamma probe intraoperatively. Lymph nodes that are identified in this manner do not necessarily contain metastatic deposits; the imaging only serves to guide the sentinel lymph node biopsy process.

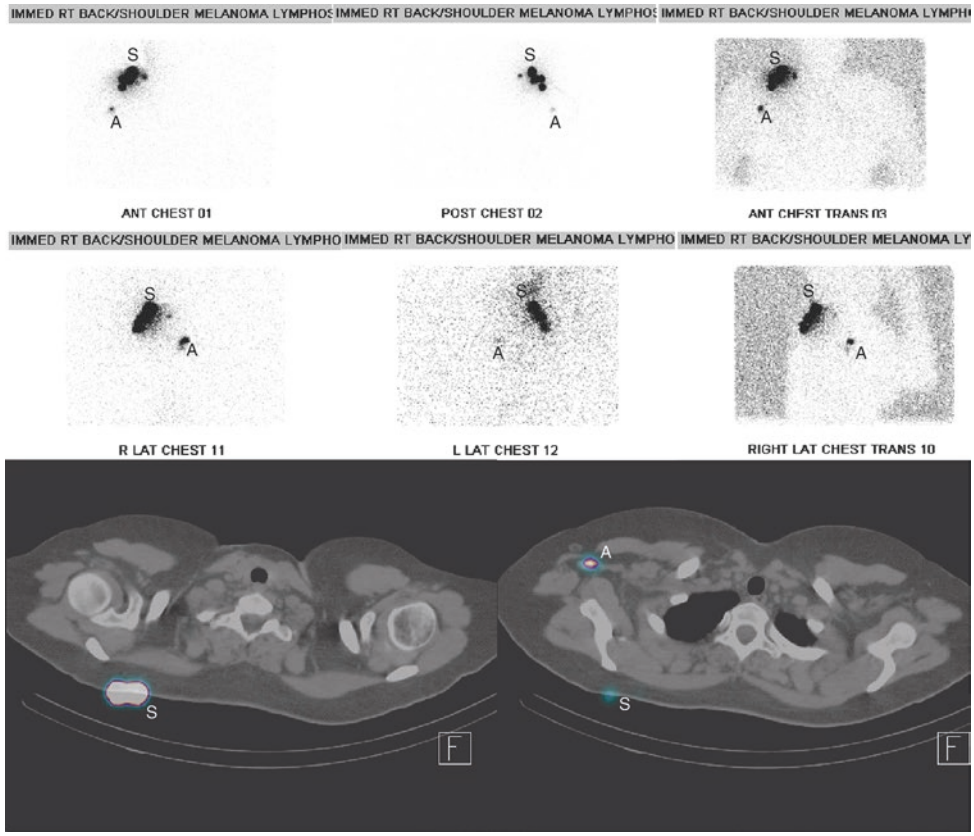

Fig. 18.8 A 36-year-old woman presented with a bleeding nodule on the right upper back. Excisional biopsy revealed a Clarks level IV melanoma, with 6.4-mm Breslow thickness. Wide local excision with sentinel lymph node biopsy was planned. Prior to surgery, lymphoscintigraphy with CT fusion was obtained. *Top row*: Anterior and posterior 2D images of the chest show a large lobulated focus of radiotracer activity at the primary site in the skin (S). Smaller adjacent foci likely represent sentinel lymph nodes. The most inferior node (A) may be an axillary or an anterior or posterior chest wall node. *Middle row*: Right and left lateral 2D images of the chest confirm that the most inferior focus of activity corresponds to a right axillary node. *Bottom*: CT images further localize the right axillary sentinel node and also confirm that all of the activity in the largest focus is in the skin rather than within nodes. At operation, the sentinel lymph nodes were negative for melanoma

Formerly, only transmission images were obtained for lymphoscintigraphy, resulting in "2D" images without cross-sections. Today, tomographic cross-sectional images can be obtained and fused with CT images [16] (Fig. 18.8). This aids in the preoperative differentiation of superficial from deeper nodes, for example, external jugular versus internal jugular nodal chains.

Strengths and Limitations

Obviously, this technique allows identification of the drainage pattern but does not indicate that the active node is actually malignant. Because head and neck drainage patterns can be variable, it offers a useful road map for the surgeon. When hybrid SPECT/CT is not available, intraoperative detection is crucial to correctly identify the sen-

tinel nodes. Optimally, the sentinel lymph node biopsy should be performed at the time of resection of the primary site [17].

Please see Table 18.1 for the exchange of information that may occur when speaking with your radiologist and Table 18.2 for suggested indications for imaging skin cancers.

Table 18.1 Speaking with your radiologist

1. What is the patient's primary malignancy and where is it located?
2. What anatomic structures would you like to include? Brain, face, neck, or sinuses?
3. What information are you interested in evaluating? Perineural spread? Skull base disease? Nodal involvement?
4. Are there any variables that may preclude certain exams? Is the patient claustrophobic? Do they have a pacemaker or other metallic foreign body?
5. Is there evidence of significant renal disease? If so, do they have a recent creatinine or calculated glomerular filtration rate (GFR)?
6. Is this a presurgical evaluation?
7. Could the radiologist correlate all the imaging modalities that have been used to assess the patient (i.e., PET/CT/MR/US)?

Table 18.2 Indications for imaging

1. Incidental perineural involvement found on biopsy
2. Clinical evidence of perineural invasion
3. Large malignancies in a nerve root distribution
4. Suspicion of bone or cartilage invasion
5. Not amenable to clinical inspection
6. Lacrimal duct involvement

Imaging Pathology

Basal Cell Carcinoma

Metastases from basal cell carcinoma (BCC) are rare, so imaging distant to the site of primary tumor is seldom necessary. Occasionally, imaging of the primary site is helpful in the assessment of nearby anatomic structures prior to surgical intervention. For example, an ulcerated basal cell cancer of the scalp may involve the skull and CT can determine whether or not cortical destruction has occurred. If perineural involvement was suspected, MRI would be the study of choice.

We have found imaging to be especially useful in cases of periorbital BCC as seen in the accompanying case illustration. Leibovitch et al. in 2005 recommended preoperative imaging for all recurrent periorbital BCC [18]. They reported 64 cases, 84% of which were recurrent and 56% of which were located at the medial canthus. Of the entire group, 21% had bony involvement seen on CT. In general, extensive orbital invasion necessitates orbital exenteration, while anterior orbital involvement alone may be treated with excision and possible radiation followed by serial MRI.

Illustrative Case 18.1

A 76-year-old man with a history of multiple basal cell carcinomas presented with a left medial canthal mass as seen in Fig. 18.9. The mass occurred 4 years following Mohs surgery at the same site, and was clinically inseparable from periosteum. The CT shown in Figs. 18.10 and 18.11 was obtained to delineate the extent of the recurrence.

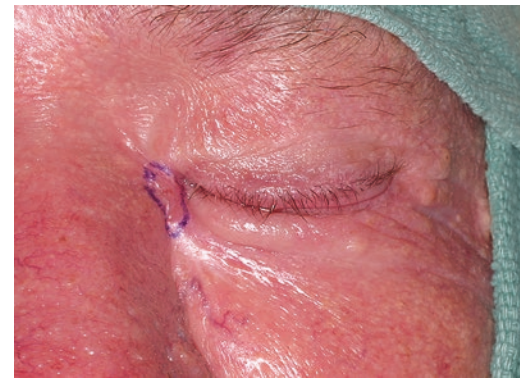

Fig. 18.9 Recurrent infiltrative basal cell carcinoma of the left medial canthus

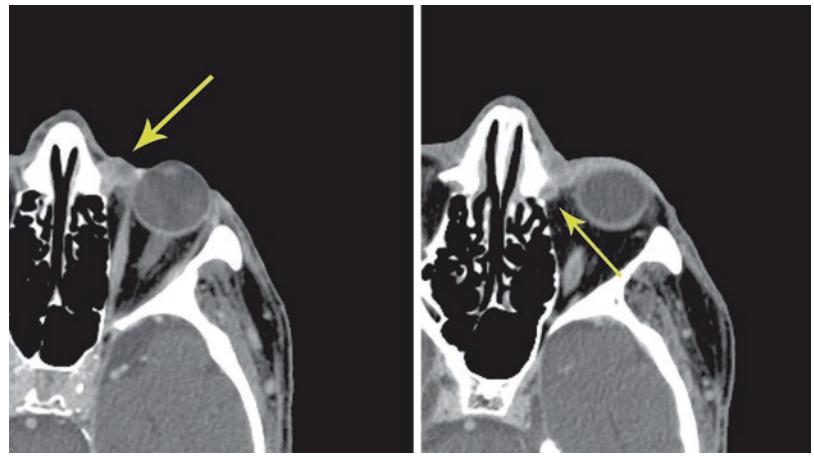

Fig. 18.10 Superior to inferior axial post-contrast images of the orbit. *Left image*: *Arrow*, left medial canthus mass, abutting the periosteum and the attachment of the medial rectus muscle on the globe. No destruction of cortical bone. *Right image*: The skin over the left side of the nose appears involved. *Arrow*, the lacrimal sac is involved

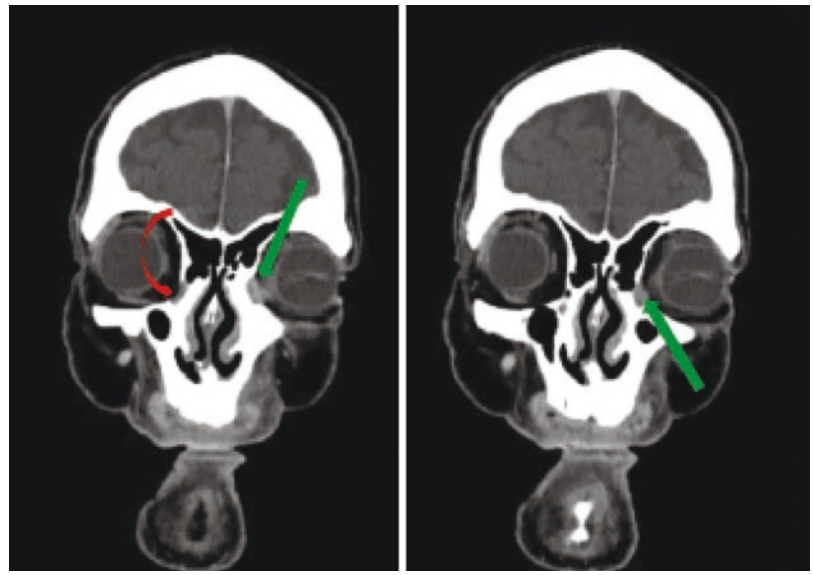

Fig. 18.11 Coronal reconstructions of the axial images seen in Fig. 18.10. Left image, *curved arrow*, normal right lacrimal sac. *Green arrows*, left lacrimal sac involved by BCC

The patient underwent resection by Mohs surgery and was referred to the oculoplastic surgery service, for further resection of the tumor. Complete resection was not possible. The patient underwent postoperative radiation treatment and continues to have imaging surveillance.

Cutaneous Squamous Cell Carcinoma

Indications for the imaging of cutaneous squamous cell (SCC) carcinoma include planning for local excision, the identification of metastatic lymph nodes, diagnosis of perineural involvement, and the early detection of recurrence. High resolution CT can provide the best spatial resolution for surgical planning and for the detection of recurrence at the resection site. Nodal metastases can be seen by CT, MR, US, and PET. In a blinded, prospective study reported by Adams et al. in 1998, 60 patients underwent all four of these studies prior to neck dissection. They found 117 metastases in 1284 lymph nodes on neck dissection [19]. PET scanning provided 90% sensitivity and 94% specificity for nodal metastases and was able to detect nodal metastases as small as 0.6 cm. However, only metastases greater than 1 cm were diagnosed as malignant by CT; in our experience, some metastatic lymph nodes smaller than 1 cm can be identified. The study found MR and CT to have similar sensitivity and specificity, ranging from 79% to 85%. The use of lymphoscintigraphy for sentinel lymph node localization

is not currently widespread, but Wagner et al. in 2004 found a sensitivity of 89% for sentinel lymph node biopsy in a population of patients with nonmelanoma skin cancers: 17 squamous cell carcinoma, 5 Merkel cell carcinoma, and 2 adenocarcinoma [20].

Illustrative Case 18.2

A 64-year-old man underwent excision of a left supraorbital SCC, which recurred 7 months later and was treated with a 5-week course of radiation. Seven months later, he had a second recurrence, which was treated with Mohs surgery at an outside institution. Histology demonstrated a positive margin at the supraorbital nerve. Almost a year later, he presented with headaches, blurred vision, proptosis, and paresthesias in the distribution of the ophthalmic division of the trigeminal nerve. The patient then referred himself to our institution for further management (Fig. 18.12).

The MRI shown in Fig. 18.13 was obtained to assess for perineural involvement.

Radical orbitectomy was performed. Pathology confirmed recurrent squamous cell carcinoma with perineural involvement of the left ophthalmic nerve. The patient underwent stereotactic radiosurgery and continues to be followed with imaging.

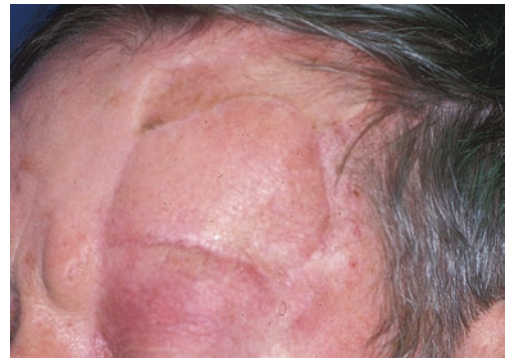

Fig. 18.12 Clinically, no tumor was apparent at the surgical site. (Photograph courtesy of Charles Butler, M.D., MD Anderson Cancer Center)

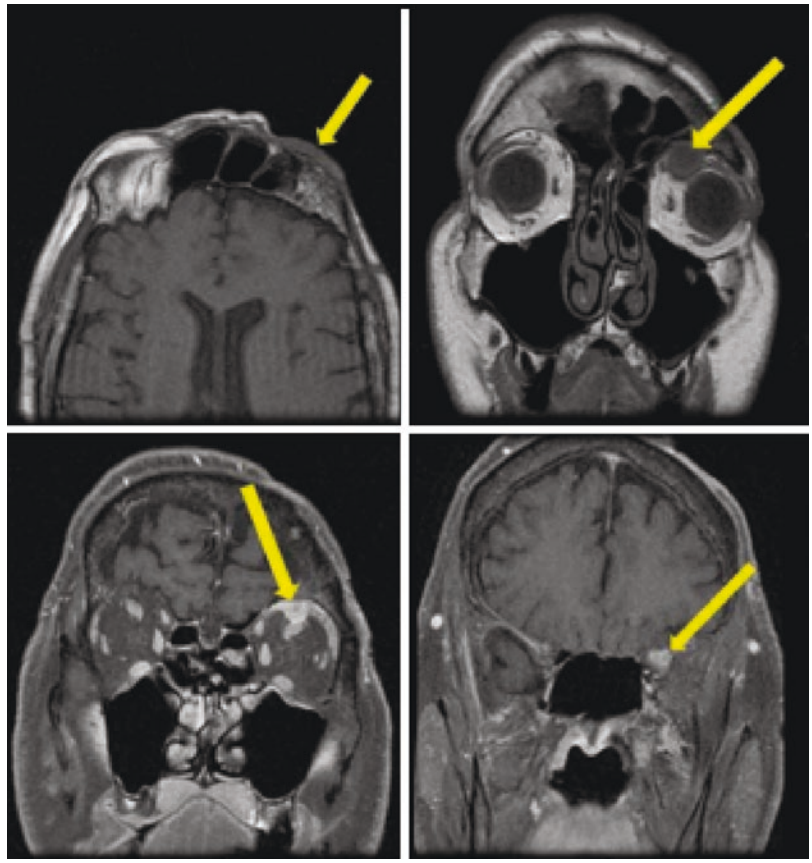

Fig. 18.13 *Top*: Noncontrast T1-weighted axial (*left*) and coronal (*right*) images. On the axial image, the focal area of decreased signal (*arrow*) overlying the frontal sinus indicates the surgical site. On the coronal image, thickening of the left ophthalmic nerve (V1) is demonstrated (*arrow*). *Bottom*: Contrast-enhanced, fat-saturated T1-weighted coronal images through the orbit (*left*) and orbital apex (*right*). Thickening and enhancement of left V1 is seen within the orbit and superior orbital fissure (*arrows*). More posterior images (*not shown*) demonstrated no involvement of Meckel's cave

Illustrative Case 18.3

A 67-year-old man with a 5-year history of a tumor on the left temple was referred for excision (Fig. 18.14). CT was obtained preoperatively to evaluate for bone involvement and nodal metastasis (Fig. 18.15). Seven months after his initial surgery, a follow-up CT demonstrated a new left preparotid lymph node suspicious for metastasis (Fig. 18.16). Ultrasound-guided fine needle aspiration (FNA) (Fig. 18.17) demonstrated metastatic squamous cell carcinoma. The patient had a left parotidectomy, confirming nodal metastasis. Left neck dissection on the same date demonstrated no cervical nodal metastases.

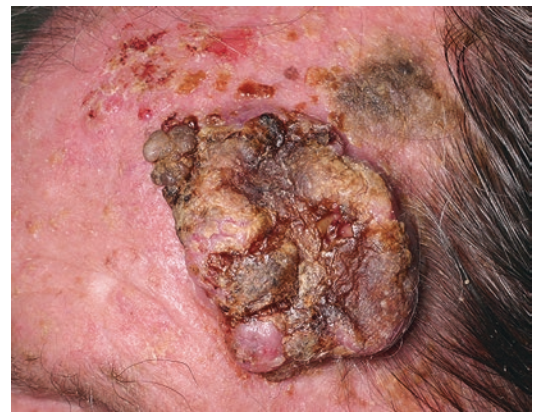

Fig. 18.14 A 6 × 4.5-cm tumor not attached to bone was apparent was on the left temple

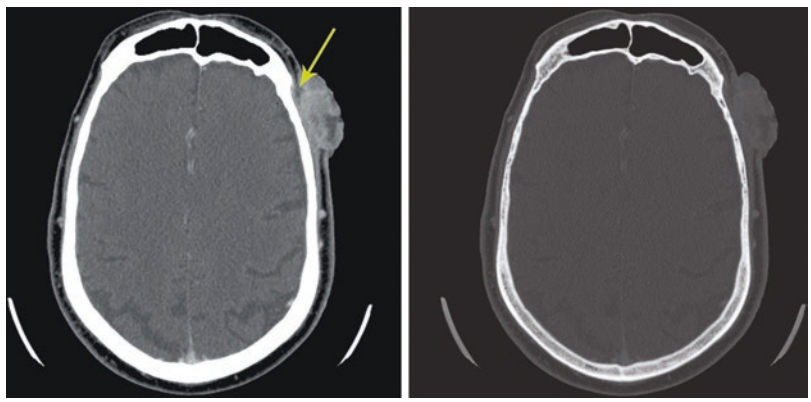

Fig. 18.15 *Left*: Axial post-contrast CT image through the frontal sinus demonstrates invasion of the temporalis musculature. *Right*: Bone window of the same CT image demonstrates no cortical erosion. No adenopathy was seen. Wide local excision was performed by head and neck surgery, and the patient underwent a further flap repair by plastic surgery. Follow-up CT obtained 5 months later is shown in Fig. 18.16

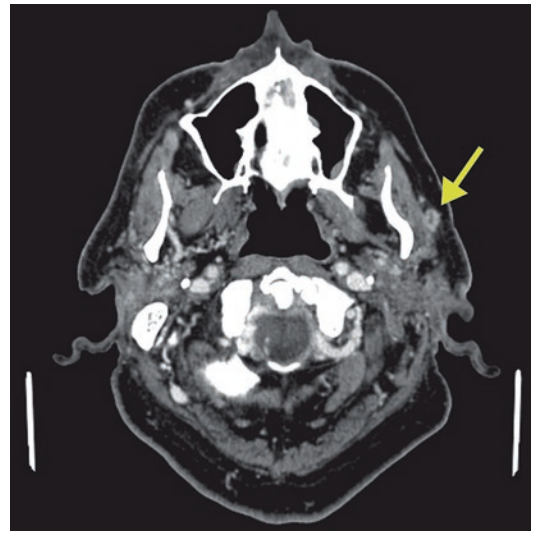

Fig. 18.16 Axial post-contrast CT image through the level of the parotid gland demonstrates a subcentimeter, enhancing, centrally necrotic preparotid lymph node suspicious for metastasis (*arrow*)

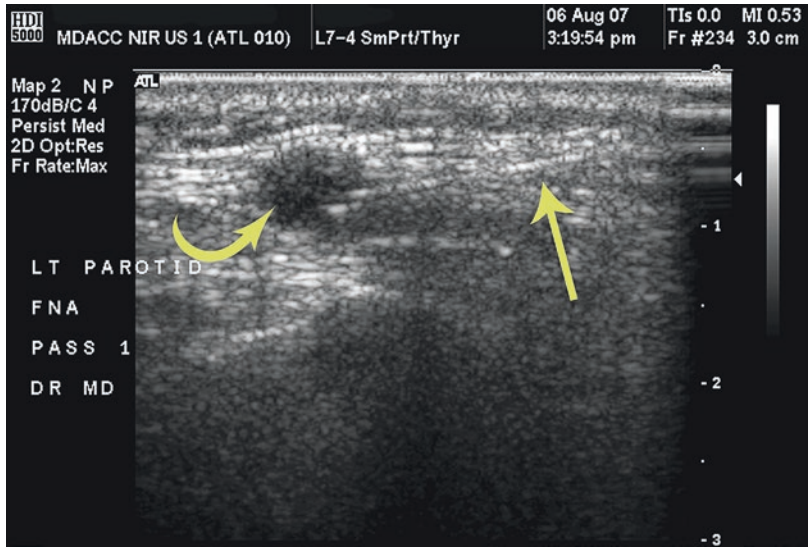

Fig. 18.17 Ultrasound-guided biopsy of the suspected nodal metastasis in Case 18.3. The needle (*straight arrow*) approaches the rounded, hypoechoic lymph node (*curved arrow*)

Illustrative Case 18.4

A 70-year-old man presented to Mohs surgery with a biopsy-proven SCC recurrence within a radial forearm flap on his left temple, which had been performed 6 months prior (Fig. 18.18). A CT was obtained as part of his preoperative work up (Fig. 18.19).

