Operative Approaches to Nipple-Sparing Mastectomy

Indications, Techniques, & Outcomes

Jay K. Harness
Shawna C. Willey
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Foreword

It is a special privilege to write the foreword to this text on nipple-sparing mastectomy edited by Shawna Willey and Jay Harness. It would be hard to overestimate how powerful and revolutionary the adoption of this technique has been to the management of breast cancer. In the first edition published in 1998 of my seminal multidisciplinary textbook, *Surgery of the Breast: Principles and Art,* there were no chapters on Nipple-Sparing Mastectomy, and the chapter on Prophylactic Mastectomy specifically recommended against retaining the nipple. Although Breast Conservation, where the remaining breast skin and nipple are retained and radiated, had been widely adopted earlier, there was a peculiar resistance regarding preserving the nipple and the breast skin envelope when the entire breast gland had been removed but not radiated. To the best of my knowledge, the first big chink in the anti-nipple preservation armor came with the publication by Lynn Hartmann in the 1999 *New England Journal of Medicine* Volume 340 describing a 90 % plus reduction in the risk of developing breast cancer after prophylactic mastectomy, over 90 % of which were nipple sparing.

Preserving the nipple and skin of the breast became a mission for the courageous early adopters. And so it started with prophylactic nipple-sparing mastectomy for ideal anatomical candidates who had the recently identified Breast Cancer genes (BRCA 1 and 2). Then came mastering mastectomy techniques in order to limit the risk of necrosis. Within a few years, the envelope got pushed to include some breast cancer patients. Then the criteria in cancer patients were expanded to include more advanced cancers so long as the nipple margins were clean. Innovations continued expanding nipple-sparing mastectomy to larger breasts, ptotic breasts, and even previously radiated breasts.

We are now over 10 years into this nipple-sparing mastectomy revolution and the effects have been extraordinary. A great many women have been spared the mutilation previously associated with other forms of mastectomy. In many centers and in the hands of many breast cancer teams, it is not at all unusual for women to end up after treatment with breasts that appear normal, natural, beautiful, and often more so than preoperatively. The power of this long overdue innovation is evident to surgeons every day with the often tearful “Thank yous” that they hear from their patients. This last weekend, I was personally approached by two separate breast cancer survivors having undergone nipple-sparing mastectomies with reconstruction who thanked me for my contribution in making this treatment happen.

We are 10 years or so into the data collection phase of this treatment, and the data have been uniformly encouraging. With experience, complication rates can be low. Patients who were facing the fear of deformity after breast cancer treatment are actually relieved and usually happy with how they look. And most importantly, breast cancer recurrence rates remain low and are very, very, low in the nipple.

And so, this volume edited by Doctors Harness and Willey arrives at the right moment to provide 23 separate chapters on the subject. I look forward to reading each of these chapters which all give testimony to how far we have come in a relatively short time.

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Preface

For more than a decade, there has been a growing interest in the preservation of the nipple-areolar complex at the time of skin-sparing mastectomy for the treatment or prevention of breast cancer. Increasing numbers of papers have appeared in the literature reporting institutional experiences as well as various review articles on nipple-sparing mastectomy (NSM), which is also called total skin-sparing mastectomy (TSSM) by some authors. These publications describe various surgical approaches to NSM, patient selection criteria, complication rates, and plastic surgery issues concerning reconstruction. What is *not* available is a *single source* summarizing the approach and outcomes from several of those centers that have evolved NSM as an option in women who need or desire a mastectomy for the treatment or prevention of breast cancer.

This textbook is the first of its kind. It is designed to present a comprehensive overview of the evolution, oncologic safety, surgical approaches, management of complications, and outcomes of NSM. The book reviews various approaches to the performance of NSM from highly experienced authors. The book examines the expanding indications for NSM, evolving operative and reconstruction techniques, increasing patient satisfaction, and longer follow-up data on safety and low recurrence rates.

The book is targeted