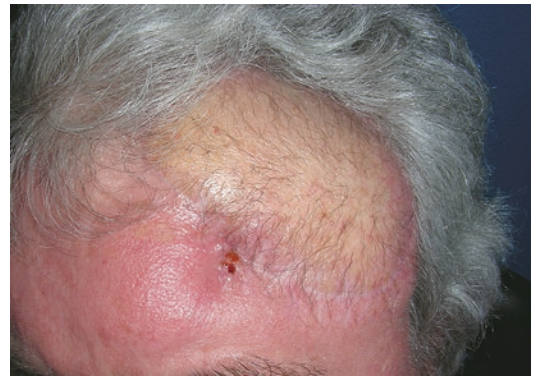

Fig. 18.18 Recurrent SCC is seen within the left forehead flap. (Photograph courtesy of Roman Skoracki, M.D., MD Anderson Cancer Center)

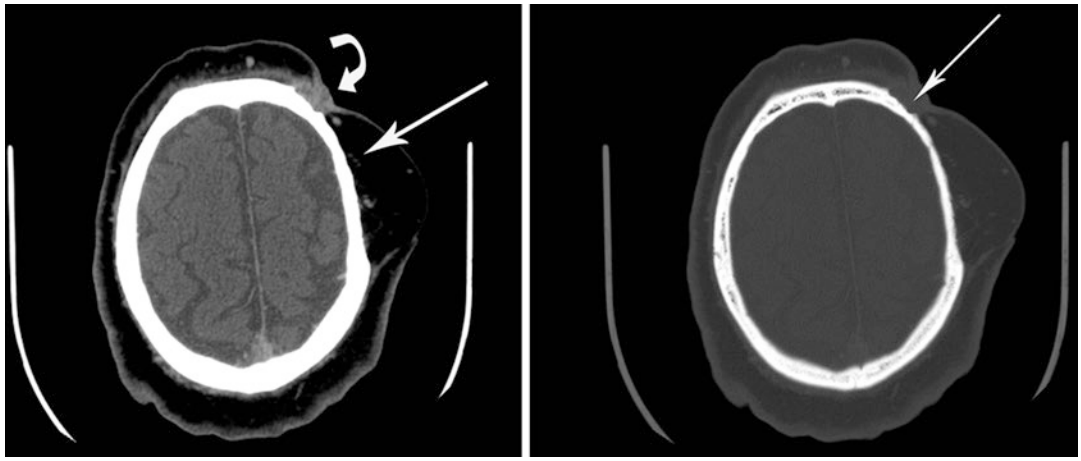

Fig. 18.19 *Left*: Axial post-contrast CT image at the level of the recurrence demonstrates an enhancing soft tissue mass (*curved arrow*) at the anterior margin of the flap (*straight arrow*). *Right*: The same image displayed in a bone window more clearly shows cortical erosion (*straight arrow*)

Melanoma

We will consider cutaneous, not mucosal, melanomas in this chapter. Patients with American Joint Committee on Cancer (AJCC) stage I or II melanoma do not need routine imaging [21]. Imaging is indispensable for M staging and for following response to treatment for systemic disease. Patients with stages III and IV disease undergo initial staging followed by regular surveillance with contrast-enhanced MRI brain and either PET/CT or CT with contrast at our institution. Lung and brain metastases are not reliably detected by PET due to factors discussed previously. Furthermore, PET cannot be used to identify locoregional nodal disease, especially axillary nodes. However, its ability to reveal extranodal metastasis is the strength of PET imaging in melanoma [22].

Preoperatively, lymphoscintigraphy (along with intraoperative blue dye) is frequently used to locate sentinel lymph nodes for sampling (Chap. 15). Cross-sectional imaging may help to identify locoregional nodal metastases. In the head and neck, detection of parotid adenopathy is critical to surgical planning. The presence of parotid adenopathy may steer the surgeon toward neck dissection even if the neck is clinically negative [23].

Illustrative Case 18.5

A 68-year-old man with a primary melanoma on the left occiput underwent radiation and excision at another hospital. One year later, the lesion recurred (Fig. 18.20). CT of the neck with contrast was obtained for restaging (Fig. 18.21).

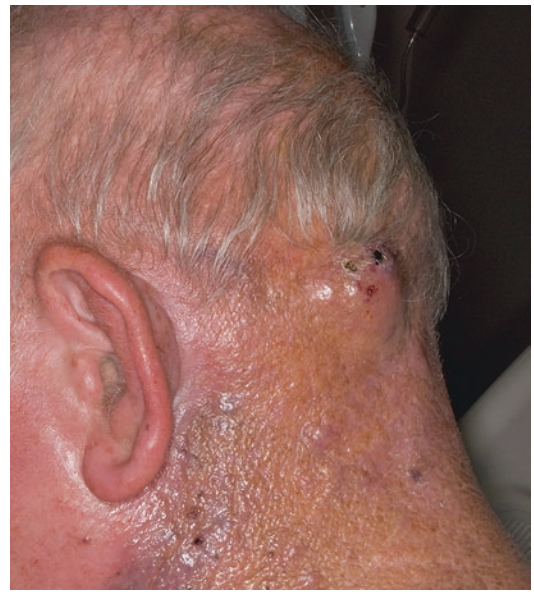

Fig. 18.20 Primary melanoma at the left occiput and dermal metastases over the angle of the jaw were apparent clinically

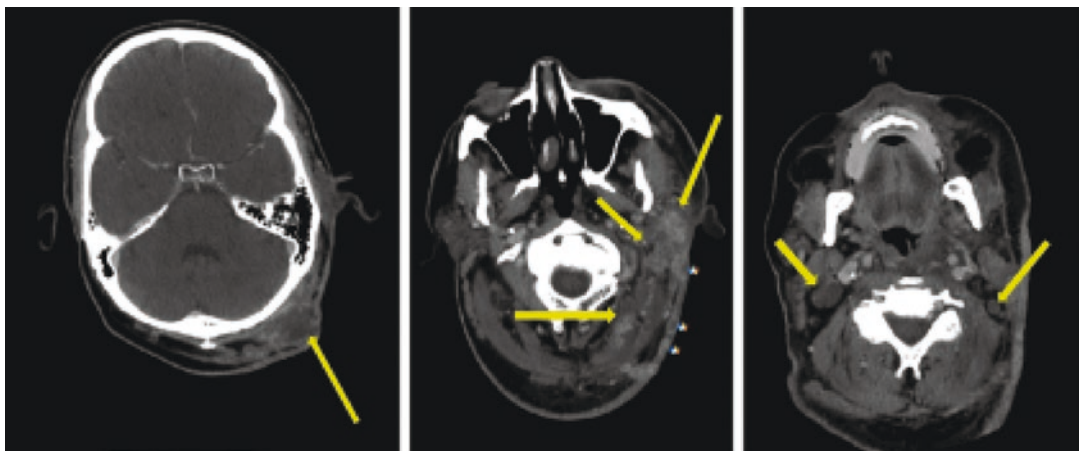

Fig. 18.21 *Left*: Primary site of melanoma in the scalp, extending from the skin almost to the periosteum (*arrow*). *Middle*: Severe left posterior neck skin thickening with nodular foci of rim enhancement in keeping with dermal metastases (*asterisks*). Deeper metastatic foci are seen within the left neck musculature and left parotid gland (*arrows*). *Right*: Appearance of a necrotic nodal metastasis on the right and subcentimeter nodal metastasis on the left (*arrows*)

Dermatofibrosarcoma Protuberans

The deep extension and actual size of this spindle cell tumor can be difficult to determine based on physical examination. In cases of residual or recurrent tumor, or large fixed masses, imaging may be helpful to define the involvement of adjacent or possibly un-resectable structures. Delineating the extent of the tumor is the most important reason to obtain imaging. Imaging can also be helpful in planning wound closure and in follow-up.

Kransdorf in 1994 first reported the use of imaging, including CT, MRI, and arteriograms, to evaluate the extent of dermatofibrosarcoma protuberans (DFSP) [24]. In 2002, Torreggiani et al. described the MRI signal characteristics of 10 cases of histologically proven DFSP [25]. These tumors demonstrated hypointensity compared to fat, and iso- or hypointensity compared to muscle on T1-weighted images. Thornton et al. in 2005 described a series of 10 pediatric patients with DFSP, 5 of whom were imaged with MR [26]. Of these 5 patients, 2 had MR evidence of deep extension, which increased the extent of surgical resection. Thus, MR has proven useful in determining subclinical extension, especially in large tumors and difficult locations.

In a series of 24 patients with head and neck sites of DFSP, most DFSP demonstrated T2 hyperintensity, as well as marked enhancement after contrast administration [27]. Because of the T2 hyperintensity and marked contrast enhancement combined with subcutaneous location, fat suppression on T2 and T1 post-contrast sequences is recommended. No perineural spread or nodal metastasis was identified in this series.

Thornton reported the use of MRI in follow-up after surgery, for a limited period [26]. Clinical surveillance is usually lifelong.

Illustrative Case 18.6

A 49-year-old man presented to the ER with a 5-year history of a growing mass on his back (Fig. 18.22). MR was obtained to evaluate the extent of the mass prior to resection (Fig. 18.23).

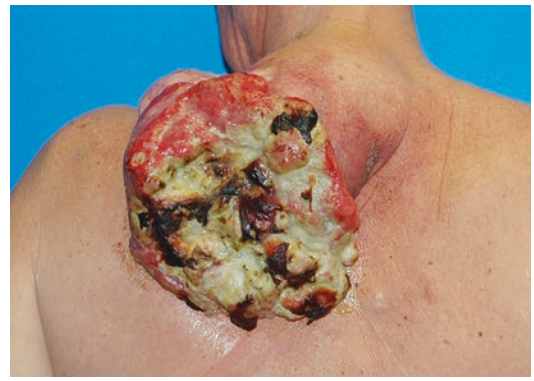

Fig. 18.22 A large tumor occupies the left upper back. (Photograph courtesy of Matthew M. Hanasono, M.D., MD Anderson Cancer Center)

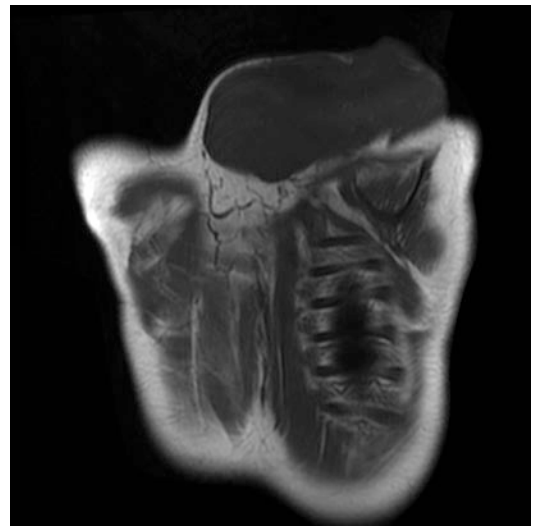

Fig. 18.23 T1-weighted noncontrast MR image of the chest. A large mass, iso-intense to muscle involves the skin of the upper back and extends into the subcutaneous fat over the posterior chest wall

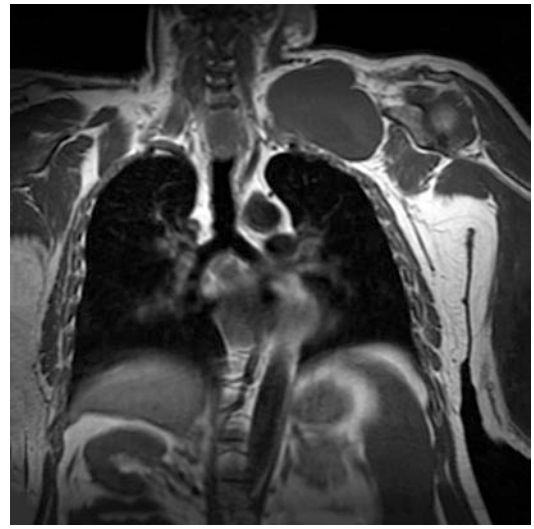

Fig. 18.24 Coronal T1-weighted noncontrast image through the chest. A new mass is seen at the *left* thoracic inlet, again iso-intense to muscle but anterior to the initial site of DFSP and no longer involving the skin. The patient underwent resection of the recurrence, followed by radiation treatment

Histology demonstrated DFSP and the patient underwent excision. Fourteen months after the surgery, the patient developed a painful mass over the left clavicle, as seen on the MR in Fig. 18.24.

Merkel Cell Carcinoma

This rare, aggressive neuroendocrine carcinoma is known to have a high risk of nodal metastasis, distant metastasis, and recurrence [28]. Imaging is very helpful in evaluating the extent of spread. The preferred evaluation may vary between centers but will include a modality with high sensitivity for regional metastasis and some method of evaluation for distant metastasis. When no regional or distant metastasis is identified, sentinel lymph node biopsy is recommended [29]. See Fig. 18.6 for an example of the use of ultrasound-guided FNA to diagnose a nodal metastasis from Merkel cell carcinoma.

18-FDG PET/CT is increasingly used for primary staging of Merkel cell carcinoma. A multicenter prospective study of 58 subjects found that this modality significantly influenced treatment in 1/3 of cases and had sensitivity and specificity of 94% and 88% for staging [30]. Belhocine explored the correlation of FDG avidity with MIB-1 labeling in MCC and found that patients whose tumors were FDG-avid had a labeling index of 10–75%, with a mean of about 50% [31]. The tumors that were not FDG-avid demonstrated a labeling index of 4–13%. Because Merkel cell carcinomas express somatostatin receptors, using somatostatin receptor agents such as 68-Ga DOTATATE and 68-Ga DOTATOC in conjunction with PET/CT shows promise in the evaluation of Merkel cell carcinoma [32, 33].

Illustrative Case 18.7

A 51-year-old man had undergone excision of an MCC on his right thigh. A few months later, CT scan demonstrated peripancreatic adenopathy. During chemoradiation, progressive lymphadenopathy was noted. PET/CT was obtained as part of restaging prior to investigational therapy (Fig. 18.25).

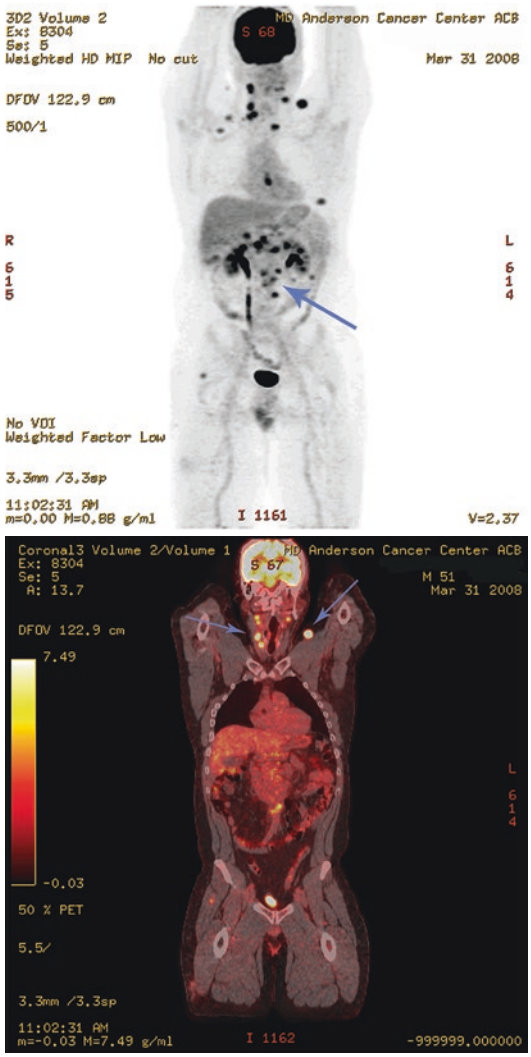

Fig. 18.25 *Top*: Maximum intensity projection reconstructed PET image. *Arrow*, one of several abdominal nodal metastases. *Bottom*: Fused PET/CT images, coronal plane through the clavicular heads and pubic symphysis. *Arrows* indicate the patient's palpable left supraclavicular subcutaneous metastasis, as well as unsuspected right neck nodal metastases

Sebaceous Carcinoma

Sebaceous carcinoma may involve the periorbital region. If there is orbital involvement, orbital exenteration may be considered [34]. Orbital CT can then be helpful for preoperative planning. In a series of 21 patients, 6 out of 7 who developed regional metastases had a T4 primary lesion [35], so surveillance CT scanning should be useful only in the most aggressive of these cancers. In one sample of four cases of metastatic eyelid sebaceous carcinoma, a patient developed metastases almost 5 years out from initial diagnosis [36]. However, it is not known how often or for how long surveillance imaging should be obtained. In cases of suspected Muir-Torre syndrome, further evaluation of GI malignancies may be best accomplished by a combination of colonoscopy and CT.

Angiosarcoma

Scalp angiosarcoma may spread rapidly through the skin [37]. The size and the extent of deep and superficial invasion may be assessed by contrast-enhanced CT or MR. MR imaging of the scalp should include post-contrast T1-weighted images with fat saturation, to null the signal from the subcutaneous fat and to allow visualization of contrast enhancement. At MDACC, we typically include images of the neck as well as the scalp, as angiosarcoma may metastasize to cervical lymph nodes.

Isoda et al. in 2005 reviewed the MRI in eight cases of angiosarcoma. In all eight, the tumor was lower in signal intensity than subcutaneous fat and enhanced intensely. Of the seven cases for which clinical findings were available, in four the extent of tumor was greater by MR than was suspected by clinical evaluation. Only one of these patients had calvarial involvement on MR [38].

Illustrative Case 18.8

An 80-year-old man presented to the ER with a rapidly growing scalp mass (Fig. 18.26). On exam, a 5-cm scalp tumor was noted and later confirmed by biopsy to be an angiosarcoma. MRI was obtained to evaluate the extent of the lesion (Fig. 18.27).

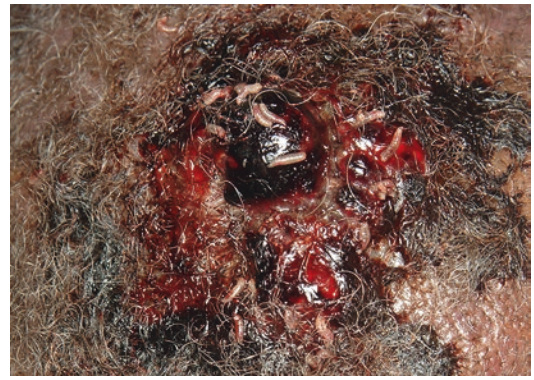

Fig. 18.26 Large hemorrhagic scalp tumor

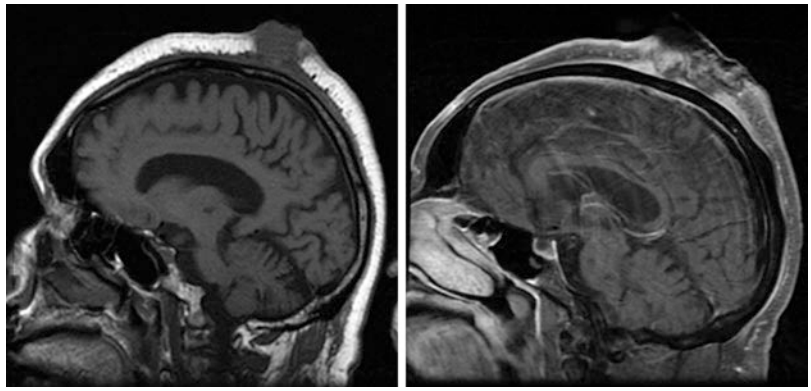

Fig. 18.27 *Left*: Sagittal T1 noncontrast MR image of the brain. The subtle *gray line* over the hyperintense subcutaneous fat represents normal skin. The angiosarcoma involves the skin and galea aponeurotica and demonstrates signal iso-intense to muscle [39]. *Right*: sagittal post-contrast fat-saturated T1 image of the brain. The angiosarcoma demonstrates intense but heterogeneous enhancement. Enhancement in the periosteum likely represents tumor involvement. The bone cortex is not well evaluated by MR, but no bone marrow extension is identified. The patient underwent a course of chemoradiation with little effect and died shortly thereafter

Summary

Imaging in skin cancer can be useful for preoperative planning and to assess for perineural involvement, bony involvement, and nodal metastasis. It can help to define tumor size and depth and identify orbital involvement of tumor. No one imaging modality is best for all purposes. Ultrasound is useful for evaluation of superficial nodes and for biopsy. Lymphoscintigraphy defines the sentinel nodes for biopsy and is most helpful in patients with melanoma. CT is also helpful for the assessment of nodes, cortical bone involvement, and for definition of the primary tumor. MR is by far the best modality for the evaluation of perineural involvement and is also more sensitive than CT for defining marrow involvement. PET/CT is best for the imaging of distant metastases.

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Chapter 19
Radiation Oncology in Skin Cancer Treatment

Wesley B. Garner, Susan L. McGovern, and Matthew T. Ballo

Radiation was first used to treat a patient with squamous cell carcinoma of the nose in 1900. Following the development of improved dermatologic and surgical techniques in the 1950s, the role for radiation in the treatment of skin cancer gradually decreased [1]. However, in most settings, radiation offers advantages over other currently available modalities. The goals of this chapter are to review the current indications for the use of radiation in the treatment of skin cancer, the techniques commonly employed in modern radiotherapy, the role of radiation in the treatment of specific skin malignancies, and the complications that arise from the use of radiation to treat skin cancers.

Indications for Radiation

The general advantages and disadvantages of external beam radiation are summarized in Table 19.1 [1, 2].

Broadly, external beam radiation is a painless outpatient procedure. It can be used in patients who are not surgical candidates due to medical reasons, particularly the elderly. It also allows for preservation of uninvolved structures adjacent to the lesion. This is especially important in the head and neck, where the cosmetic and functional consequences of treatment can be significant.

Practically, radiation requires a longer investment of time than surgery; typical regimens require daily treatments for 3–6 weeks [1]. Although the side effects of radiation are usually limited to the treated field, they can persist or worsen over time. For instance, the doses required for adequate tumor kill also usually cause permanent alopecia within the treated field [3]. The cosmetic sequelae of radiation, including dermatitis and telangiectases, also worsen over the decades following treatment [2, 4]. Because radiation is a known carcinogen, there is also a risk of a second malignancy within the treated field. Due to these late effects, we typically do not recommend radiation for patients younger than 50 years of age if an equally effective, alternative method is available [4].

These issues, as well as several patient-specific ones, are generally addressed during the patient's initial consultation with a radiation oncologist. Table 19.2 lists some of the factors that will be considered during that first visit; many of these questions are ideally addressed prior to the patient's arrival in the radiation clinic. One of the most important issues to discuss is the patient's expectation of radiation. Many patients have an inaccurate perception of the process and sequelae of radiation; this should be addressed up front and clearly during the initial visit.

Prior to the delivery of any radiation treatment, confirmation of the diagnosis with biopsy is necessary [1]. This establishes the histology of the lesion, which dictates subsequent decisions about the applicability and technique of radiation treatment. As shown in Table 19.3, the indications for radiation depend on the histology and location of the lesion. For instance, some cutaneous lym-

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Table 19.1 Advantages and disadvantages of radiation therapy [1, 2]

Advantages	Disadvantages
Outpatient procedure	Typically requires a treatment course of 3–6 weeks
Treatment is painless	Can cause permanent alopecia
Can be used in patients that are medically inoperable, particularly the elderly	Long-term cosmetic sequelae of radiation, including dermatitis and telangiectases, worsen over the decades following treatment
Allows for preservation of uninvolved structures	Risk of second malignancy within the treated field

Table 19.2 Some questions that will typically be considered during the initial interview with a radiation oncologist. Communication between the referring physician and the radiation oncologist prior to the initial interview can address many of these issues

Typical radiation oncology questions
Has the histologic diagnosis been adequately established?
Has appropriate staging been completed?
Has this lesion occurred before?
Has the patient had any treatment for this lesion? If so, what? Have these treatments helped or not?
What treatments, if any, are planned?
What are the anticipated goals of radiation treatment—primary or adjuvant therapy? Definitive or palliative?
Has the patient undergone any previous radiation? If so, what site was treated? What was the duration (or, more ideally, dose) of the treatment? What facility performed the treatment? How long ago was treatment completed?
Does the patient have any other cancer diagnoses? If so, how were those conditions treated?
What is the patient's overall medical condition?
What are the patient's comorbidities?
Does the patient have a history of any conditions that may be exacerbated by radiation, such as CREST syndrome, dermatofibrosis, lupus, or scleroderma?
What are the patient's expectations regarding radiation?

Table 19.3 Indications for radiation therapy [1, 2]

Highly indicated	Cutaneous T-cell lymphoma Some B-cell lymphomas Kaposi's sarcoma
Good indication	Basal cell carcinoma Squamous cell carcinoma Merkel cell tumors
Sometimes indicated	Angiosarcoma Melanoma
Rarely indicated	Carcinoma of the scrotum, palms, soles

phomas, including mycosis fungoides, are highly radiosensitive lesions, and radiation can offer a unique therapeutic advantage [5].

Most basal and squamous cell carcinomas are successfully addressed with surgical methods. Primary radiotherapy is preferred for the treatment of tumors that cannot be excised without causing a significant cosmetic or functional deformity, such as lesions on or near the nose, ears, and eyelids [6, 7]. Similarly, lesions of the cheek, lip, or oral commissure that would require a full-thickness resection can also be effectively managed with radiotherapy [4]. For carcinomas that have been excised, postoperative radiation can be used to treat positive surgical margins, perineural invasion, bone or cartilage invasion, or extensive skeletal muscle involvement at the primary site [4, 8]. Radiation can also address disease that has spread to the lymph nodes, particularly if there is extranodal extension or multiple positive lymph nodes [4, 8].

Radiation Modalities Used to Treat Skin Tumors

Early-stage skin lesions are ideally treated with orthovoltage or electron beam radiation. Orthovoltage generators can provide beam energies in the range of 75–125 kV and offer beam

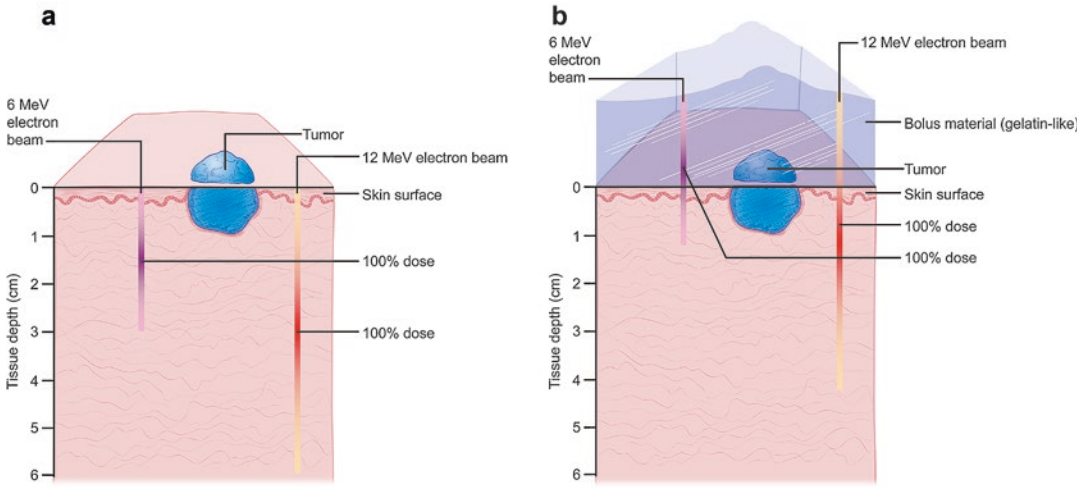

Fig. 19.1 Depth dose of electron beams and the influence of bolus [1]. (**a**) Depth doses of 6-MeV and 12-MeV electron beams without bolus. (**b**) Depth doses of 6-MeV and 12-MeV electron after passing through bolus placed on the skin. The bolus pulls up the dose to improve tumor coverage and spare underlying tissue. (Illustration by Alice Y. Chen)

characteristics that are favorable for the treatment of lesions less than 5 mm in thickness [3]. Because of their limited applicability, orthovoltage units have generally been replaced by linear accelerators that can produce both high-energy photon and electron beams.

Electron beams are well-suited for the treatment of skin lesions [9]. The depth dose behavior of electron beams is illustrated in Fig. 19.1. The energy of a given electron beam determines the depth of tissue it will adequately cover. For instance, a 6-MeV beam will cover approximately 2-cm depth, and a 20-MeV beam will cover approximately 6-cm depth [1]. Generally, electron beams homogeneously cover a region of tissue to a specific depth and then dissipate rapidly [8]. This beam profile makes electrons almost ideal for the treatment of skin malignancies where critical normal structures such as the brain are often immediately below the lesion.

To improve the coverage of certain lesions, a bolus of 0.3–2-cm thickness is often applied to the skin (Fig. 19.1). Bolus is a gelatinous tissue-equivalent material that effectively pulls the dose toward the skin, thereby enhancing coverage of more superficial lesions and allowing for increased sparing of underlying normal structures [10]. An example of the use of bolus is presented in Fig. 19.2, which shows the setup used for treatment of a locally advanced preauricular squamous cell carcinoma.

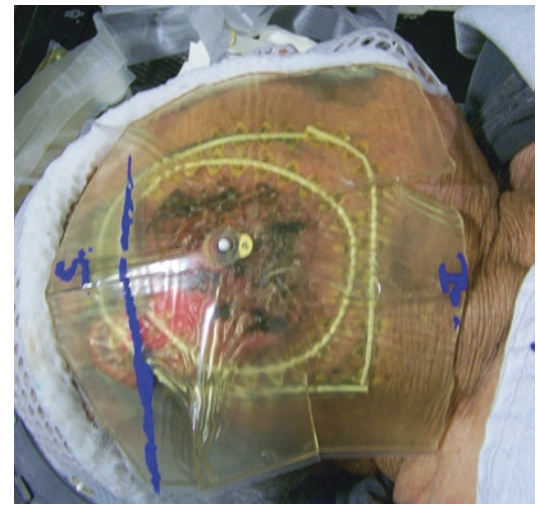

Fig. 19.2 Setup for electron beam treatment of a 93-year-old man with a locally advanced squamous cell carcinoma of the right preauricular region. The head and neck are immobilized with a custom-made mask. The lesion and the desired treatment field are outlined with radiopaque wire, which allows for visualization of the area on the planning CT scan. The external auditory canal is filled with Domeboro drops and TX-151, a pink tissue-equivalent putty, to alleviate dose inhomogeneities caused by the irregular surface of the ear. The entire field plus a wide margin is covered with 3-mm bolus to produce a homogenous dose distribution throughout the treated field. Not shown here, an additional piece of bolus 2-cm thick was applied to the superior aspect of the treatment field to further pull the dose away from the underlying temporal lobe

Shielding is often required to protect the lens of the eye, which is an exceptionally radiosensitive tissue. Treatment of an eyelid tumor can easily expose the lens to more than 5–10 Gy, the threshold dose for the formation of cataracts [3]. Consequently, lead or tungsten shields [11] must be used when indicated to reduce the radiation dose to the lens. Similarly, lead can also be used to define the field limits and shape the beam such that surrounding uninvolved tissues are further spared from radiation exposure.

There are particular situations that might require a larger volume or deeper coverage. In the setting of perineural invasion of a large nerve fiber from a carcinoma of the face, you should consider tracking the relevant nerves potentially to the skull base or intracranial routes to the brainstem [12]. Intensity-modulated radiotherapy (IMRT) is the optimal treatment modality in this situation as it allows for the accurate treatment of the necessary pathways and can limit the dose received by normal critical structures [13].

Certain skin cancers, particularly those of the nose, are amenable to treatment by an interstitial technique in which radioactive sources are directly inserted into the tumor (Fig. 19.3). This form of radiation is called brachytherapy, Greek for "short" therapy [14]. For the treatment of skin tumors, iridium-192 is the most commonly used source [3]. The dose of radiation decreases with the inverse square of the distance from the source, allowing for high doses close to the source and a rapid drop-off in dose with distance [3]. The clinical advantage of this is that it enables us to deliver a high dose to the tumor while sparing much of the surrounding normal tissues. The disadvantages of this approach are that it requires general anesthesia for the placement of the radiation catheters and 4–6 days for the delivery of treatment [3]. Brachytherapy is usually combined with external beam radiation to deliver an adequate dose both to the tumor and to the surrounding tissue at risk.

Another form of brachytherapy can be achieved when a radioactive source is applied on a surface mold. This type of treatment is usually amenable to well-circumscribed, superficial skin cancers [14]. Surface mold brachytherapy is

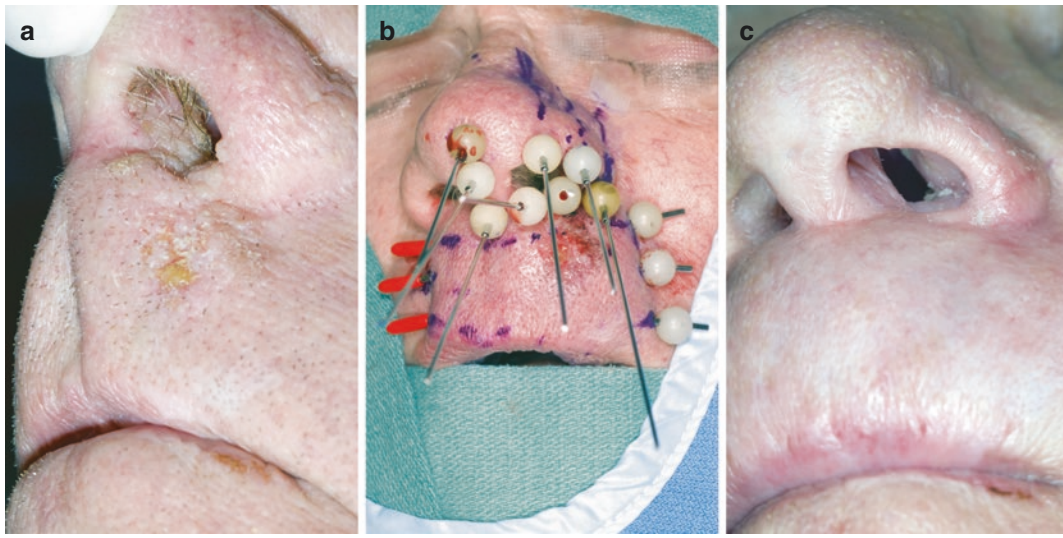

Fig. 19.3 (**a**) A 65-year-old man with squamous cell carcinoma of the left nasal vestibule that extended to the skin inferior to the nasal vestibule and ala. Because the patient had a history of hypertension, hyperlipidemia, and heart disease requiring coronary artery bypass grafting, he was dispositioned to receive treatment with definitive radiation alone. (**b**) The left nasal ala and nasolabial skin were initially treated with brachytherapy. Catheters were placed intraoperatively as shown. Following recovery from anesthesia, iridium-192 sources were placed in the catheters to deliver a dose of 25 Gy over 51 h. After catheter removal and discharge from the hospital, the region was then treated with external beam radiation at 2 Gy per fraction to 50 Gy in 25 fractions, delivered over 5 weeks. (**c**) Four months after the completion of radiation, the lesion was completely resolved, and he had no sign of recurrent disease. Note the expected alopecia within the treated field

generally delivered using a high dose rate (HDR). This can be achieved in a shorter amount of time and does not require general anesthesia. The disadvantage to this type of treatment modality is there is a higher rate of failure for recurrent, larger (>2 cm), and deeper (>2 mm) tumors, likely due to the sharp decline of dose achieved at increased depth [14]. In general, brachytherapy is reserved for very select situations, and it is not used nearly as often as external beam radiotherapy.

Radiation in the Treatment of Specific Skin Malignancies

Basal and Squamous Cell Carcinomas

Basal and squamous cell carcinomas are the skin tumors most commonly treated with radiation, and the general approach to them is similar. Although surgery effectively manages most lesions, carcinomas that cannot be resected without a significant cosmetic or functional deficit can often be treated with definitive radiation. These include lesions of the nose, eyelid, ear, lip, and cheek, as described previously [8].

Orthovoltage X-rays or, more commonly, electron beam radiation may be used for the treatment of carcinomas. The radiation portal typically encompasses the visible or palpable tumor plus an additional margin of 0.5–1.0 cm for lesions less than 1 cm and up to 2.0 cm for larger or poorly defined lesions [15]. When low-energy electrons will be used for treatment, an additional 0.5-cm margin is added to the field at the skin surface because the beam constricts with depth [16]. The final margins may be reduced when regions close to the eye are treated [4].

The approach to postoperative radiation is similar. In the case of perineural invasion, the target volume is extended to include the potential route of perineural spread. This can be achieved using intensity-modulated radiotherapy, or IMRT. This modality allows for greater depth to the treatment field and routinely covers areas adjacent to the base of the skull in head and neck cancers [17]. For instance, the patient shown in Fig. 19.4 had a multiple recurrent squamous cell carcinoma of the right lower eyelid. Pathology from her surgical resection revealed invasion of the infraorbital nerve; she then received adjuvant radiation that

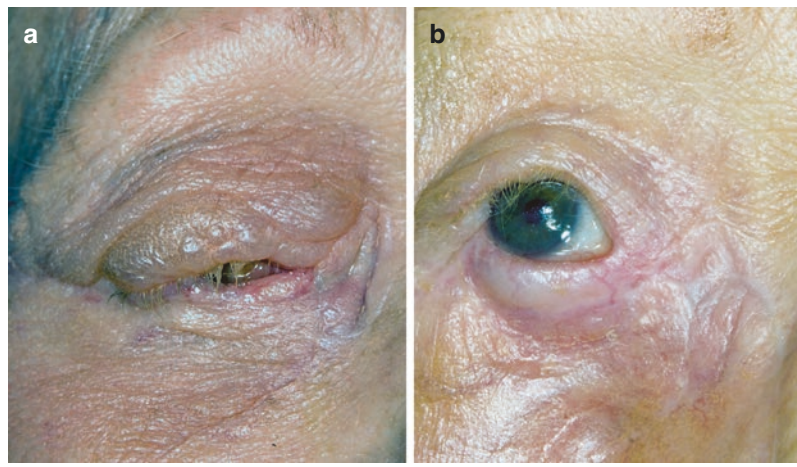

Fig. 19.4 (**a**) A 77-year-old woman with multiple recurrent squamous cell carcinoma of the right lower eyelid. The lesion had previously been resected three times. She underwent extensive surgical resection and reconstruction, with a right partial maxillectomy, right intraorbital nerve resection, and dissection of the pterygopalatine fossa to the skull base. Pathologic review revealed invasion of the infraorbital nerve. She then received adjuvant radiation of 60 Gy in 30 fractions, which covered the operative bed as well as the infraorbital nerve path to the skull base and the ipsilateral neck nodes. (**b**) Two months after the completion of radiation, she had recovered well from the acute radiation changes and was without sign of recurrent disease

Table 19.4 Common radiation schedules for the treatment of basal and squamous cell carcinoma [4]

Clinical scenario	Possible fractionation schemes	Total dose (Gy)	Total duration (days)
Most patients, most tumors	4 Gy × 10 fractions 3 Gy × 15 fractions 2.5–2.75 Gy × 20 fractions	40 45 50–55	12–14 19–21 26–28
Large treatment field and a good cosmetic outcome is desired [3] or near the eye [18]	2 Gy × 30 fractions 2 Gy × 35 fractions	60 70	42–44 49–51
Elderly patient with ≤1-cm tumor	5 Gy × 8 fractions	40	10–12
Elderly patient in poor health	8 Gy × 4 fractions 20 Gy × 1 fraction	32 20	4–7 1

treated the nerve all the way to the skull base. For pathologically positive lymph nodes, the treatment field is extended to include regional lymphatics [8]. After a sufficient dose has been delivered to these regional areas, the field may be reduced to cover the primary lesion [4].

A variety of dose and fractionation regimens have been used to treat skin carcinomas. Obviously, a shorter treatment course allows the patient to complete treatment more rapidly, but a more protracted course generally yields the best cosmetic results. The choice of a treatment schedule depends on the size of the lesion, its location, and patient convenience [8]. Some commonly used treatment schemes are shown in Table 19.4. Because of the large treatment fields required, radiation for positive nodes is delivered at 2 Gy per fraction [4]. Postoperative radiation is also given at 2 Gy per fraction to minimize radiation-related sequelae in a healing operative bed [4].

Almost all treatment modalities result in 5-year recurrence rates of 1–10% for previously untreated cutaneous basal or squamous cell carcinomas [18, 19]. The primary determinant of local control after radiation is the size of the primary lesion [4]. In a series of 646 patients with basal cell, squamous cell, or mixed carcinomas of the face treated with radiation, the 8-year local control rate for lesions larger than 5 cm was 53%, whereas the 10-year local control rate for lesions less than 2 cm was 98% [18]. After accounting for size of the primary lesion, basal cell carcinomas (BCC) have slightly better local control rates than squamous cell carcinomas [7]. Because basal cell carcinomas rarely metastasize [8], elective nodal irradiation is not performed for basal cell carcinomas of the skin [4]. It is indicated for large, infiltrative cutaneous squamous cell carcinomas, which have a much higher rate of lymphatic spread. Generally, nodal disease up to 3 cm without extracapsular spread can be addressed by either surgery or radiation alone [15].

For locally advanced or metastatic basal cell carcinoma, systemic therapy can be considered [20]. Multiple case reports have been published suggesting the use of concurrent vismodegib and radiotherapy in locally advanced BCC is well-tolerated [21–23]. There is some concern of an increased risk for secondary malignancy, most commonly cutaneous squamous cell carcinoma, after the use of vismodegib [24] (see Chap. 22).

Carcinomas that recur after radiation are more difficult to control than previously untreated lesions [16]. These lesions may be most appropriately addressed by surgical resection. The current experience with re-irradiation to address recurrent disease is quite limited [25] but could be considered if the patient is not a candidate for resection.

Melanoma

Melanoma has long been labeled a radioresistant cancer. Many patients are not considered candidates for radiation simply because of this stigma. Indeed, radiation is unlikely to improve overall survival. However, several studies suggest that adjuvant radiation increases locoregional control, particularly when high-risk features are present

[26–28]. Because locoregional failures can carry significant morbidity, especially in the head and neck, we advocate the use of radiation in appropriately selected patients. In this section, we will review the role of radiation in the treatment of melanoma, with a particular emphasis on the indications for radiation that should trigger a referral to a radiation oncologist.

Wide local excision is the standard of care for localized (stage I or II) cutaneous melanoma [4, 8]. Radiation alone is seldom indicated for treatment of primary disease, except in the case of large facial lentigo maligna melanomas that would require extensive reconstruction after wide excision [29]. Patients with close or positive margins after excision should ideally be taken back to the operating room so that adequate margins can be obtained. In cases where additional excision is cosmetic or functionally undesirable, adjuvant radiation to address the close or positive margin should be considered [26, 30]. Adjuvant radiation should be considered postoperatively for desmoplastic melanoma as it has been shown to provide a local control benefit [31] (Fig. 19.5).

Patients with known lymph node metastases (stage III) are typically treated with wide local excision and therapeutic lymph node dissection. Adjuvant radiotherapy to the involved nodal basin has been shown to decrease the local lymph node recurrence [28, 32]. Potential benefits of radiotherapy must be weighed against possible side effects. Generally, the threshold for administering radiation to the cervical lymph nodes is lower than that of the inguinal lymph nodes due to the morbidity associated with lower-extremity lymphedema. There are criteria outlined for consideration of adjuvant radiotherapy based on location of the regional disease. Figure 19.5 outlines these criteria based on the benefits of improved regional control [28, 32].

These recommendations are supported by the observation that 5-year regional control for such patients can be as high as 89% with nodal radiation [33], compared to 50–70% for patients who do not receive adjuvant radiation [34, 35]. This was again shown in a multicenter, randomized controlled trial, as adjuvant radiation revealed 5-year regional control rates of 79% for any lymph node field relapse versus 64% for observation alone [28]. Although radiation does not have an impact on overall survival, the potential regional control benefit for patients with the above risk factors should prompt consideration of adjuvant radiation.

In recent years, there has been more consensus on initial management of regional lymph nodes in melanoma. This is particularly true regard-

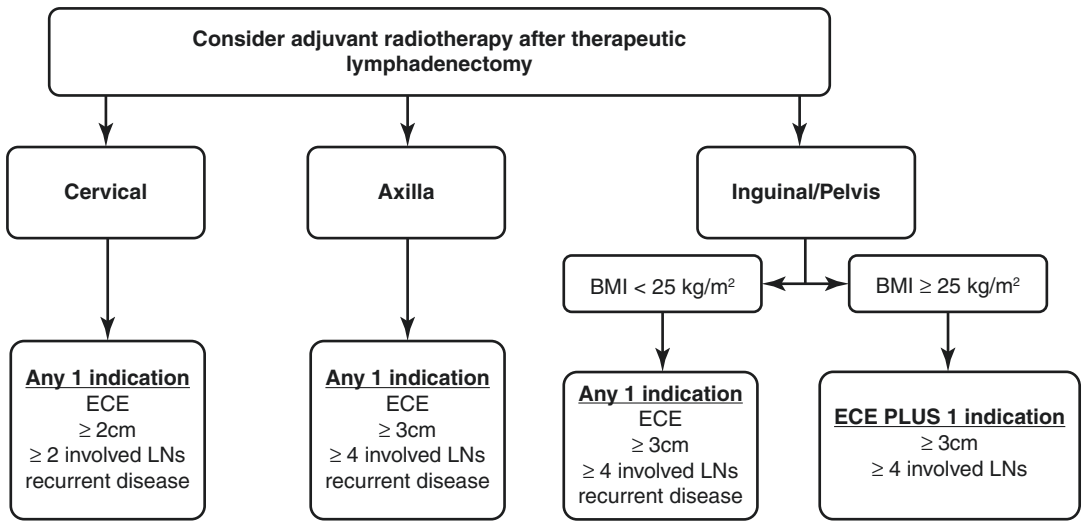

Fig. 19.5 Indications for referral to a radiation oncologist for patients with stage III melanoma [28, 32]. ECE—extracapsular extension

ing the value of the sentinel lymph node (SLN) biopsy [36–39]. Before the development of sentinel lymph node biopsy, elective nodal radiation was routinely performed for patients with melanomas of the head and neck at least 1.5-mm thick or Clark level IV or V [40]. Presently, sentinel lymph node biopsy for staging and prognostic information is recommended by several national professional organizations when appropriate. Those patients that are considered higher risk for regional disease should be more strongly considered for SLN biopsy [36–39]. These recommendations are supported by recent data showing that doing so not only provides important prognostic information but also will decrease recurrences of melanoma when compared to wide excision plus observation [41]. If the sentinel lymph node is positive for malignancy, then the patient undergoing immediate completion lymph node dissection will tend to have better regional control of their disease compared to nodal observation with ultrasound [42]. Patients who are not eligible for surgery or clinical trial can be considered for elective nodal irradiation [4].

Based on our experience and the pervasive belief that melanoma is radioresistant, we continue to recommend a hypofractionated schedule for the treatment of melanoma [43–45]. This means giving a higher dose of radiation per fraction but fewer total fractions. There are two different fractionation schedules we generally consider. For melanoma, we prescribe 30 Gy divided into five fractions over 2½ weeks. Practically, this means treatment is delivered either every Monday and Thursday or every Tuesday and Friday. The maximum allowed dose to the brain or spinal cord is 24 Gy in four fractions over 2 weeks; if this is problematic, a more conventional schedule should be used [4]. The other hypofractionated schedule that has shown good results is 48 Gy in 20 fractions which would be delivered with daily treatments Monday thru Friday over 4 weeks [27, 28].

For adjuvant treatment of the primary site, the radiation field encompasses the surgical bed plus at least an additional 2-cm margin. Treatment is typically delivered with an electron beam using a bolus of appropriate thickness [46].

For nodal radiation, the treatment portal is tailored to the appropriate nodal basin such that it encompasses the draining lymphatics and spares adjacent critical structures. The cervical nodes are usually treated with an appositional electron beam field that covers the ipsilateral nodes down to the clavicle [46]. If greater depth is called for or there is potential to spare normal tissues, IMRT would be more appropriate using megavoltage photons [17]. The axilla is treated with anterior–posterior fields using megavoltage photons from a linear accelerator [4]. Similarly, inguinal nodes are treated with anterior–posterior photon fields, with matched electron fields as needed to entirely cover the surgical scar [4].

Merkel Cell Carcinoma

Merkel cell carcinoma is an aggressive tumor. Lymph node metastases occur in at least half of patients, and distant metastases occur in approximately one-third of patients [47–49]. Furthermore, patients with nodal involvement at presentation have a much poorer prognosis compared to node-negative patients [50, 51]. Fortunately, Merkel cell carcinoma is radiosensitive. It has been established that gross disease can be controlled with surgery and adjuvant radiation with low rates of recurrence within the irradiated field [52–55]. However, in a series of 31 patients who received radiation at MD Anderson, three developed recurrences on the edge of the radiation field [50], suggesting that an appropriate treatment field should encompass large margins around the surgical bed.

Therefore, our current recommendations for treatment of the primary site of disease are surgical excision followed by adjuvant radiation. The surgical procedure needs not be extensive, as postoperative radiation should always be given and include a generous 5-cm margin, except when limited by the tolerance of adjacent critical structures [8]. When the primary site is in the head and neck, we recommend treatment of the entire ipsilateral neck [4].

Given the propensity of Merkel cell carcinoma to spread to regional lymph nodes, routine elective nodal irradiation was previously advised. However, current guidelines support the use of sentinel node biopsy [16]; if the sentinel node is positive, nodal irradiation is preferred over lymphadenectomy. For patients who present with involved lymph nodes, we recommend excision of the primary disease and therapeutic lymphadenectomy, followed by radiation of the primary surgical bed and draining lymphatics [4].

Radiation is typically delivered in 2-Gy fractions using electrons with an appropriate bolus. The elective region is treated to 46–50 Gy, followed by an additional 10-Gy boost in five fractions to a smaller volume encompassing the microscopic or gross residual disease. Large, bulky tumors should receive a total dose of 66 Gy [4].

Adnexal Carcinoma

Carcinomas of the adnexal structures of the skin are uncommon. Sebaceous carcinomas are typically treated with wide local excision and lymphadenectomy if lymph nodes are involved [56]. Because of the rarity of this tumor, recommendations for postoperative radiation are not well-described, but general indications for adjuvant radiation can be suggested based on the behavior of other carcinomas. These indications include positive margins, perineural invasion, bone or cartilage invasion, extensive muscle invasion, an involved lymph node larger than 3 cm, extracapsular extension, and multiple positive lymph nodes [4].

Eccrine and apocrine carcinomas are addressed by wide local excision and postoperative radiation [4]. Adjuvant radiation is particularly important for eccrine tumors, which tend to recur locally when treated with surgery alone [57]. Patients with adenopathy should undergo therapeutic nodal dissection and postoperative radiation to the nodal basin.

For all adnexal carcinomas, the radiation target is the surgical bed plus 2–3-cm margins and the draining lymphatics. The typical postoperative dose is 60 Gy administered at 2 Gy per fraction [4].

Mycosis Fungoides

The first documented use of radiation to treat mycosis fungoides, a low-grade cutaneous T-cell lymphoma, was in 1902 [5]. Because lymphocytes are extremely radiosensitive, dramatic responses could be obtained with early methods of radiation, but achieving a sustained response was practically impossible due to the difficulty of safely treating the entire skin surface [5]. Improvements in radiation technology over the last several decades have led to the development of total skin electron irradiation (TSEI) as a safe and highly effective treatment for mycosis fungoides.

TSEI can be used in the management of almost all stages of mycosis fungoides [58, 59]. The target is the entire skin surface, including the epidermis, adnexal structures, and dermis [58]. The goal of treatment is to provide sufficient dose to the skin so that a durable remission is obtained while ensuring patient comfort and minimizing toxicity.

TSEI is technically complex. We recommend using a modified Stanford technique [5] in which patients are typically placed in a standing position at least 3.5 m from the linear accelerator source. A Lucite plate is placed between the patient and the linear accelerator to scatter and degrade the electron beam, which has a nominal energy of 9 MeV. Over the entire course of treatment, the patient is positioned in six different positions relative to the linear accelerator (anterior, posterior, and four oblique stances) to ensure that the entire skin surface is exposed to the electron beam [60, 61]. In each position, the patient is treated with the beam angled 18° above and then again with the beam angled 18° below the central axis. This technique and the use of a Lucite plate result in the production of a homogeneous dose distribution in which 80% of the dose is located at 0.7-cm depth. This is almost ideal coverage, as the malignant infiltrates are generally limited to the epidermis and upper dermis [5, 60].

Until recently, the total skin surface was treated to at least 30 Gy in 2-Gy fractions. Sites of gross disease were boosted with appositional electron fields for an additional 8–16 Gy as clinically indicated. In this situation, treatments are delivered 2–4 days per week such that the entire treatment course takes 9–10 weeks [5].

Multiple small prospective studies have evaluated the tolerability and efficacy associated with lower-dose TSEI using a 12-Gy regimen. This regimen provided rapid reduction of skin disease for patients with stage IB to IIIA disease with response rates exceeding 88%. Using this regimen was associated with a lower complete response rate than the standard higher dose and would possibly provide a shorter duration of response [59]. It was also generally better tolerated than the higher dose regimen and is likely more amenable to retreatment [59, 60].

For either regimen, the soles of the feet, which are shielded from the radiation while the patient is standing, are boosted with additional appositional fields so that they receive an adequate dose. If the scalp has gross disease, it will also be boosted to ensure adequate coverage. Appositional fields are usually treated with 1-cm bolus to ensure adequate dose is delivered to the skin. To protect the lens of the eye, specialized lead shields are placed in the eye during treatment. The feet are also shielded with lead boots for half of the treatment [5].

The initial response occurs over the first few weeks of treatment. Figure 19.6a shows a representative lesion on the arm of a 71-year-old woman with stage IB mycosis fungoides that showed a good response after the first 20 Gy of treatment (Fig. 19.6b). Although the treatment effect is often durable, TSEI may be repeated for recurrent disease, especially if the patient had a good response to the first course.

With good supportive care, many patients can tolerate the entire treatment course without an unscheduled break. However, the side effects of TSEI require diligent management, particularly with the higher dose regimen. Table 19.5 shows acute and chronic side effects of TSEI, which

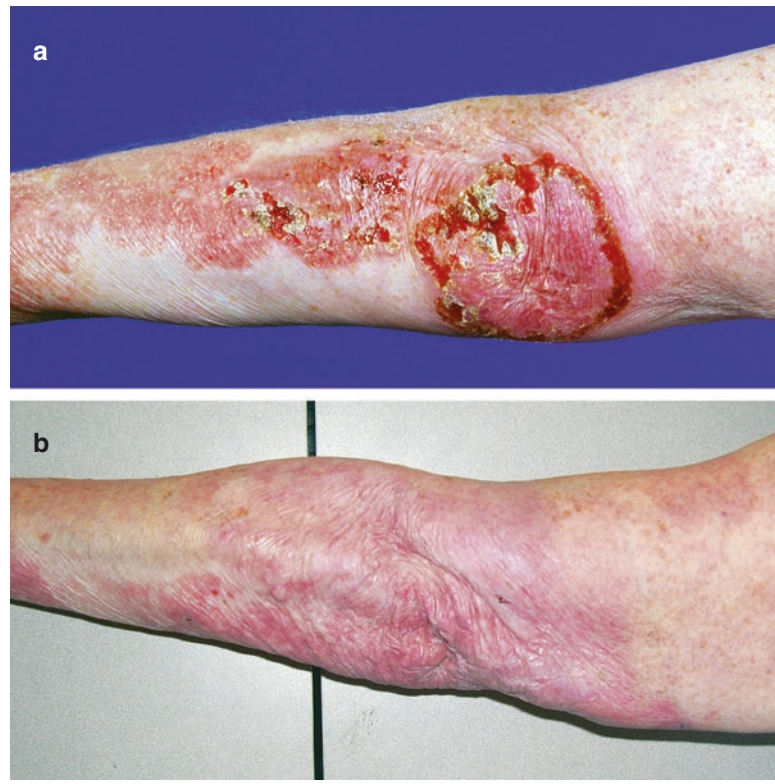

Fig. 19.6 Representative lesion on the arm of a 71-year-old woman with progressive stage IB mycosis fungoides unresponsive to medical therapy. (**a**) The lesion prior to total skin electron irradiation. (**b**) The lesion 1 month later, after 20 Gy of total skin electron irradiation. After 32-Gy total skin irradiation, her residual lesions received an additional 8–24 Gy each. She completed the treatment in 9 weeks, with resolution of all of her lesions

Table 19.5 Side effects of total skin electron irradiation [1, 58, 59, 62]

Acute side effects
Erythema and hyperpigmentation, greater in areas of previous ultraviolet exposure
Desquamation, particularly in tissue folds
Pruritus
Bullae, typically over the hands and feet
Fatigue
Xerosis
Temporary, complete alopecia
Temporary loss of fingernails and toenails
Hypohidrosis/anhidrosis
Chronic side effects
Dyspigmentation
Telangiectases
Atrophy of the skin
Xerosis
Alopecia
Hypohidrosis/anhidrosis
Skin cancer development

must be clearly communicated to the patient prior to the beginning of treatment. The lower-dose regimen was associated with fewer side effects, particularly noting no anhidrosis, less common loss of fingernails, and alopecia that was reversible [59].

Radiation for Advanced Disease and for Palliation

For patients with locally advanced inoperable skin cancers, radiation can often provide local control and symptomatic relief [4]. The outcome depends on the tumor size, location, and expected toxicity of the treatment. Doses up to 60–70 Gy delivered over 6–8 weeks can provide local control [63], although the likelihood of such control is decreased by adverse features such as bone involvement and perineural spread [63, 64].

The fractionation schedule used for palliation of inoperable or metastatic disease depends on the patient's life expectancy and the tumor location. For carcinomas, the most commonly used regimens are 30 Gy in ten fractions over 2 weeks or 45–50 Gy in 18–25 fractions over 4–5 weeks [4]. For melanoma, a hypofractionated schedule of 30 Gy in five fractions over 3 weeks may be used for metastatic disease outside the brain. For melanoma patients with brain metastases but otherwise good disease control, stereotactic radiosurgery should be considered [65].

Complications from Radiation

Even with modern methods, the doses of radiation necessary to control tumors cause acute and chronic side effects that should be reviewed in detail with the patient prior to the initiation of treatment. One of the earliest responses to treatment is erythema within the treated field [8], which constitutes the first stage of acute radiation dermatitis [62]. This usually progresses to dry and then moist desquamation, especially as tumoricidal doses are reached. When this occurs, the affected area should be treated with mild, low-pH cleansing agents that do not exacerbate the existing dermatitis and may reduce the bacterial load. Petrolatum-based emollients with or without hydrogel dressings may also be used to maintain a moist environment, which will enhance reepithelialization. Topical or oral antibacterial agents should be considered in wounds that are at high risk for infection or are already infected (see Fig. 19.7). Additionally, silver-based dressings are antibacterial and may also be helpful. Consultation with a multidisciplinary wound care team should be considered for radiation-related dermatitis that does not respond to these measures [62].

Depending on the individual, the skin reaction peaks at about 3–6 weeks and then resolves. The skin should be shielded from additional injury during and after treatment [8]. This includes protection from sunlight, heat, cold, and friction [4, 62]. Patients should be advised to apply sunscreens with protection factors of at least 15 to the treated area [4]. When the head or neck has been treated, patients should wear a hat when

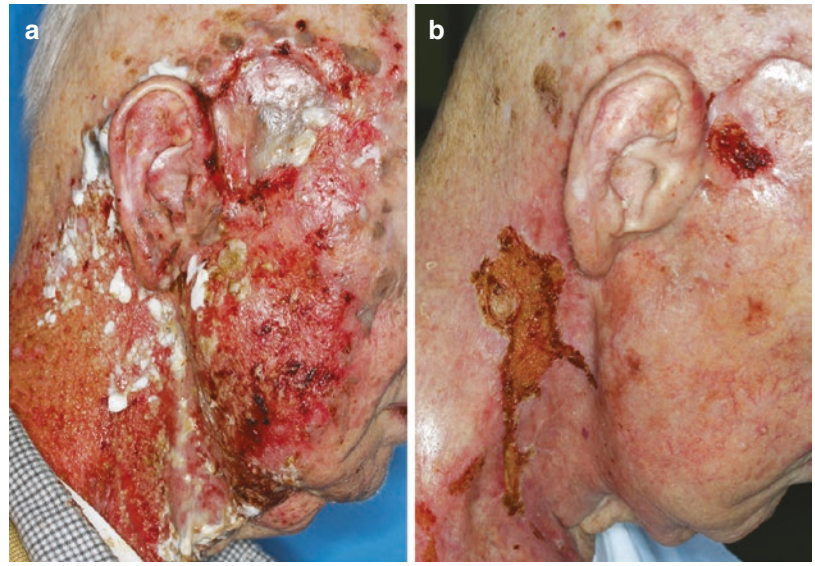

Fig. 19.7 (**a**) Radiation dermatitis and superinfection in the irradiated field in a patient receiving radiation for a metastatic SCC. (**b**) Marked improvement following topical emollients, antibacterial cream, and antibiotics

outdoors. These habits should continue throughout and after the completion of treatment.

Additional specific acute effects depend on the size and location of the treated lesion. These include mucositis of the oral and nasal mucosa, dryness of the nasal passages, synechiae, conjunctivitis, and alopecia [4]. These reactions generally worsen over the treatment course and typically resolve over the days to weeks following the completion of treatment; they can usually be managed conservatively.

Long-term complications can develop over the months to years following radiation and are generally limited to the irradiated field. The likelihood of late effects increases with larger fraction sizes, higher total doses, and larger volumes of irradiated tissue. Common long-term effects include fibrosis, hyperpigmentation, hypopigmentation, telangiectasias, and atrophy of the skin [4]. To reduce the risk of chronic fibrosis, physical therapy as well as active and passive range of motion exercises can help maintain mobility and prevent contractures [62]. Dryness of the skin due to loss of sweat gland function and alopecia are usually permanent. Because of vascular changes, irradiated skin may heal more poorly from surgery [8]. Additional long-term effects also depend on the location of the irradiated field. For instance, radiation near the eye can cause ectropion, cataracts, or epiphora [4].

The risk of tissue necrosis from modern therapeutic radiation is much lower than commonly believed. Using contemporary methods, the rate of soft tissue necrosis should be less than 3% [3], while the risk of bone necrosis is approximately 1% [4].

Ionizing radiation also increases the risk of skin cancers within the treated field. In particular, an increased incidence of BCC has been observed following radiation, and this risk is greater for radiation exposure at young ages [66, 67] (Fig. 19.8).

The occurrence of other tumors including radiation keratoses, SCC, and melanoma is not as well documented [62] (Fig. 19.9). Of interest, it appears from available evidence that the excess risk of skin cancer lasts 45 years or more following treatment [68]. While an individual patient's risk is low, they are generally at higher risk if they are young and female or as their time since radiotherapy increases [69].

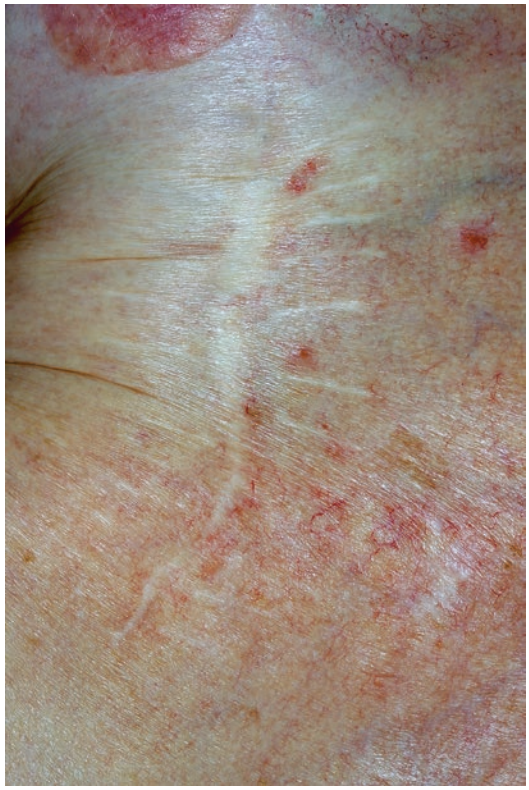

Fig. 19.8 Telangiectasias and superficial BCC have developed in the irradiation field of this 66-year-old female who received irradiation for breast cancer some 30 years previously. The superficial BCC responded well to imiquimod

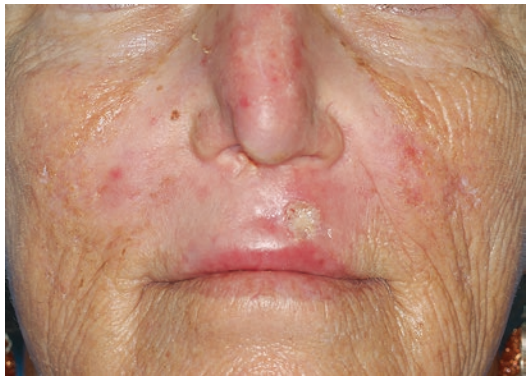

Fig. 19.9 Development of SCC on the lip in this 53-year-old patient who underwent irradiation for SCC of the nasal cavity 6 months previously

Summary

In appropriately selected skin cancer patients, radiation can be useful primary or adjuvant therapy that allows for the preservation of adjacent normal tissues. A variety of techniques are available that can provide good tumor coverage while minimizing the exposure of critical normal structures. With attentive patient care during treatment, most side effects can be managed conservatively. Long-term follow-up of irradiated patients is important to monitor for the development of late effects and new, metachronous tumors.

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Chapter 20
When to Refer Out

Daniel Mark Siegel, Laura T. Cepeda, and Deborah F. MacFarlane

As physicians treating skin cancers, our training and experience vary. Regardless, many of us have the need and opportunity to perform varying degrees of skin surgery. The procedures we perform will be based on our experiences and particular areas of expertise, but for even the most experienced practitioner, there are patients whom one should refer out instead of treating. Deciding just which patients to refer out may be difficult and is a skill that is often acquired painfully through experience. It is our hope to provide some guidelines to aid in the decision to refer out so that one may avoid some potential medical, surgical, psychological or legal headaches. The following might be written from the viewpoint of the Mohs surgeon, but hopefully, there will be insights to be gleaned by anyone treating skin cancers.

Reasons to Refer Out

The Lesion

Some lesions are simply too large to be excised under local anesthesia. While one can perform appendectomies under local anesthetic in certain dire situations, there is no reason why they should not be performed under general anesthetic; the same applies to certain large skin cancers. Morbidity, patient discomfort, and operative time may all be reduced in such procedures. Very large skin cancers near anatomically vital structures can be referred out. While Frederick Mohs, for instance, successfully treated two cases of carcinoma of the larynx under local anesthesia, there is no reason to perform such procedures under local anesthetic [1].

Similarly, extensive skin cancers of the genital and/or rectal area can often more easily be treated under general anesthesia, but cure rates may be lower.

The patient who presents with a multiply recurrent skin cancer following several Mohs procedures is probably best referred on to a head and neck surgeon to have the area excised under general anesthesia with the same concern regarding cure rates.

The Patient

While very elderly patients with various comorbidities can safely undergo Mohs surgery [2], some patients of any age are simply too frail physically and/or mentally to withstand the challenges of prolonged conscious surgery plus possible revisions.

Other patients will mention up front that they are extremely nervous about having procedures performed under local anesthetic. Listen to them and explore their past surgical experiences. Nothing is to be gained by trying to convince such a patient that an excision performed under

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local will be easy. It is better to spell out the entire procedure at length to the patient and their family members and/or caregivers. Patients who are unable to communicate, for example, those who have had prior cerebral events, may be better managed with excision under general anesthetic if the risks of the anesthesia do not outweigh its benefits.

Listen to your patients' esthetic concerns.

Even though they may be paralyzed and in a wheelchair, do not assume that their facial appearance will be less important to them; often, quite the reverse is true.

Psychological Referrals

This is probably the most difficult area for the majority of physicians to deal with. Successful management requires that the surgeon first consider the patient's psychological needs and put aside the knowledge that their skills may be entirely adequate to treat the patient. This relates both to oncologic and cosmetic procedures.

Take note if your staff comments on a patient's belligerent attitude toward them.

Screening these sorts of patients can at times be difficult, but over the years, we have noticed that there are certain features that many of these patients share:

1. The patient will often be hostile and unpleasant on the phone with staff members but especially pleasant when in the room with the physician.
2. The patient spontaneously, during the course of the consultation, blurts out, "Shouldn't this be done by a plastic surgeon?"
3. The patient has unrealistic expectations and is most concerned with maintaining their appearance from their premorbid state regardless of how large a tumor may be.
4. The patient has very distinct anatomy whereby obtaining the desired outcome can be rendered difficult. Examples include individuals with petite, pert noses where even the smallest distortion would be noticeable. Similar anatomic issues could be raised with regard to lips and eyelids in some individuals. Ears are a less common cause of this concern as one can generally only see one ear at a time, and slight to significant asymmetry of ears is often the norm even in the premorbid state.
5. Other warning signs include the patient in whom you preoperatively point out that they have a deviated septum or other abnormality of symmetry and the patient expresses a complete unawareness of the problem. Although it sounds a bit paranoid, the physician must be aware that sometimes this asymmetry, if not well documented in the premorbid state, can be used in legal claims postoperatively as something that was done to the patient.

The importance of photography, pre- and postoperatively, cannot be overemphasized.

Dermatologic surgeons do not infrequently see patients with body dysmorphic disorder (BDD). Also known as dysmorphobia, this is a psychiatric condition that consists of a distressing and/or impairing preoccupation with a nonexistent or slight defect in the appearance [3–5]. The outcome with surgery may be poor with complications including dissatisfaction, litigation, and violence toward the surgeon, depression, or suicide [6, 7].

The reported rates of suicidal ideation of 57.8% in such patients emphasize the importance of identifying patients with this disorder [8]. Although primarily a psychiatric condition, patients with BDD are more likely to present to a dermatologist and/or plastic surgeon than to a psychiatrist [9]. Estimated to have a prevalence of 1.8%–2.4% [10] in the general population, higher rates of BDD are observed in patients attending dermatology and cosmetic clinics [11]. While any area of the body may be the focus of concern, the most common areas are the skin, the hair, and the nose [12, 13]. This should be borne in mind when evaluating patients with nasal skin cancers. We have encountered several patients with coarse rhinophymatous noses who perseverated postoperatively upon small surgical scars left on their noses. This was despite extensive preop-

erative education that surgery upon sebaceous skin does not produce fine scars. Such patients may push for numerous surgical revisions.

Recognition of this disorder is essential to avoid unnecessary and often unsatisfying surgical outcomes. However, this disorder often goes unrecognized [14].

Preoperative assessment with validated tools in addition to a detailed face-to-face component is crucial. The Body Dysmorphic Disorder (BDDQ) is a validated self-administered brief (1–2 minutes) screening instrument that patients can complete while waiting to see the surgeon. Developed in the psychiatric setting, the BDDQ was validated in the facial plastic surgery patient population and found in the surgical setting to have a sensitivity of 100% and a specificity of 89% [15]. The BDDQ-DV (dermatology version) has a sensitivity of 100% and a specificity of 94.7% [15]. BDD has also been observed to occur postoperatively in some patients [16]. These observations should be considered by anyone performing reconstruction following cancer surgery.

The dermatologic surgeon can provide education about the diagnosis of BDD and refer the patient to a psychiatrist or other qualified mental health professional familiar with this disorder. Serotonin-reuptake inhibitors and cognitive-behavioral therapy are often effective [17].

The Doctor

As we progress in our medical careers, we find that we may not be as current with newer therapies as those who have specialized in particular areas. In such instances, we should not hesitate to share patients who need these therapies with those in our communities who are most enthusiastic about their use, skilled in their application, and best equipped to handle these patients. These are often easy decisions to make. We see a patient who has an obvious disease of a severity beyond which we are comfortable managing, and we simply refer that person on. Alternatively, we see some patients, scratch our heads, and, in a state of slightly embarrassed confusion, send these patients on to someone in the community for diagnosis and management of their conditions. Sometimes, we refer these patients with the intent of having the accepting consultant take over the care of the patient, while other times we simply want their wisdom and advice so that we may continue to manage the patient. A decision as to which way to proceed here becomes an individual one.

Our threshold for referral out for reconstruction after a Mohs procedure tends to be low. Our philosophy is that, if the patient requests to have a plastic surgeon perform the reconstruction, we are more than happy to arrange this. To try to argue the patient out of their decision may cause them to be ultimately unhappy with the result. Some patients are not pleased no matter who performs the reconstruction. Although our skills may be perfectly adequate with regard to achieving the desired outcome, if there is any doubt, we prefer to sleep well that night knowing that, while we have cleared the tumor, someone else will deal with the less absolute process of helping this patient regain or develop the appearance they wish to have.

The Doctor's Colleagues

This is important so that you may work together not only for the unexpected disaster but also for the less complex cases where their skills will enhance the patient's final outcome. Ideally, get to know your surgical colleagues on a first-name basis and learn what their particular interests and areas of expertise are. This is helpful for those times when you may wish to have uncensored conversations with them about difficult or complex patients.

> Developing relationships with your colleagues in the other surgical disciplines is vital.

Remember, what you put in the medical record lasts forever, but what you say on the phone only reverberates between the two of you. These relationships are also very helpful for facilitating emergent situations, such as when a "simple" Mohs excision evolves into a much more complex process involving vital structures and necessitating general anesthesia to complete the tumor

removal or undertake reconstruction. Similarly, be available to treat their patients as soon as possible once you receive the request. If you are in a position to do so, offer to have their fellows rotate with you, agree to lecture at their rounds, write or coauthor chapters with them, and participate in their research. These same tenets are applicable to developing relationships with your neuroradiologists, radiation oncologists, medical oncologists, and indeed anyone whose expertise you may seek while caring for your skin cancer patients.

It is advantageous to find colleagues to refer to whose approach to esthetics and to handling patients mirrors your own. Not uncommonly, one may have a patient with a small wound, for which second intention healing would be optimal, but who demands to see a plastic surgeon. It can be reaffirming when the patient returns the following week saying that the plastic surgeon suggested letting the wound heal on its own first before doing anything. Having your recommendations reinforced by colleagues not only validates your knowledge in a patient's eyes but can also be reassuring to a patient who initially has difficulty accepting a diagnosis or necessary treatment option.

Specialists to Whom You May Need to Refer

Medical Oncology

The management of basal cell and squamous cell carcinoma has not changed dramatically in the past few decades. However, the medical oncologist can be a valuable adjunct for the patient with the rare metastatic basal cell carcinoma or the less rare patient with metastatic squamous cell carcinoma. With the advent of oral hedgehog pathway inhibitors for Basal Cell Carcinoma (BCC) and checkpoint inhibitors for Squamous Cell Carcinoma (SCC), these patterns may change. In the authors' opinion, patients with BCC who might benefit from a hedgehog inhibitor are still best managed by the dermatologist, and we are comfortable managing the side effects profiles. For SCC managed with checkpoint inhibitors, comanagement with an oncologist would be preferred due a slightly more complex side effect profile.

Geneticists

These colleagues are especially useful for the management of those genodermatoses associated with skin cancer. Muir-Torre is one notable example, and it is particularly helpful to have a geneticist perform the necessary diagnostic tests and to take over the medical management of these patients and their relatives.

Surgical Oncology

A head and neck surgeon with expertise and interest in oncology can be your most valuable ally in the management of aggressive head and neck cancers that may invade the ear canal or nasal cavity. Remember that they have specialized equipment that allows them to better visualize these areas. Fiber-optic telescopes are used for intranasal illumination and magnification, and microscopic visualization is available for the ear canal.

Similarly, an oculoplastic surgeon is especially helpful when it comes to infiltrative carcinomas involving the medial canthal area [18]. Lesions suspected to invade the lacrimal drainage system are probably best investigated preoperatively by an oculoplastic surgeon by cannulating and irrigating the drainage system combined with an intranasal examination from the middle meatus to the inferior meatus. In addition, lesions known to extend down the lacrimal drainage system beyond the common canaliculus should be referred on for consideration of a partial maxillectomy (either direct external or endoscopic internal) and eventual tear drain reconstruction via either a dacryocystorhinostomy or conjunctivodacryocystorhinostomy once disease is clearly eradicated. Oculoplastic surgeons also

have access to instruments that may be useful in skin cancer management. Slit lamp examinations, for instance, coupled with special vital stains, such as Rose Bengal, may be helpful in identifying the extent of conjunctival and corneal lesions.

> Err on the side of over-involving your surgical colleagues preoperatively.

Who knows if the skin cancer you are planning on excising will reach a level of invasion that either/both you and/or the patient is not comfortable with excising further under local anesthesia. It is far better to refer patients out liberally and to send on the occasional patient whom you might have handled well than to be overly possessive and conservative with regard to referrals out and to then have long and deep regrets over the one that should have gotten away but did not.

Radiation Oncology

The most costly way to treat skin cancer in the United States today is by radiation oncology. The cost of a fractionated course of radiation therapy may run more than $8000 [19] for even a very small skin cancer. Linguistically, the radiation oncologist uses the term "control" of cancer with treatment instead of "cure" that is preferred for most tumors. While radiation is not the preferred primary therapy for most skin cancers, it can be used as an adjunct for certain patients (see Chap. 19). Squamous cell carcinomas that exhibit aggressive histologic patterns such as perineural, perivascular, intravascular, or intraneural invasion may benefit from an adjunctive course of radiation to potentially treat a field even if negative margins are achieved with excision. Of course, checkpoint inhibitors may be an alternative or addition to RT. One must consider the downside of radiation, which, depending on the site, can result in permanently dry eyes, dry mouth, and other alterations of activities of daily living, in addition to esthetic deformities such as hair loss.

For the younger patient, we do not, in general, advocate radiation therapy, as the margin is blind and the recurrences are often more technically challenging than the primary tumor might have been.

For the nursing home-bound patient with multiple comorbidities who might be a radiation candidate, consider as an alternative cryosurgery with well-measured halo-thaw times or a thermocouple (see Chap. 7). While the same limitation exists here as for radiotherapy (blind margin), the cost, not only in dollars but also in terms of time, is far less to the patient and healthcare system. An oozing and weeping, but infection-resistant, wound for 10–20 days is the only appreciable side effect.

Prosthetics

Prosthetic rehabilitation is used where successful surgical reconstruction is not an option due to factors such as poor prognosis, comorbidities, and compromised healing and where patients refuse to have further surgery. Prostheses can also function as an interim measure for later reconstruction. Treatment involves the creation of a custom-made device usually from polydimethylsiloxane (PDMS). The use of extraoral endosseous implants aids the retention and stability of maxillofacial prostheses. An evolving area is the use of 3D printing techniques to create custom-made facial prostheses, which are flexible, nondegradable, and in patient-specific skin tones. Plastic surgery can also use 3D printing technologies to create fixation and implanted medical devices to improve patient outcomes. 3D printing can be used to create either scaffolds or living cellular constructs to signal tissue-forming cells to regenerate defect regions [20].

If a patient has a tumor that you suspect will be extensive and the patient is not a candidate for reconstruction, it is advantageous to involve a maxillofacial prosthodontist or anaplastologist preoperatively, so that they may observe the patient's premorbid appearance. They may need to perform imaging and measurements preoperatively as well as postoperatively to create

the best prosthesis in an appropriate time frame. Indeed, the physical and mental well-being of these patients demands good organization and communication among the health professionals involved in their treatments [21].

It is not uncommon for a patient who initially considers a prosthesis to be a "temporary" solution, to keep it, often avoiding multiple prolonged reconstructive procedures and allowing easier surveillance of the defect frequently associated with an aggressive tumor [22].

Wearing such prostheses has been found to lessen the psychological impact of the facial defect (Figs. 20.1 and 20.2) [22].

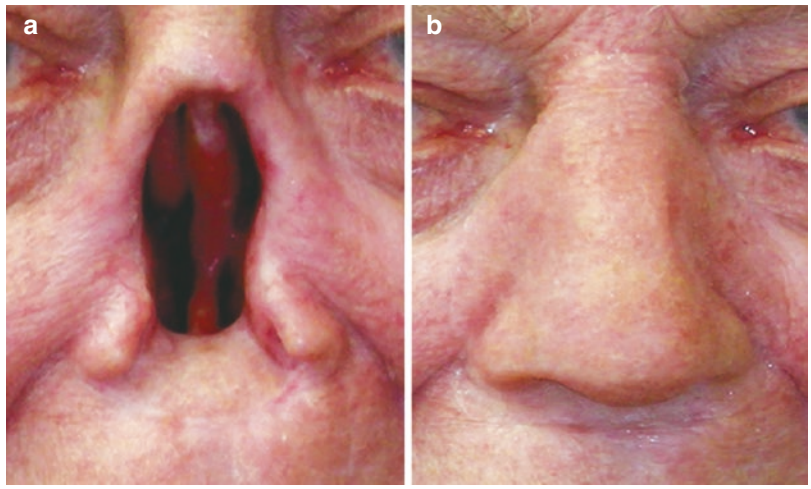

Fig. 20.1 (**a**) A 73-year-old female with history of adenoid basal cell carcinoma of the right nasal region, following surgical resection of right nasal ala. (**b**) Nasal defect restored with silicone nasal prosthesis characterized to patient's unique skin tones. Medical grade liquid adhesive is used to retain the prosthesis but must be removed daily to avoid irritation of the bearing tissue. (Photographs courtesy of Patricia C. Montgomery Anaplastologist, Section of Dental Oncology and Prosthodontics Department of Head and Neck Surgery, MDACC)

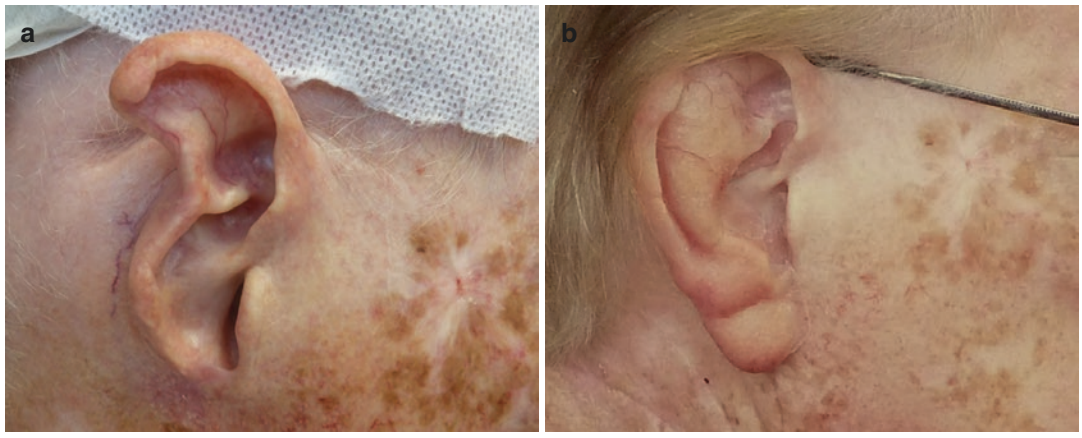

Fig. 20.2 (**a**) A 76-year-old male with a history of an auricular squamous cell cancer following partial auriculectomy and radiation. (**b**) Total auricular defect restored with silicone auricular prosthesis. (Photographs courtesy of Patricia C. Montgomery Anaplastologist, Section of Dental Oncology and Prosthodontics Department of Head and Neck Surgery, MDACC)

Given the ever-increasing number of nonmelanoma skin cancers, it is increasingly important that, as physicians, we educate ourselves not only as to the best techniques to manage our patients with skin cancers but also to be knowledgeable of the various skill sets of our medical and surgical colleagues who are addressing the same problem.

As detailed previously, there will always be patients who should be referred out, and it is our hope that this discussion has provided the practitioner with a few points as to how to identify and manage such patients.

Acknowledgments University of Wisconsin School of Medicine and Public Health for access to F.E. Mohs text, Chemosurgery in Cancer, Gangrene and Infections 1956. Charles N.S. Sopakar, M.D., Ph.D., oculoplastic surgeon, Clinical Associate Professor Ophthalmology and Plastic Surgery, Weill Cornell Houston Methodist, Clinical Associate Professor of Plastic Surgery, Baylor College of Medicine, Clinical Specialist, Head and Neck Surgery. M.D., Anderson Cancer Center; Mark S. Chambers, D.M.D., M.S. Professor, Chief, Section of Oncologic Dentistry and Prosthodontics, Department of Head and Neck Surgery, University of Texas M.D. Anderson Cancer Center. Therese M. Hofstede, D.D.S., BSc, Associate Professor, Department of Head and Neck Surgery, University of Texas M.D. Anderson Cancer Center. Photographs courtesy of Patricia C. Montgomery Anaplastologist, Section of Dental Oncology and Prosthodontics Department of Head and Neck Surgery, MDACC.

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Chapter 21
Chemoprevention of Keratinocyte Carcinomas

Olivia M. Lucero, Fiona O'Reilly Zwald, and David Lambert

The overall incidence of keratinocyte carcinomas (KC), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is increasing with current estimates predicting that one in five Americans will develop skin cancer in their lifetime [1–4]. It is important to identify those patients with the greatest risk for the development of numerous or catastrophic tumors (Table 21.1) [5]. Solid organ transplant recipients (OTR), in particular, are at a heightened risk compared to the general population, with the incidence of cutaneous carcinogenesis increasing with age and the duration of immunosuppression [6, 7]. With an improvement in transplant care leading to an increase in posttransplant survival time, strategies to reduce KC are critical [8].

> High-risk populations in chemoprevention studies include those with a history of multiple skin cancers, xeroderma pigmentosum, basal cell nevus syndrome, psoralen-UVA exposure, and solid organ transplants.

Before considering chemoprevention with systemic agents, the physician must first balance the adverse effects of therapy versus the morbidity and inconvenience of surgery. It must be emphasized that systemic chemoprevention augments but does not completely replace surgical intervention as definitive treatment of skin cancers that arise during therapy will still be needed. Furthermore, it should be noted that the FDA has only approved topical imiquimod, 5-FU, and aminolevulinic acid for the treatment of precancerous lesions; there are no systemic agents that have been approved for skin cancer chemoprevention [9]. As a result, the out-of-pocket cost for these medications might be prohibitive. This has increasingly been the case for systemic retinoids where side effects and cost are the two main barriers for use.

Lastly, it is important to note that ultraviolet radiation (UVR) is an established carcinogen that initiates and promotes cutaneous carcinogenesis. Accordingly, the standard of care for prevention of cutaneous malignancies is minimization of UVR exposure through use of sunscreen and protective clothing [5]. Furthermore, the approach outlined below should be considered a basic guide that should be individualized for each patient.

D. F. MacFarlane (ed.), *Skin Cancer Management*, https://doi.org/10.1007/978-3-030-50593-6_21

Table 21.1 Populations at an increased risk of keratinocyte carcinomas

Diagnosis	Mechanism of cutaneous carcinogenesis	Studies with KC incidence as an endpoint
Multiple NMSC or AKs	Multifactorial including cumulative UV damage	Retinoids DNA repair enzymes Vismodegib Nicotinamide
Xeroderma pigmentosum	Hereditary defect in DNA mismatch repair	Retinoids DNA repair enzymes
Basal cell nevus syndrome	Loss of *PTCH* tumor suppressor	Retinoids Vismodegib
Solid organ transplant recipients	Immunosuppression and carcinogenic regimen	Retinoids Nicotinamide Capecitabine mTOR inhibitors
PUVA treatment	Immunosuppressive, carcinogenic exposure	Retinoids
AIDS	Immunodeficiency	*
CLL	Immunodeficiency	*
Arsenic exposure	Carcinogenic exposure	*
Vitiligo	Lack of protective melanin	*
Recessive dystrophic epidermolysis bullosa	Attributed to chronic, nonhealing wounds	*
Albinism	Lack of protective melanin	*

KC keratinocyte carcinomas, *AIDS* acquired immunodeficiency syndrome, *CLL*, chronic lymphocytic leukemia, *AK* actinic keratoses
*No KC chemoprevention studies in this population

Oral Retinoids

While promising new agents have emerged, retinoids have been used in dermatology for years. Retinoids are natural or synthetic compounds that have the biological activity of vitamin A. The correlation between a vitamin A-deficient diet and epithelial dysplasia was first noted in the 1950s in rodent models. Since this time, retinoids have been shown to have antitumor activity in a variety of malignant contexts [10]. In keratinocytes, their complex mechanism of action has been suggested to include induction of apoptosis, cell cycle modulation, and differentiation [11–13].

Oral retinoids, including isotretinoin 0.5–1.0 mg/kg/day, etretinate 50 mg/day (now off the market), and acitretin 25–50 mg/day, have been used to prevent and treat keratinocyte carcinomas in high-risk patients for years (Fig. 21.1). Patients with xeroderma pigmentosum (XP) treated with isotretinoin 2 mg/kg/day for two years experienced an average of 63% fewer tumors during the treatment period [14]. In a 15-year cohort study of patients with psoriasis treated with oral psoralen-UVA and retinoids for greater than one

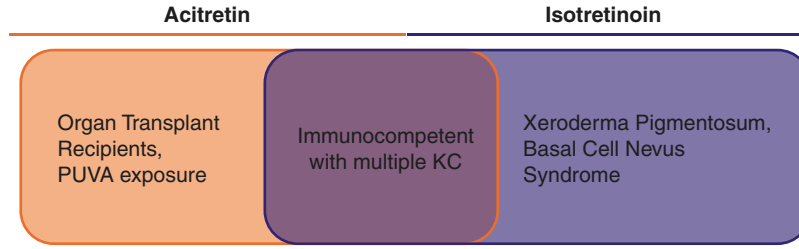


Fig. 21.1 Populations studied in systemic retinoid chemoprevention trials

year, active retinoid use was associated with a 30% reduction in SCCs compared to periods off the medication ($P = 0.002$) [15].

There is a wealth of supportive data in the literature on the use of acitretin as chemoprevention in the organ transplant recipient (OTR) population [16–23]. Please see Chap. 17. Two prospective trials were included in a Cochrane Review [24]. In a population of 44 renal transplant recipients with a history of KC, patients taking acitretin 30 mg daily had a 42% reduction in keratotic lesions compared to placebo (95% confidence interval (CI): 11.5–71.7) [22]. In a second open-label randomized crossover trial, the number of SCCs observed was significantly lower than in the drug-free period ($P = 0.002$) [21]. Although there is no comparative study of acitretin and isotretinoin, the latter has been safely used in reports and is a preferred option in patients of childbearing age because of its shorter half-life [25].

In immunocompetent patients with a history of KC, trials have used lower doses of retinoids with less efficacy. One study found that 25,000 IU of daily retinol significantly reduced the risk of a first new SCC; however, when pooled with a second trial, there was no significant difference in time to first SCC or BCC [24, 26, 27]. Similarly, pooled date from two studies examining isotretinoin 5–10 mg daily vs placebo found no difference in the risk of a new KC [24, 27]. In a more recent trial, the use of acitretin 25 mg 5 days weekly was not associated with a significant reduction of KC; however, an umbrella test utilizing KC incidence, time to new lesion, and total tumor counts did indicate a significant trend that favored acitretin (chi-square statistic, 3.94; $P = 0.47$) [28].

Indications

Retinoids should be considered as chemoprevention only in patients with significant KC development (Table 21.2). This includes the development of five to ten KC per year or high-risk SCC characterized by poor differentiation, large size, or position in a high-risk location [30–32]. A lower threshold should be considered in OTR with numerous actinic keratosis (AK) and an increasing development of aggressive KC. A more aggressive approach in those who are immunosuppressed due to lymphoma/leukemia should also be weighed. In advanced chronic lymphocytic leukemia, for instance, the risk of death from skin cancer is equivalent to the risk of death from leukemia [33]. Lastly, systemic retinoid therapy may also be offered to reduce the morbidity and mortality associated with a high-risk tumor or metastatic disease in which surgery is not an option.

Table 21.2 Clinical scenarios that prompt consideration of systemic retinoids [29]

Multiple skin cancers per year (5–10 per year)
Multiple KC in high-risk locations, e.g., the head and neck
Multiple AKs or KC in high-risk patient, e.g., transplant recipients in conjunction with decreased immunosuppression or those with lymphoma/leukemia
Explosive SCC or keratoacanthoma development
Single skin cancer with high metastatic risk
Metastatic squamous cell carcinoma
Patient undergoing prolonged UV phototherapy with a history of KC

> Retinoids remain the most well-characterized agent utilized in chemoprevention. The target dose should be adjusted to balance efficacy and adverse effects.

Contraindications

Retinoids are teratogens and should not be used in women who are pregnant (Table 21.3). Another contraindication is a history of severe hyperlipidemia refractory to standard treatments or markedly elevated liver function enzymes. Chemoprevention with oral retinoids is a continuous lifelong treatment; therefore, further elevation of hyperlipidemia or liver function enzymes—should this occur despite standard therapy—would be considered injurious to the patient. The package insert for acitretin provides

details on the required safeguards. Readers are encouraged to consult the package insert prior to commencement of systemic therapy.

Table 21.3 Contraindications for the use of systemic retinoids as chemoprevention

Pregnancy and lactation
Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years following discontinuation of acitretin
Moderate to severe liver dysfunction
Severe kidney dysfunction
Recalcitrant hyperlipidemia, especially hypertriglyceridemia
Concomitant medications that interfere with retinoids
Concomitant hepatotoxic drugs
Alcohol abuse

Dosing Recommendations

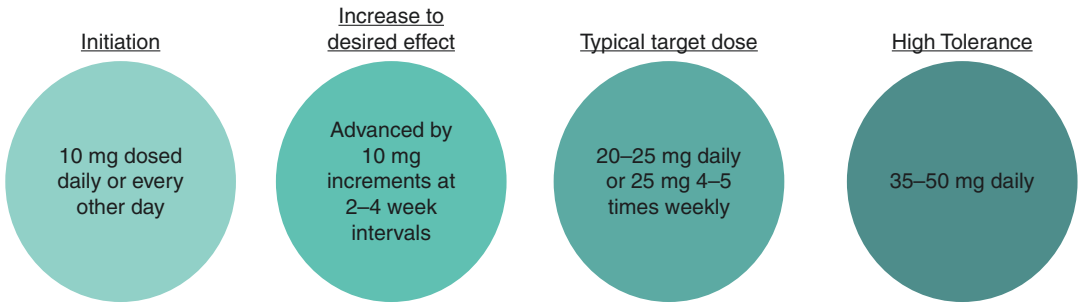
In general, adverse side effects are dose related. To promote tolerance, gradual dose escalation to the effective dose is recommended (Fig. 21.2). Pills are available in 10, 17.5, and 25 mg allowing for convenient titration. The medication is started at a low dose of 10 mg/day and increased by 10-mg increments at 2- to 4-week intervals to achieve the desired effect. The target dose is 20–25 mg/day as tolerance decreases swiftly at higher doses [34]. In some patients who are highly motivated, dosages of 50 mg/day or alternating 25 and 50 mg/day have been used. Higher dosages might also be necessary in those with KC at high risk for metastasis or those with inoperable disease. In these settings, retinoid chemoprevention might be used as an adjunctive to chemotherapeutic agents.

Patients must be maintained on systemic retinoids to achieve suppression of cutaneous malignancies. Abrupt discontinuation should be avoided as a rebound effect characterized by the eruption of aggressive SCCs can occur [22]. Therefore, it is preferable that side effects be aggressively managed and the dosage be reduced to a tolerable level.

> Rebound will occur in all patients if retinoid is discontinued; therefore, plan on long-term/lifelong therapy.

Adverse Effects

Early studies with systemic retinoid therapy involved the use of higher doses of isotretinoin and etretinate than current therapy, resulting in more adverse events.



Dosing Realities
- Response and side effects are dose dependent
- Low-dose and slow-dose increments may decrease side effects
- Manage mucocutaneous side effects aggressively
- Some patients may tolerate only average of 10–15 mg/ day while few will tolerate 35–50 mg/day
- Some patients may develop "tolerance" after having been at a suppressive level and may require and tolerate an increased dose

Fig. 21.2 Suggested acitretin dose escalation considerations and schedule

Mucocutaneous Side Effects

Mucocutaneous side effects are typically seen at doses of 20 mg daily (Figs. 21.3, 21.4, and 21.5). Cheilitis and dry skin are the most troublesome, especially at higher doses, and can be managed proactively with emollient therapy (Table 21.4) [34, 35]. As therapy continues, patients are often better able to tolerate these side effects. Alopecia and paronychia may occur at higher doses and often reverse with dose reduction. Periungual pyogenic granulomas have been observed (Fig. 21.3). Consider decreasing retinoid dose by 25% for severe mucocutaneous adverse events.

> Consider decreasing retinoid dose by 25% for severe mucocutaneous adverse events.

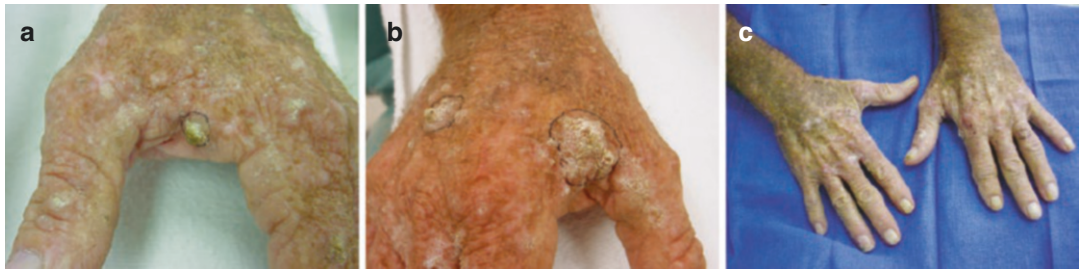


Fig. 21.3 Dorsal hands prior to treatment with systemic retinoids: (**a**) left hand and (**b**) right hand. (**c**) Improved dorsal hands and forearms after 14 months of acitretin 25 mg/day. Photographs courtesy of Dr. Thomas Stasko, Vanderbilt University

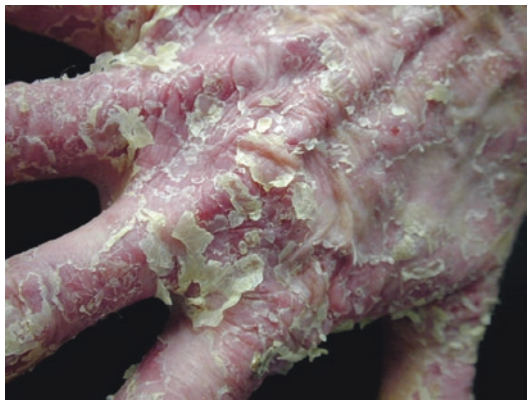


Fig. 21.4 Marked desquamation of the hands. Dose reduced to 25 mg, alternating with 50-mg acitretin per day. Photograph courtesy of Dr. Thomas Stasko, Vanderbilt University

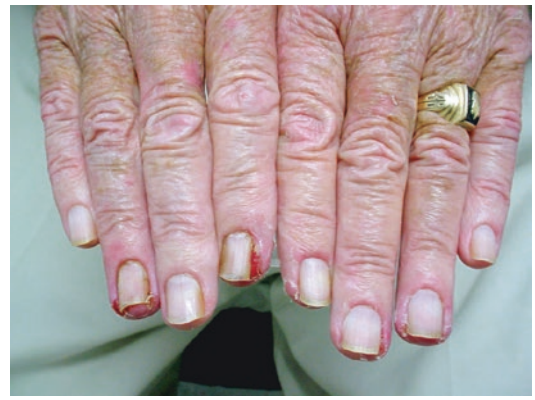


Fig. 21.5 Periungual pyogenic granulomas in a patient being treated with acitretin 25 mg/day. Photograph courtesy of Dr. Thomas Stasko, Vanderbilt University

Table 21.4 Management of mucocutaneous side effects of systemic retinoid therapy

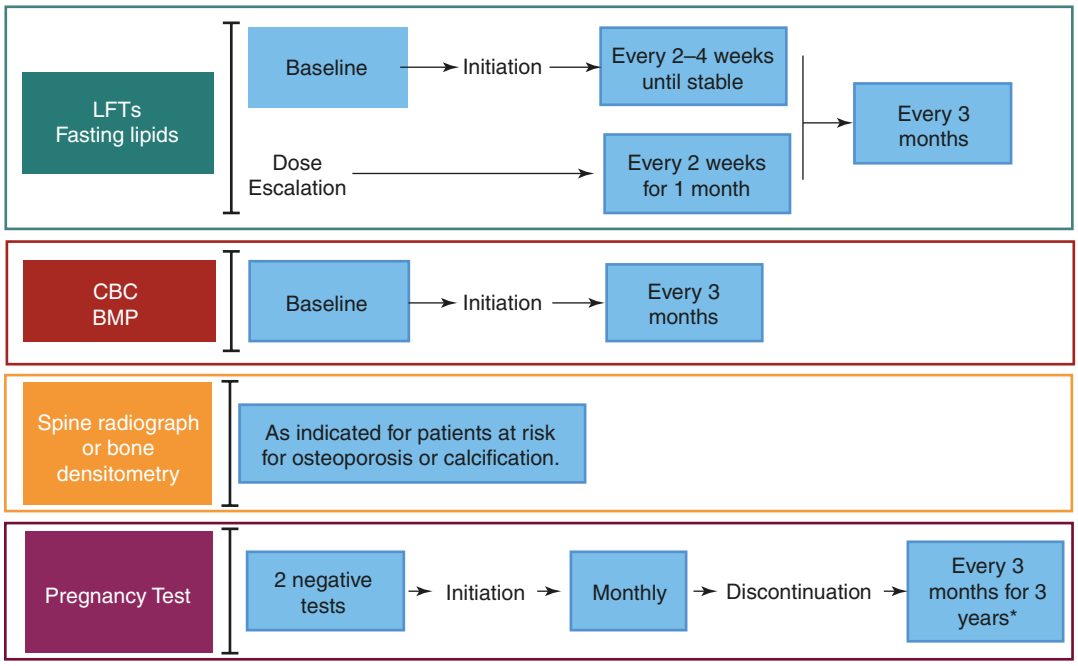
Hair loss can be a problem at higher doses and is variable between patients
Cheilitis, dry skin, and hair loss may cause many to discontinue therapy
Use emollients frequently from start of low-dose therapy Cheilitis/rhinitis: Apply Aquaphor® or petrolatum to the lips 5–10 times daily and inside the nose at bedtime Xerosis/pruritus: Tepid showers/bath; apply moisturizer after bathing and multiple times during the day Xerophthalmia: Artificial tears; avoid contact lenses
Pyogenic granulomas: Reduce dose

Laboratory Monitoring

A baseline fasting lipid panel, liver function tests (LFTs), renal function tests (BMP), serum glucose level, and complete blood count (CBC) should be performed before commencing therapy (Fig. 21.6). LFTs and fasting lipids are rechecked at 2–4 weeks and monthly thereafter for the first 3 months. If laboratory tests remain stable, the dose may be increased to the target dose. Laboratory tests may be rechecked at 2 weeks after every dose elevation. If the dose is not increased, CMP, CBC, and lipid panel should be checked every 3 months.

Management of laboratory abnormalities should be accomplished in conjunction with the patient's primary care provider or the transplant medical team. Because elevated lipids can increase cardiac risk, hyperlipidemia should be aggressively managed. The lipid elevation associated with oral retinoids is reversible upon cessation of therapy.

Elevation of LFTs of two or three times the normal requires reduction of retinoid dose by 50% and reevaluation in 2 weeks. Alcohol converts acitretin to etretinate with resultant toxicity and should be avoided [34]. If persistent elevation or elevation of LFTs more than three times the normal occurs, the drug should be discontinued. Repeat LFTs should be checked every 2 weeks until resolved, and reintroduction of retinoid therapy can be considered at 25% of prior maintenance dose.



*Acitretin requires monitoring for 3 years. Isotretinoin requires 1 month.
LFT, Liver function tests; CBC, Complete blood count; BMP, Basic metabolic panel.

Fig. 21.6 Laboratory monitoring for patients on systemic retinoid therapy

Pregnancy Testing

Since retinoids are well-known teratogens, retinoid chemoprevention is only for nonpregnant women who are severely affected by KC and are unresponsive to other therapies. Isotretinoin is preferred as the medication is more quickly eliminated following cessation. Two negative pregnancy tests must be recorded before treatment initiation and monthly during therapy. If the medication is discontinued, then a pregnancy test must be performed monthly for at least 3 years in the case of acitretin or for 1 month in the case of isotretinoin. Importantly, a patient must commit to using two forms of birth control throughout this entire duration.

Skeletal Toxicities

Controversy exists on the impact of systemic retinoids on accelerating osteoporosis and hyperostosis given the high prevalence of these conditions in the general population and lack of case-controlled studies [36]. Bone radiographs are not routinely ordered prior to therapy, but may be necessary if the patient describes symptoms that could suggest calcification or in a pediatric patient or if the patient is at high risk for skeletal abnormalities such as those treated with chronic corticosteroids. When concerned, a baseline skeletal survey should be obtained, and initiation of calcium, vitamin D, or bisphosphonates can be considered.

Use in Organ Transplant Recipients

There has been some discussion regarding a potential immunostimulatory effect of systemic retinoid therapy and consequent organ rejection. One study demonstrated that etretinate enhanced natural killer cell activity, whereas isotretinoin did not have such an effect [37]. However, other studies did not report any change in cell-mediated immunity in renal transplant patients treated with etretinate [16]. In essence, there have been no reports of increased organ rejection due to systemic retinoid therapy in over 25 years of use.

Wound Healing

Healing of repaired wounds is generally not impeded by systemic retinoids [38]. It is possible that retinoid-induced xerosis may predispose to increased colonization by bacteria on the skin, theoretically increasing the risk of infection to recent surgical sites; however, one study demonstrated that there was no difference in the incidence of infection, dehiscence, hypertrophic granulation tissue, or hypertrophic scarring in organ transplant recipients treated with oral acitretin following surgical excision and treatment for skin cancer [39].

Topical Retinoid Therapy

The use of topical retinoids, which include tretinoin, adapalene, and tazarotene, to improve the appearance of sun-damaged skin has been well documented. Although topical retinoids have shown efficacy in the treatment and prevention of AK, only two studies evaluating KC as an endpoint in a high-risk population have been performed with no significant benefit observed. This suggests topical retinoids are best reserved for lower-risk patients and might not be an efficacious monotherapy in high-risk populations. Rather, adjuvant use with low-dose systemic retinoids or 5-FU is more appropriate [40, 41].

Topical Tretinoin

Topical tretinoin has been used to treat AKs in a number of studies dating to the 1960s [42]. Among immunocompetent patients, 75% of patients with a history of AK demonstrated a complete or partial response in AK reduction using 0.1% tretinoin daily [42, 43]. In a small study of OTR, the majority of patients reported improvement in AKs and verrucae using tretinoin 0.05% daily for three months. One trial has examined KC incidence as an endpoint. In a large

randomized controlled trial (RCT) of Veterans Affairs patients with history of KC, 1131 patients used topical 0.1% tretinoin or a matching vehicle control for 1.5–5.5 years; there was no significant benefit in the incidence of KC or AK in the treatment arm [44].

Adapalene

Adapalene is a synthetic retinoid used topically for indications similar to those of tretinoin. In a randomized control trial of patients with history of AK, adapalene 0.1% gel nightly for 9 months was well tolerated. Following treatment, 13% of patients demonstrated clearance or marked improvement in AK, while 49% showed moderate improvement [45].

Adapalene may be a good choice for patients with sensitive skin.

Tazarotene

Topical tazarotene therapy is effective against superficial KC. Complete clinical responses of 50–70% of superficial BCC lesions have been reported, and preliminary evidence suggests efficacy in superficial SCC [46–48]. Chemopreventive effects were recently examined in a placebo-controlled RCT and open-label trial in patients with basal cell nevus syndrome (BCNS) with only 6% of patients demonstrating benefit [49].

Application of Topical Retinoids

Topical retinoid use is outlined in Tables 21.5 and 21.6. Topical retinoids are used once daily at night and require on average 6–12 months for significant benefit to occur. Limitations to use include irritant retinoid dermatitis and prolonged redness. Alternate nightly application may be necessary for successful long-term use. Adapalene is reportedly less irritating than tretinoin and may be more suitable for sensitive skin than tretinoin.

Advocate mild cleansing and use of emollients along with topical retinoid therapy.

Table 21.5 Indications for use of topical retinoid therapy

Mild to moderate sun-damaged skin
Fine rhytides, mottled hyperpigmentation
Actinic keratoses
Superficial NMSC (tazarotene)
Contraindicated in pregnancy

Table 21.6 How to use a topical retinoid for the treatment of actinic keratoses

Start every other night, apply sparingly to freshly cleaned skin
Advance to nightly as tolerated over weeks to months
Initial agent is tretinoin cream 0.05%
Apply a pea-sized amount to the affected areas and smooth in gently
Moisturize the skin after application
Use sunscreen SPF >30 daily before going outdoors, and avoid strong sunlight
Increase the amount of cream applied as tolerated
If irritation develops, stop treatment for 2 days, apply plenty of moisturizer, and restart with smaller amounts of cream initially at alternate day usage
If no improvement after 2 months of use, switch to a stronger agent
Milder agents include tretinoin emollient cream 0.02% and adapalene cream 0.1%. Stronger agents include tretinoin cream 0.1%, tazarotene cream, or gel 0.1%
Combine therapy with oral retinoids for immunosuppressed patients

Nicotinamide

Nicotinamide is a vitamin B3 that is precursor to nicotinamide adenine dinucleotide (NAD), an essential component of ATP production that also participates in multiple cellular processes implicated in carcinogenesis and the tumor immune response. In murine models and cultured human

cells, UVB irradiation induces NAD depletion resulting in genomic instability via alteration of p53 expression and a depletion of the cellular energy needed for DNA repair [50]. Furthermore, oral nicotinamide has been shown to significantly reduce UV-induced immunosuppression in a dose-dependent manner [51]. Two phase-two double-blind, placebo-controlled RCTs illustrated a reduction in AK incidence at four months in Australians with sun-damaged skin, with a 29% reduction (95% CI = 11–44%; p = 0.005) in those taking 500 mg daily and 35% reduction (95% CI = 18–48%; p = 0.0006) in those dosed 500 mg twice daily [52]. In a phase-three, double-blind RCT of a population of patients with a history of two KC in the past 5 years, those receiving 500-mg nicotinamide twice daily compared to placebo had a 23% reduction in KC (95% CI = 4–38%; p = 0.02) and a 13% reduction in AKs (p = 0.001) at 12 months. This reduction was seen at the first 3-month appointment and was lost shortly after discontinuation. The largest reduction was observed in superficial and nodular BCCs [53].

In solid organ transplant recipients, a small RCT of 22 renal transplant recipients illustrated a statistically nonsignificant 35% reduction in KC (p = 0.36) and statistically nonsignificant 16% reduction in AKs (p = 0.15) [54]. Larger trials are needed to more completely assess efficacy and safety in this population.

The side-effect profile of nicotinamide is favorable as it does not cause the vasodilatory effects seen with nicotinic acid. According to the literature, the drug is well tolerated at doses not exceeding 3 gm/day [55]. The only contraindication is a history of hypersensitivity to niacin, nicotinamide, or a component of the formulation.

Given the low side-effect profile and strong evidence supporting the use of nicotinamide as a chemopreventative, providers should consider starting nicotinamide in those at high risk for KC.

Vismodegib

Vismodegib is a small-molecule inhibitor of the Hedgehog signaling pathway, activation of which is a molecular hallmark of basal cell carcinogenesis. It has established efficacy in the control of advanced BCC [56]. It has been examined as a chemopreventive agent in patients with multiple BCCs. In a phase-two placebo-controlled RCT of 26 patients with BCNS, patients in the treatment arm had a significant reduction in the number of BCCs and required less frequent surgeries compared to placebo. The drug was poorly tolerated, however, with nearly half of patients discontinuing treatment within 12 months [57]. In another phase-two regimen-controlled RCT, patients with multiple BCCs (including BCNS) were randomized to receive two different pulsed dosing schedules. Both groups had a greater than 60% reduction in the total number of BCCs compared to baseline, and nearly three-quarters of patients had no new BCCs at the end of the treatment period; 23% of patients discontinued treatment early, suggesting the pulsed regimen is better tolerated than continuous treatment [58]. Accordingly, it is preferable to utilize the pulsed dosing schedule for chemoprevention. Importantly, discontinuation does not seem to compromise therapeutic activity.

Vismodegib is equally efficacious and better tolerated when using a pulsed dosing schedule.

Of note, a handful of reports have illustrated an emergence of SCC incidence in patients treated with vismodegib [59–61]. This was analyzed in two retrospective analyses. Mohan et al. demonstrated an increased risk of SCC following vismodegib therapy (hazard ratio (HR) = 8.12; 95% CI = 3.89–16.97; $p < 0.001$); however, this study had limitations including defining entry time as the time of BCC diagnosis rather than vismodegib initiation, a higher age in the control group that when corrected enhanced the HR,

and no adjustment or control for frequency of skin cancer screening [62, 63]. A recent study designed without these limitations illustrated no significant association between vismodegib and SCC incidence (HR = 0.57; 95% CI = 0.28–1.16; $p = 0.122$) [64].

Commonly reported adverse events are weight loss, muscle spasms, diarrhea, and alopecia which should be addressed with medical intervention [65]. Vismodegib is a teratogen that can potentially be transmitted through semen; thus, patients of childbearing potential should use contraception throughout therapy, and females should have a verified negative pregnancy result within one week of initiation. The medication should not be used while breast-feeding.

Newer agents with demonstrated efficacy include COX-2 inhibitors, vismodegib, and nicotinamide. The use of EGFR inhibitors, mTOR inhibitors, and capecitabine in the solid organ transplant population has also shown promise.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with a reduced risk of malignancy in a variety of tissues [66]. In human keratinocytes, it has been observed that acute exposure to UVB irradiation resulted in an increase in cyclooxygenase-2 (COX-2) and in production of prostaglandin E2 (PGE_2). Mechanistic analyses support the role of COX-2 in the development of skin cancers, while COX1 is thought to primarily drive tissue homeostasis [67].

In clinical trials, the association of NSAIDs with KC reduction has borne conflicting results likely due to differences in study design, type of NSAID used, exposure assessment, and enrollment criteria in a body of data that is largely driven by cohort and population-based case control studies [68, 69]. Utilizing a random effect model on nine studies, Zhang et al. showed that NSAID use was not associated with a reduced risk of SCC (pooled RR = 0.86, 95% CI, 0.73–1.02) or BCC (pooled RR = 0.94, 95% CI, 0.85–1.04); separate subgroup analysis of aspirin, nonaspirin NSAIDs, and celecoxib also did not support a chemopreventative effect in regular users [69]. Conversely, Maranushi et al. utilized more recent studies to demonstrate a significantly reduced risk of SCC among users of nonaspirin NSAIDS (RR = 0.85, 95% CI 0.78–0.94). Although limited in number, interventional studies have provided further insight. One multi-institutional RCT with 220 participants demonstrated a 60% reduced risk of BCC and SCC (RR = 0.43, 95% CI 0.24–0.745, $P = 0.003$) in high-risk patients randomized to celecoxib 200-mg BID for 9 months compared to placebo. Surprisingly, the primary endpoint of this trial was AK incidence which was not significantly different [70].

Of note, COX-2 inhibitors are associated with a higher risk of adverse cardiovascular events and a decrease in renal function [71–73]. This side-effect profile, when combined with unclear efficacy, lessens the appeal of NSAIDS as a primary KC chemopreventative.

Topical retinoids and diclofenac are best utilized as monotherapy in lower-risk patients to treat actinic keratosis.

Topical Diclofenac

Diclofenac is a nonspecific NSAID that was anecdotally noted to induce clinical regression of AKs when used as a topical inflammatory agent for arthritis [74]. It is now approved by the FDA for twice-daily treatment of AKs for 60–90 days and is most commonly used as field treatment for multiple AK. Two phase-three double-blind RCTs using diclofenac formulated in 3% hyaluronic acid (hyaluronan) for 60 or 90 days have since established its efficacy in reducing actinic keratosis [75, 76]. In OTR with a history of AKs, an RCT composed of 28 patients treated twice daily over 16 weeks, complete clearance of AKs was seen in 41% of participants (9/22) in the treatment arm compared to 0% (0/6) in the control group. Furthermore, no patients developed SCCs in the 24-month

follow-up period, and no adverse effects on the surgical graft were noted [77].

> Although side effects are less for diclofenac than 5-FU, the longer duration of therapy may be a disadvantage. However, for some patients, who cannot tolerate the significant side effects of 5-FU, diclofenac may be a useful alternative.

Topical diclofenac should be used twice daily over sun-damaged skin (Table 21.7). The average duration of treatment is 75 days; however, treatment can be discontinued once clinical resolution is noted [74]. The efficacy of diclofenac appears to be dependent on the dosage or amount of gel used with studies utilizing 0.25 g twice daily showing a lower response rate relative to those using 0.5 or 1.0 g [74, 75, 78]. A head-to-head trial with 5-FU revealed that although both agents were effective, patients using 5-FU experienced a better therapeutic response relative to diclofenac while the latter had fewer adverse effects and the drug was more tolerable [79]. The most common adverse effects are pruritus, erythema, crusting, and irritant dermatitis.

Table 21.7 How to use topical diclofenac

Apply twice daily for 60–90 days to the affected areas
Treatment times are on average 75 days
Apply sunscreen during treatment to minimize photosensitivity
Diclofenac is contraindicated in patients with a known allergy to aspirin or other NSAIDs
Therapeutic benefit is maintained for more than 1 month after cessation of therapy

Solid Organ Transplant Recipients

Mammalian Target of Rapamycin Inhibitors (mTOR-I)

Immunosuppressive regimens contribute to carcinogenesis through reduction in immune surveillance and cell-autonomous mechanisms. Cyclosporine, in particular, promotes tumor growth through numerous mechanisms including inhibition of DNA repair and apoptosis [80]. In contrast, mTOR-I, particularly sirolimus, have been shown to protect against allograft reception while also inhibiting tumor development in murine models and reducing vascularization and tumor thickness in transplant patients, thus making it a compelling immunosuppressant and chemopreventative candidate [81, 82].

The data on mTOR-I has evolved as the dose has changed, and the role of cyclosporine as a confounder has been dissected. In a 2015 meta-analysis combining data on renal transplant patients from 20 RCT, sirolimus use was associated with a 51% decrease in KC incidence (IRR = 0.49, 95% CI = 0.32–0.76). This association was much stronger in trials comparing sirolimus against cyclosporine (IRR = 0.19, 95% CI = 0.04–0.84). If cyclosporine use was the same across treatment arms, the reduction in KC incidence was smaller and not significant (IRR = 0.57, 95% CI = 0.13–2.42) [83]. This suggested cyclosporine discontinuation was partially responsible for the protective effect observed with sirolimus. Supporting this observation, a 9-year study examining the risk of NMSC and mortality across four clinical trials in Australia and New Zealand was undertaken. Compared to control, everolimus was not associated with a decreased risk of KC (HR 0.58; 95% CI = 0.30–1.120); however, subgroup analyses showed a 56% reduction in KC in patients randomized to everolimus and reduced-dose calcineurin inhibitors (HR 0.44; 95% CI = 0.21–0.92) [84]. Conversely, a meta-analysis from 2018 primarily including trials with a lower-dose, modern mTOR-I regimen demonstrated a modest but significant reduction in all malignancies, including KC, with or without inclusion of cyclosporine. However, in the absence of cyclosporine, graft survival was minimally decreased (RR = 0.99, CI = 0.98–1.00, $P = 0.054$) [85].

Of further note, use of mTOR-I is significantly impacted by adverse events. Sirolimus is associated with more serious adverse events compared to calcineurin inhibitors driving a withdrawal rate that approaches 25% [86]. Furthermore, one longitudinal cohort study of 9353 renal

transplants demonstrated an increased risk of all-cause mortality (hazard ratio (HR) = 1.43, 95% confidence interval (CI) = 1.21–1.71), an effect that was also seen in meta-analysis of 31 RCTs, although when analysis was restricted to a lower-dose sirolimus skin cancer reduction was preserved while the mortality association was no longer significant (HR = 1.07, 95% CI = 0.81–1.41; $P = 0.65$) [87, 88].

Collectively, the data supports careful consideration of the use of mTOR-I in modern regimens in patients with a history of aggressive SCC where the benefits outweigh the risks and the regimen can be tolerated. Further studies are needed to elucidate the optimal timing of mTOR-I initiation, optimal immunosuppressant regimen, and clinical characteristics best suited to this intervention.

Capecitabine

Capecitabine is an oral fluoropyrimidine agent that is metabolized to 5-FU and has been shown to have equal efficacy and a marginally improved side-effect profile compared to administration of the active metabolite [89]. It was initially improved for the treatment of metastatic breast and colorectal carcinoma where inflammation of AKs was noted [90]. Capecitabine has been examined as an adjuvant to interferon alpha in four patients with advanced SCC where complete remission was noted in two patients [91]. As a preventative agent, its use has been examined in OTR with history of KC, demonstrating a statistically significant reduction of SCCs prospectively in nine out of ten patients and retrospectively in ten out of 13 patients [92, 93]. Future studies with larger cohorts and longer durations are needed to establish efficacy and safety profile.

Common side effects include fatigue, nausea, hand-and-foot syndrome, gout, and poor renal function; side effects prompted dose reductions or delay in seven out of ten patients with two of these patients eventually withdrawing from the study. No patients experienced transplant rejection [93]. Capecitabine is dosed at 0.5 to 1.5 mg/kg on days 1–14 of a 21-day cycle. Prior to initiation, patients should be screened for dihydropyrimidine dehydrogenase deficiency, as lack of this enzymatic activity can lead to severe multiorgan toxicity [29] (see Table 21.8).

Table 21.8 Dosing regimens utilized in clinical trials

Agent	Dose
Celecoxib	200 mg twice daily [70]
Nicotinamide	500 mg once to twice daily [52, 53]
Vismodegib	Intermittent dosing more tolerable and equally efficacious 1. 150 mg daily [56, 57] 2. 150 mg daily for 12 weeks ➔ 24 weeks off ➔ 12 weeks on [58] 3. 150 mg for 24 weeks ➔24 weeks off ➔ 8 weeks on [58]
Capecitabine	0.5–1.5 mg/kg on days 1–14 of a 21-day cycle [92, 93]

Other Promising Agents

DNA Repair Enzymes

Failure to repair UV-induced pyrimidine dimers can lead to carcinogenesis when mutational events occur in critical genes. Humans utilize a series of enzymes in the nucleotide excision repair pathway to repair these defects; however, if germline or somatic mutations occur in this pathway, then the cell is unable to repair UVR damage. A second mechanism, termed the "base excision repair pathway," cannot be utilized by humans due to the absence of a catalytic glycosylase. The efficacy of utilizing a topical formulation containing this enzyme to repair UV-induced DNA damaged in keratinocytes and reduce UVB-induced tumors has been successful in murine models [94, 95]. In patients with XP, topical T4 endonuclease used once daily over one year resulted in 17 fewer AKs (95% CI = 11.8–26.5; $P = 0.004$) and 1.6 fewer BCCs (95% CI = 0.38–2.82) compared to placebo, a 68% and 30% reduction, respectively. The study group was not large enough to evaluate the impact on SCC development [96]. A more recent study composed of 13 patients with AKs on their

face or scalp was randomized to receive topical DNA repair enzyme or lotion for eight consecutive weeks; those in the treatment group noted a 46.6% decrease in AKs compared to a 32.7% decrease in the placebo group. At the 12-week follow-up, there was an additional 29.2% reduction in the treatment arm, while the placebo group had a 31.4% increase in AKs ($p = 0.0026$) [97]. The literature would benefit from further trials characterizing the effect in high-risk groups like OTR with the incidence of KC as a primary endpoint.

Other agents with their proposed protective mechanisms are summarized in Table 21.9. Agents in this list that have been tested in clinical trials include difuoromethylornithine which showed a significant reduction in new BCC but not SCC in a 4-year double-blind, placebo-controlled RCT of 291 patients with a history of KC [101].

Table 21.9 Proposed preventive agents for keratinocyte carcinomas

Agent	Reasoning
Afamelanotide	Chemical analogue of α-melanocyte-stimulating hormone [98]
β-HPV vaccine	Protection against β-human papilloma virus which is associated with KC development in OTR [98]
Resveratrol	Polyphenol in berries and red wine with antioxidant, anti-inflammatory, and inhibition of keratinocyte proliferation [99]
Polypodium leucotomos	Fern-derived antioxidant and anti-inflammatory [100]
Epigallocatechin-3-gallate	Green tea flavonoid that promotes cell cycle arrest and apoptosis, inhibits angiogenesis, and acts as antioxidant [99]
Difluoromethylornithine	Ornithine decarboxylase inhibitor that diminishes polyamines, limiting tumor growth [101]
Vitamin E	Antioxidant [99]
N-Acetylcysteine	Antioxidant [102]
Sulforaphane	Antioxidant present in cruciferous vegetables [103]

Conclusion

Cutaneous carcinogenesis encompasses a series of events from malignant initiation arising from DNA damage to the progression of transformed keratinocytes. Current agents utilized in chemoprevention target events along the spectrum of carcinogenesis, and further studies combined with more reformed molecular techniques will allow for development of agents that more elegantly address the root of a patient's risk while also informing our understanding of malignant transformation in different populations. Accordingly, a mastery of chemoprevention requires an understanding of the population at risk and the type of keratinocytic carcinoma and an assessment of the risks, benefits, and limitations of systemic and topical agents. Although a handful of agents have been tested in populations with a history of multiple skin cancers, OTR, XP, and BCNS and those exposed to PUVA, studies examining chemoprevention in other high-risk populations such as those with albinism, cutaneous trauma, burns, or recessive dystrophic epidermolysis bullosa are needed.

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Chapter 22
Systemic Therapy for Locally Advanced and Metastatic Non-Melanoma Skin Cancer

Leon Chen and Michael R. Migden

Non-melanoma skin cancer (NMSC) is the most common form of cancer diagnosed in the United States, affecting 3.3 million individuals with a total of 5.4 million NMSCs diagnosed in the United States annually [1]. NMSC is typically considered a localized neoplasm with variable metastatic potential (0.0028–0.55% for basal cell carcinoma (BCC) and 5.2% for primary cutaneous squamous cell carcinoma (cSCC)) [2–4]. In general, the standard treatment modality for NMSC has been surgical excision; nevertheless, those patients with inoperable tumors or metastatic disease necessitate a different treatment approach. A recent retrospective study demonstrated that only 30% of patients with unresectable cSCC responded to treatment of any kind, and the overall survival for these individuals is only 10.9 months [5, 6]. Therefore, recent advances in research have been driven by the unmet medical need of patients with advanced NMSC disease. This chapter focuses on the discussion of systemic therapeutic options with hedgehog pathway inhibitors and immunotherapy.

Hedgehog Pathway Inhibitor

Mutations in protein patched homolog-1 (PTCH-1) and smoothened (SMO) in the hedgehog signaling pathway have been linked in the pathogenesis of BCC (Fig. 22.1) [7]. Approximately 95% of patients with sporadic BCCs have mutations identified in this signaling pathway [8, 9]. Currently, there are two US Food and Drug Administration (FDA)-approved medications: vismodegib and sonidegib. Vismodegib is approved in the United States, European Union, Switzerland, Australia, and other countries for locally advanced basal cell carcinoma (laBCC) and metastatic basal cell carcinoma (mBCC). Sonidegib has been approved in the United States, European Union, Switzerland, and Australia for the treatment of laBCC. Additionally, sonidegib is also approved in Switzerland and Australia for mBCC. Similarities and differences between vismodegib and sonidegib are summarized in Table 22.1.

Vismodegib

Given the promising result from the phase I trial of vismodegib, a phase II international, multicenter trial (ERIVANCE) was initiated to assess the objective response rate (ORR) of vismodegib at a dosage of 150 mg daily in patients with either laBCC or mBCC [9, 10]. The efficacy data including the 12-month update and long-term analysis are summarized in Table 22.2. In the ERIVANCE trial, the most common reported adverse events were muscle spasm (68%), followed by alopecia (63%), dysgeusia (51%), weight loss (46%), and

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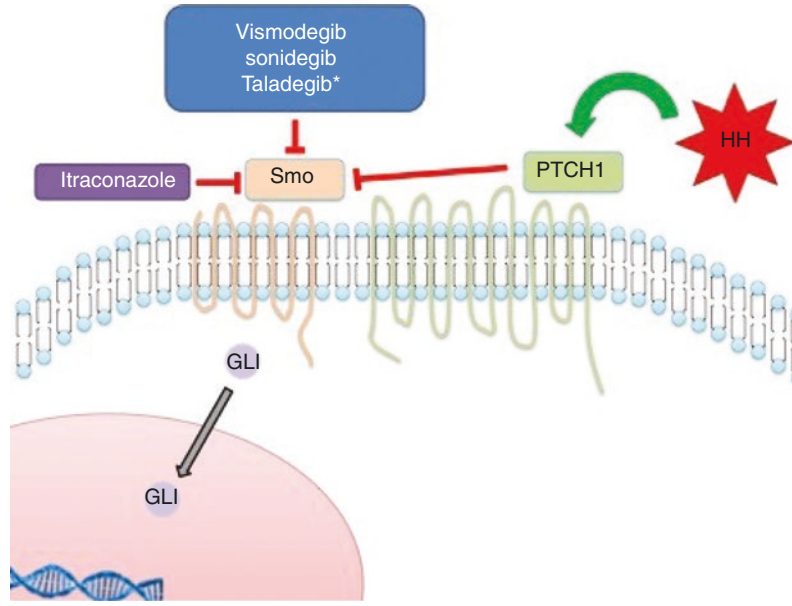

Fig. 22.1 In the absence of the hedgehog signal (HH), the PTCH1 cell surface transmembrane protein suppresses SMO. However, when the HH is present and bound to PTCH-1, SMO is no longer inhibited and allows the transcription factor Gli to enter the cell nucleus, stimulating cell division and tumorigenesis

Table 22.1 Comparison between sonidegib and vismodegib

	Sonidegib	Vismodegib
Brane name	Odomzo®	Erivedge®
Year of approval in the United States	2015	2012
Countries with approval for laBCC	USA, EU, Switzerland, and Australia	USA, EU, Switzerland, Australia, and other countries
Countries with approval for mBCC	Switzerland and Australia	USA, EU, Switzerland, Australia, and other countries
Dosing recommendation	200 mg daily	150 mg daily
Pill picture		
Name of pivotal trial	BOLT	ERIVANCE
Drug interaction with CYP3A hepatic enzyme	Yes	No
Most common adverse events	Muscle spasm, alopecia, and dysgeusia	Muscle spasm, alopecia, and dysgeusia

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laBCC locally advanced basal cell carcinoma, *mBCC* metastatic basal cell carcinoma, *EU* European Union

fatigue (36%). Seven patients had a fatal grade 5 adverse event; however, none of these cases were thought to be related to the study drug. At the time of cutoff for the 12-month update, 75 out of 104 enrolled patients discontinued treatment due to adverse events, disease progression, or patient decision. The incidence of treatment-emergent adverse events was higher in patients who were on vismodegib treatment longer than 12 months; however, the risk of another adverse

Table 22.2 Response rate comparison between sonidegib in BOLT versus vismodegib in ERIVANCE

	BOLT (sonidegib 200 mg only)						ERIVANCE (vismodegib 150 mg daily)					
	Primary analysis		12-month update		30-month update		Primary analysis		12-month update		Long-term analysis[a]	
	laBCC ($n = 66$)	mBCC ($n = 13$)	laBCC ($n = 66$)	mBCC ($n = 13$)	laBCC ($n = 66$)	mBCC ($n = 13$)	laBCC ($n = 63$)	mBCC ($n = 33$)	laBCC ($n = 63$)	mBCC ($n = 33$)	laBCC ($n = 63$)	mBCC ($n = 33$)
ORR, % (n)	47.0, (31)	15.4, (2)	57.6, (38)	7.7, (1)	56.1 (37)	7.7, (1)	42.9, (27)	30.3 (10)	47.6, (30)	33.3 (11)	60.3, (38)	48.5, (16)
CR, %	3.0	0	4.5	0	4.5	0	20.6	0	22.2	0	31.7	0
PR, %	43.9	15.4	53.0	7.7	51.5	7.7	22.2	30.3	25.4	33.3	28.6	100
SD, %	43.9	76.9	33.3	84.6	34.8	84.6	38.1	63.6	34.9	60.6	23.8	87.5
PD, %	1.5	0	1.5	0	1.5	0	12.7	3.0	12.7	3.0	9.5	12.5
Median DOR, mo	NR	NR	NR	NR	26.1	NR	7.6	7.6	9.5	7.6	26.2	14.8
Median PFS, mo	NR	13.1	NE	13.1	NE	13.1	9.5	9.5	9.5	9.5	12.9	9.3

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All data reported are based on central review except for data from ERIVANCE long-term analysis where only investigator-assessed response is available. The ORR assessed by the investigator review is often found to be higher than that of central review
ORR objective response rate, *CR* compete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *DOR* duration of response, *PFS* progression-free survival, *NR* not reached, *NE* not estimable, *mo* month
[a]Data from investigator-assessed response; 39 months after completion of accrual

event was reduced beyond the first year of treatment. None of the 17 reported deaths was thought to be related to vismodegib [10, 11].

Vismodegib (Erivedge®) comes in 150-mg capsules that have a pink opaque body and a gray opaque cap. The recommended dose is 150 mg once daily by mouth until disease progression or until patients can no longer tolerate its associated toxicity. Patients may take the capsule with or without food. No known clinically relevant interactions were found between vismodegib and other substrates or inducer/inhibitor of cytochrome 450 enzymes [11, 12].

Figures 22.2 and 22.3 illustrate clinical outcomes following vismodegib treatment.

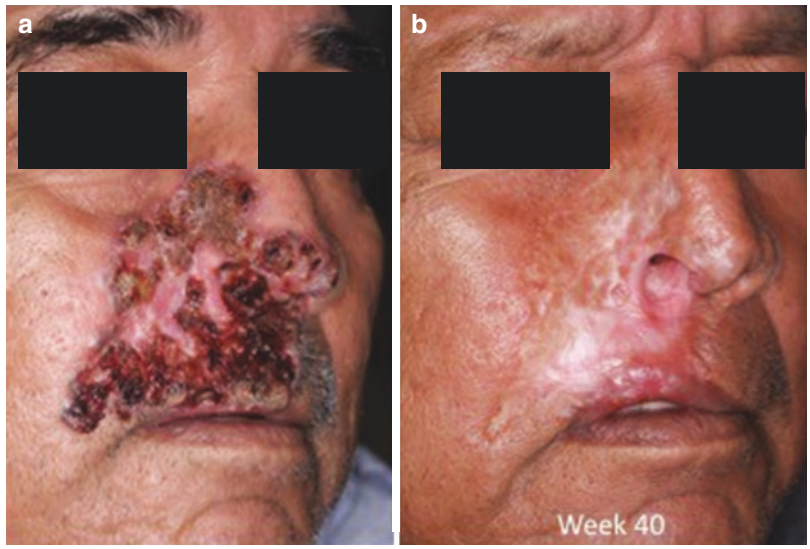

Fig. 22.2 (**a**) A 62-year-old Hispanic male patient with locally advanced basal cell carcinoma involving the medial cheek, distal nose, and the upper lip prior to initiation of HPI therapy with vismodegib at 150 mg daily. (**b**) Apparent tumor resolution with residual scarring at week 40 of the vismodegib treatment. (Reprinted from Chen et al. [70], © 2019, https://journals.lww.com/dermatologicsurgery/Abstract/2019/01000/Emerging_Nonsurgical_Therapies_for_Locally.1.aspx, with permission from Wolters Kluwer Health, Inc. [13])

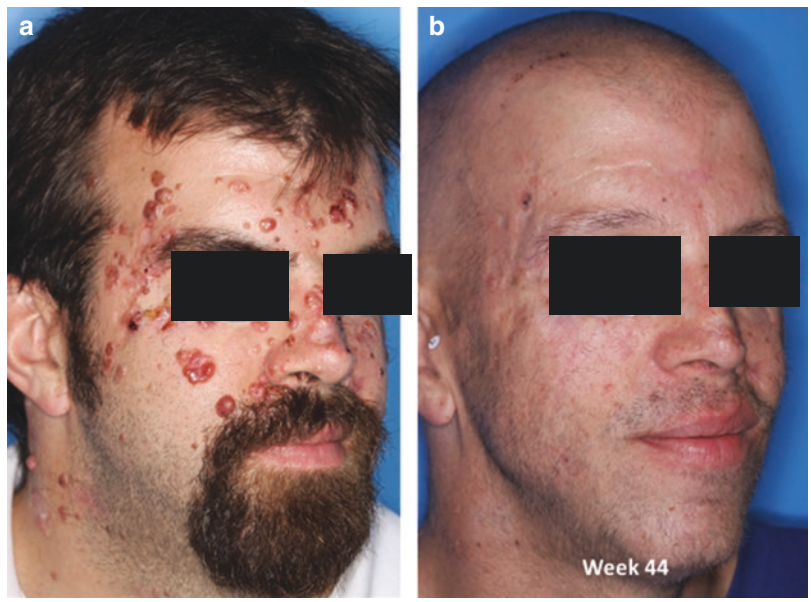

Fig. 22.3 (**a**) A 34-year-old Caucasian male patient with basal cell nevus syndrome prior to initiation of HPI therapy with vismodegib at 150 mg daily. (**b**) Apparent tumor shrinkage with residual scarring at week 44 of the vismodegib treatment. Note the alopecia from the vismodegib treatment

Sonidegib

The Basal cell carcinoma Outcomes with LDE225 Treatment (BOLT) trial was a multicenter, phase II, randomized, double-blind clinical trial studying the use of two different doses of sonidegib for the treatment of laBCC and mBCC [8, 9]. Patients 18 years of age and older were randomized into two treatment arms of 200 mg (dose with lowest efficacy) and 800 mg (maximum tolerated daily dose) sonidegib once daily in a 1:2 ratio, respectively [8, 9]. The efficacy data for 12-month and 30-month updates are summarized in Table 22.2. Although the efficacy for both the 200-mg and 800-mg treatment arms was comparable, patients in the 200-mg treatment arm were found to have a lower rate of reported adverse events, longer treatment duration, and a lower treatment discontinuation rate. Thus, the 200-mg dosing was considered to have a more favorable benefit-to-risk profile than the 800-mg dosing [8, 9].

The most common adverse events seen in the BOLT trials include muscle spasm, alopecia, dysgeusia, nausea, elevated blood creatinine kinase (CK), and fatigue, and they occurred more frequently in the 800-mg treatment arm than in the 200-mg arm. In the primary efficacy analysis, CK concentration was the most frequently reported grade 3–4 adverse event. As of the primary efficacy analysis data cutoff, three of 79 patients in the 200-mg arm and 13 of 150 patients in the 800-mg arm had discontinued the treatment due to muscle spasm. Rhabdomyolysis was the most frequently reported serious adverse event and was seen in 14% of patients in the 200-mg arm and 30% of patients in the 800-mg arm. These rhabdomyolysis cases failed to meet the criteria set forth by the independent safety review committee of muscle toxicity, which were a tenfold increase in CK concentration from baseline and a 1.5-fold increase in serum creatinine concertation from baseline. The safety profile of sonidegib in the 12-month and 30-month follow-up data remained consistent with what was previously reported in the primary efficacy analysis. By the 30-month data cutoff, eight patients had died while receiving treatment, but none of the deaths were thought to be related to sonidegib [12, 14].

Sonidegib (Odomzo®) comes as 200-mg opaque pink-colored capsules to be taken 200 mg orally once daily until disease progression or unacceptable toxicity. Because sonidegib is metabolized by hepatic enzyme CYP3A, drug interaction with CYP3A inhibitors can potentially increase the risk of further muscle toxicity; therefore, concomitant administration of sonidegib and strong CYP3A inhibitors should be avoided. Also, moderate or strong CYP3A inducers might increase metabolism of sonidegib and therefore decrease the efficacy of this medication [13, 15].

Laboratory Monitoring

Myositis or myopathy-associated CK elevation was observed in 6% of patients who were on a 200 mg daily dose of sonidegib [8, 16]. The package insert for sonidegib indicates that baseline serum CK and creatinine levels should be obtained prior to initiating the medication and periodically checked during the treatment. Prior to starting the treatment, patients should be encouraged to increase fluid intake and counseled on the symptoms and signs associated with CK elevation such as dark urine and muscle pain. For patients with serum CK elevation greater than 2.5 times the upper limit of normal, serum creatinine and CK levels should be checked at least weekly until resolution of clinical signs and symptoms.

In contrast to sonidegib, CK level is unaffected in vismodegib due to its pharmacokinetics as a result of high-affinity binding to the acute phase protein, a 1-acid glycoprotein [15, 17]. There are also no clinical guidelines for laboratory monitoring for vismodegib; however, grade 3 or higher hyponatremia, azotemia, hypokalemia and creatine phosphokinase (CPK) elevation as well as potential hepatic injury have been reported. A baseline screening and routine interval monitoring of complete blood count, comprehensive metabolic panel, and CPK are warranted at the discretion of clinicians. Table 22.3 provides the summary of laboratory monitoring.

Table 22.3 Suggested laboratory monitoring for non-melanoma skin cancer systemic therapy

Therapeutic agent	Suggested laboratory monitoring
Vismodegib	Baseline and routine CBC, CMP, and CPK
Sonidegib	Baseline CK and creatinine per PI. Baseline and routine CBC and CMP. If >2.5 of ULN, CK and creatinine should be checked weekly
PD-1 inhibitors	Baseline and routine CBC, CMP, and thyroid function panel. If treatment-related hypophysitis is suspected in patients, labs such as free T4, TSH, ACTH, morning cortisol, cosyntropin simulation test, LH, FSH, testosterone, and prolactin

CBC complete blood count, *CMP* comprehensive metabolic panel, *CPK* creatine phosphokinase, *CK* creatine kinase, *PI* package insert, *ULN* upper limit of normal, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *ACTH* adrenocorticotropic hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone

Management of Adverse Events

Proper management of HPI-associated adverse effects such as muscle spasm, dysgeusia, and alopecia may extend treatment duration. The practical tips for managing the common adverse effects are summarized below.

Management of Muscle Spasm

Muscle spasm is the most commonly reported side effect of HPI, affecting approximately 66% of patients taking vismodegib and 49% of patients taking sonidegib. To reduce the risk and severity of muscle spasm during HPI therapy, patients should be advised to keep hydrated and limit physical activity [16, 18]. Amlodipine, a calcium channel blocker, was shown to lessen vismodegib-induced muscle cramps when given for a 2-week period at 10 mg [17, 19]. Quinine 200 mg also demonstrated some benefit to reduce symptoms of muscle spasm [16, 18]. When adverse effects of HPI treatment become intolerable, treatment breaks can be beneficial. Exploratory analysis from the SafeTy Events in VIsmodEgib (STEVIE) trial showed an increase in treatment median duration corresponding with an increase in the number of treatment breaks, with no effect on the overall efficacy of vismodegib [18, 20]. However, a more recent study demonstrated that quiescent residual BCCs regrew in mice treated with vismodegib after treatment cessation, likely due to rapid Wnt pathway activation [19, 21]. Muscle spasms typically take around 2–3 months to develop and generally resolve over the course of 4–8 weeks after treatment discontinuation.

Management of Alopecia

Alopecia occurs in 61% and 43% of patients taking vismodegib and sonidegib, respectively [20, 22]. It has been suggested that HPIs disrupt the normal hair cycle, but they do not destroy the hair follicle [21, 23]. Therefore, hair regrowth is typically expected after drug cessation, and alopecia may take up to 6–12 months to resolve. Nevertheless, a longer duration of HPI treatment and an increased degree of treatment-related alopecia can potentially lead to permanent hair loss even after treatment completion [22, 24]. Treatment options include 2%–5% topical minoxidil that can be used in addition to concealment measures such as wearing a wig [16, 18, 23, 25]. Interestingly, hair regrowth while on HPIs may indicate treatment resistance [24, 26].

Management of Dysgeusia

Dysgeusia (taste alteration) was reported in 57% and 38% of vismodegib and sonidegib-treated patients, respectively [20, 22]. For dysgeusia, finding the types of food that are more pleasant for the patient and dietician referral have been suggested, as it is only temporary and typically resolves 2–6 months after stopping HPI due to the limited life span of taste buds (10–16 days) [25, 27].

Pregnancy and Fertility Warnings and Precautions

The significance of the hedgehog signaling pathway in fetal development and the teratogenic-

ity of hedgehog pathway inhibitors (HPIs) have been well described. Females of childbearing potential should have a negative pregnancy test within 7 days prior to vismodegib administration and use effective contraception during treatment and for 24 months after the last dose. Vismodegib is also present in semen. Although a potential link to embryo-fetal harm has not been established, male patients should wear condoms and avoid donating semen during treatment and for 3 months after the last dose of vismodegib [11].

Sonidegib can cause embryo-fetal death or severe birth defects when given to pregnant women. Females of childbearing potential should use effective contraception during treatment and for at least 20 months after the final dose. Because of the potential risk of exposure through semen, male patients, while on treatment with sonidegib and for at least 8 months after the final dose, should wear condoms during sexual intercourse.

For young basal cell nevus syndrome patients on HPIs, referral to a fertility specialist should be offered.

Treatment Resistance

A major concern of HPIs is acquired resistance which happened to at least 29% of patients taking vismodegib [26, 28]. Molecular analysis of BCC biopsies from patients taking vismodegib has shown that resistance to this agent is consistently associated with hedgehog pathway reactivation [27, 29]. Nevertheless, patients with acquired resistance to one specific HPI due to mutations in SMO may still respond to a different HPI depending on the binding location, specific mutation/residue affected, and whether a conformational change is triggered to block drug binding in a direct or indirect manner [28, 30].

Potential Risk for Squamous Cell Carcinoma Development

The possible development of squamous cell carcinoma (SCC) while on HPI has been reported in the literature [29–32]. However, a recent study comparing the risk of cutaneous SCC development in patients treated with vismodegib as part of phase I and phase II clinical studies versus patients who received standard therapy for primary BCC, found no association between vismodegib and an increased risk of subsequent SCC development. Rather, elevated cutaneous SCC risk in patients treated with vismodegib is most likely a result of more frequent screening in the setting of patients having cumulative ultraviolet exposure [31, 33].

Immunotherapy

The concept of immunosurveillance proposed by Burnert in the 1950s shed new light on the immune system's capability to identify and destroy a nascent tumor [32 34]. Immunosuppression plays a major role in the pathogenesis of NMSC as the incidence of cSCC and BCC increases 65- to 250-fold and tenfold, respectively, after organ transplantation [33–36]. cSCC typically develops within a few years after the initiation of immunosuppressive medication, and the number of cSCCs a patient develops has a positive correlation with increasing number of years after transplantation as well as the overall aggressiveness of immunosuppressive therapy [35–39]. Furthermore, the overall metastatic rate of cSCC in patients on long-term immunosuppressive therapy for organ transplants reportedly exceeds 10% [38, 40]. The association between cSCC and immunosuppression is also supported by the fact that aggressive cSCC arises more frequently in patients with chronic lymphocytic leukemia (CLL) due to deficits in both humoral and cell-mediated immunity [39, 41]. It has been shown that mononuclear cells surround tumor nests of BCC and cSCC, suggesting that an immune response may be attempting to regulate tumor proliferation [40, 42]. Ultraviolet radiation, a major risk factor for the development of NMSC, also induces dose-dependent suppression of cellular immunity, thereby interfering with the body's immunosurveillance of skin cancer [41–46].

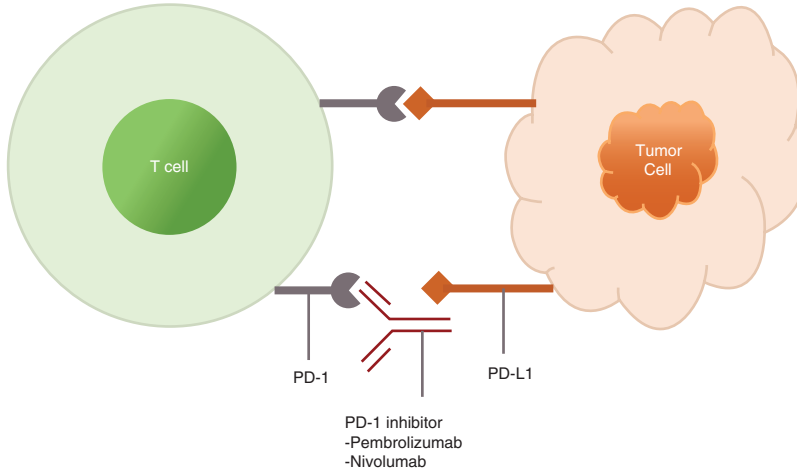

Fig. 22.4 Simplified schematic drawing demonstrating the interaction between a tumor cell, T cell and antigen-presenting cell (APC). Binding of PD-1 and PD-L1 results in the inhibition of the body's immune response to fight tumor cells. A PD-1 inhibitor binds to PD-1 and thus prevents binding of PD-L1, resulting in less T-cell inhibition and activation of an immune response. Normally CTLA-4 on the surface of T cell binds to B7, which is a co-stimulatory protein receptor on the surface of an APC, thus downregulating the T cell's activity. A CTLA-4 inhibitor binding to CTLA-4 results in T-cell activation. (Reprinted by permission from Springer Nature, Chen et al. [71], © 2020)

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to *Tasuku Honjo* MD, PhD, and *James P. Allison*, PhD, for their discovery of immunotherapy for cancer treatment. In 1992, Dr. Honjo first identified PD-1 as an inducible gene on activated T-lymphocytes, and this breakthrough has led to the establishment of cancer immunotherapy based on the principle of PD-1 blockade. Similarly, Dr. Allison was the first to demonstrate that antibody blockade of a T-cell inhibitory molecule T-lymphocyte-associated antigen 4 (CTLA-4) could lead to enhanced anti-tumor immune responses and tumor rejection. Since then, studies have demonstrated that melanoma patients with a high mutation load who receive immune checkpoint inhibitor treatment have a substantial clinical benefit [45, 47]. cSCC reportedly exhibits one of the highest mutation rates among human malignancies (33 to 50 per Mb of coding sequences) [46–49]. Thus, NMSCs are believed to be suitable for immunotherapy, as they express tumor-associated antigens, which illicit tumor-specific immune responses. CTLA-4 is a T-cell protein receptor that prevents T-cell activation when bound to a co-stimulatory protein receptor called B7, which is present on the surface of an antigen-presenting cell (APC). The use of a CTLA-4 inhibitor shows that regulation of tumor-associated antigen-presenting cells can inhibit cancer proliferation [48, 50].

Program Death-1 Inhibitor

Program death-1 (PD-1) is a checkpoint molecule heavily expressed on T cells in the tumor microenvironment that, when stimulated, leads to the activation of apoptosis in antigen-recognizing T cells and the suppression of apoptosis in regulatory T cells [49–52]. PD-L1, a ligand for PD-1 receptor expressed on the surface of tumor cells, binds to PD-1 to promote this inhibitory interaction (Fig. 22.4). Preclinical data suggest that PD-1 blockade may delay cSCC development in murine models [51, 53]. Recent success of immunotherapy with PD-1/PD-L1 axis blockade have been shown in the treatment of classic Hodgkin's lymphoma, metastatic non-small cell lung cancer (NSCLC), clear cell renal cell carcinoma, urothelial cancer, metastatic melanoma, cutaneous squamous cell carcinoma, and many others [52–59]. Different PD-1 checkpoint inhibitor agents will be summarized in Table 22.4.

Table 22.4 PD-1 checkpoint inhibitor agent comparison

	Nivolumab	Pembrolizumab	Cemiplimab-rwlc
Brand name	Opdivo®	Keytruda®	Libtayo®
Company	Bristol-Myers Squibb	Merck	Regeneron
Antibody tType	Human monoclonal	Humanized mouse monoclonal	Human monoclonal
Approval for SCC	No	No	Yes
Approval for BCC	No	No	No
Dosing	3 mg/kg IV every 14 days	2 mg/kg IV every 3 weeks	350 mg as IV every 3 weeks
Common AEs	Fatigue, diarrhea, rash	Fatigue, diarrhea, rash, pruritus	Fatigue, diarrhea, rash

Pembrolizumab

Pembrolizumab (Keytruda; Merk Inc., Kenilworth, NJ), a humanized PD-1 blocking antibody, was approved by the US FDA in September 2014 for use in patients with ipilimumab (an anti-CTLA-4 antibody) refractory melanoma or advanced melanoma patients who carry a BRAF (proto-oncogene) mutation who were previously treated with a combination of ipilimumab and a BRAF inhibitor. As of early 2019, pembrolizumab has been approved for the treatment of patients with unresectable or metastatic melanoma, NSCLC meeting certain criteria, patients with recurrent or metastatic mucosal squamous cell carcinoma of the head and neck with disease progression during or after platinum-containing chemotherapy, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, and Merkel cell carcinoma. The most common adverse reactions reported in a cohort study of 174 patients receiving pembrolizumab for the treatment of oral mucosal squamous cell carcinoma were fatigue, hypothyroidism, rash, decreased appetite, and dyspnea. These reactions were similar to those seen in the use of pembrolizumab for treatment of melanoma or NSCLC. The most frequent serious adverse reactions included pneumonitis, dyspnea, increased ALT/AST, hypernatremia, facial swelling, and confusion [58, 61].

An investigator-initiated, proof-of-concept study conducted by Chang et al. had two nonrandomized arms for open label study of pembrolizumb (200 mg IV every 3 weeks), with or without vismodegib (150 mg orally daily) for patients with advanced BCCs [59, 62]. Out of 16 participants, 9 received monotherapy with pembrolizumb only and 7 received both pembrolizumab and vismodegib [59, 62]. Using the revised Response Evaluation Criteria in Solid Tumor (version 1.1), the objective response rate (ORR) for all evaluable subjects reached 38% (6/16 patients) at 18 weeks. The ORR at 18 weeks for the monotherapy group was 44% (4/9 patients), higher than that of the dual therapy group (29%, 2/7 patients). The medium duration of response for all responders (n = 6) was 67.3 weeks with a 70% 1-year progression-free survival probability and a 94% 1-year overall survival probability for all evaluable subjects (n = 16). The study did not have any life-threatening adverse events or deaths, and only one of the severe AEs, hyponatremia, was thought to be linked to pembrolizumab. Dermatitis and fatigue were the most common immune-related AEs. The author concluded that pembrolizumab is active against BCCs with a reasonable safety profile, although the study is limited by its sample size.

Nivolumab

Nivolumab (Opdivo; Bristol Myers Squibb, Princeton, NJ) is a fully human PD-1 blocking antibody approved initially for metastatic melanoma in December 2014. It is also used to treat patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy. Borradori et al. reported a favorable treatment response with the use of either pembrolizumab or nivolumab in four patients with cSCC and one

patient with basosquamous carcinoma whose cutaneous malignancies were locally advanced and/or metastatic and refractory to other therapies. Of the patients treated with pembrolizumab ($n = 2$), one achieved stable disease and one had a partial response that was maintained during the follow-up period of more than 4 and 7 months, respectively. Similar results were seen in patients receiving nivolumab ($n = 3$), although two patients died due to reasons unrelated to the treatment (arrhythmia and bacterial pneumonia) [51, 53].

Cemiplimab

In September 2018, the US Food and Drug Administration approved Cemplimab-rwlc (LIBTAYO, Regeneron Pharmaceuticals Inc.), a fully human monoclonal antibody that targets PD-1 as a checkpoint inhibitor and previously known as REGN2810, for patients with metastatic cutaneous squamous cell carcinoma (CsCC) or locally advanced CsCC who are not candidates for curative surgery or curative radiation. The approval of this medication was based on durable ORR observed in patients with advanced CsCC in the expansion cohorts of the phase I study as well as the results of the pivotal phase II study for the metastatic-disease cohort [60]. In both studies, the patients were assessed for a response to cemiplimab every 8 weeks based on the results of whole-body imaging studies per RECIST version 1.1. In the expansion cohorts of the phase I study, a total of 26 patients with advanced CsCC were enrolled, and the response rate assessed by independent central review was 50% with 65% of patients achieving durable disease control. The duration of response exceeded 6 months in more than half of the patients (7/13) who had a response. In the metastatic-disease cohort of the phase II study, a total of 59 patients with metastatic CsCC were enrolled, and the response rate assessed by independent central review was 47% with 61% of patients achieving durable disease control. Although the median duration of response had not been reached at the time of the analysis, 57% of the patients who recorded a response had a duration of response exceeded 6 months.

The most common adverse events were diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%). Forty-two percent of the patients in the metastatic-disease cohort study had adverse event of grade 3 or higher with cellulitis, pneumonitis, hypercalcemia, pleural effusion, and death being the most common. Of the 11 deaths, eight were due to disease progression and the other three patients died from adverse events.

The recommended dosage of cemiplimab-rwlc is 350 mg (350 mg/7 ml solution in a single vial) as an intravenous infusion over 30 minutes every 3 weeks, until disease progression or the toxicity is no longer tolerable. To date, cemiplimab-rwlc is the only anti PD-1 agent approved for the treatment of advanced cSCC.

Laboratory Monitoring and Special Considerations

There are currently no clear guidelines for the monitoring of PD-1 inhibitors but given the associated immune-mediated toxicity, most clinicians check baseline and routine labs: complete blood count, comprehensive metabolic panel that include liver enzymes, and thyroid function studies (free T4 and TSH). However, if treatment-related hypophysitis is suspected in patients, labs such as free T4, TSH, ACTH, morning cortisol, cosyntropin simulation test, LH, FSH, testosterone, and prolactin may provide additional information. If AST or ALT increases to more than three times the upper limit of normal or if the total bilirubin increases up to three times the upper limit of normal, treatment should be withheld. However, the treatment should be permanently discontinued if AST or ALT increases to more than ten times the upper limit of normal or total bilirubin increases to more than three times the upper limit of normal. Table 22.3 provides the summary of laboratory monitoring.

Special consideration is warranted prior to initiation of anti-PD-1 in organ transplant patients due to the risk of acute allograft rejection [61, 64].

Cytotoxic T Lymphocyte-Associated Antigen 4 Inhibitor

Normally, cytotoxic T cells (CTLs) recognize antigens produced by cancer cells and destroy these aberrant cells. When the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor binds to the co-stimulatory protein receptor B7, the cytotoxic reaction produced by CTLs is switched off, permitting unregulated proliferation of cancer cells (Fig. **22.4**) [48, 50]. Ipilimumab (Yervoy; Bristol Myers Squibb, Princeton, NJ) is a monoclonal antibody that inhibits CTLA-4. It was approved by the US FDA in 2011 for the treatment of unresectable or metastatic melanoma. Data regarding the role of anti-CTLA-4 antibody in NMSC treatment are limited.

Future Directions

Substantial effort has been made to identify biomarkers which can predict the likelihood of patients' responses to different types of immunotherapy. As PD-L1 expression alone is not useful when selecting metastatic melanoma patients for nivolumab therapy, studies of PD-L1 expression in NMSC have also shown a discrepancy in the relationship between PD-L1 expression and an objective response to PD-1 inhibitor treatment [57, 59, 62–67]. Future studies may identify potential biomarkers that can be used to guide patient selection for immunotherapy [65, 68].

One potential concern of anti-PD-1 immunotherapy is the possibility of developing acquired resistance once the treatment is initiated. Ribas et al. reported that as high as 25% of melanoma patients who demonstrated an objective response to anti-PD-1 therapy subsequently developed acquired resistance; this conclusion was based on disease progression at a median follow-up of 21 months [66, 67, 69, 70]. Zaretsky et al. identified loss-of-function mutation within the genes encoding Janus kinase 1 or 2 (JAK1 or JAK2) in two patients. A mutation in the gene encoding beta-2-microglobulin, the protein product responsible for the folding and transport of MHC class I molecules to the cell surface was also found [69, 71].

Conclusion

Patients with locally advanced and metastatic NMSC continue to have a significant need for effective systemic therapeutic options. Following the development of hedgehog pathway inhibitors, immunotherapy with PD-1 inhibitors has emerged as a promising therapy for difficult-to-treat NMSC. Future studies are necessary to optimize the treatment response of patients receiving immunotherapy by possibly identifying key biomarkers, finding a solution to overcome treatment resistance, and exploring possibilities of combination therapy.

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A modified version of Table 10.8 was not used in the original publication. The table has been corrected now.

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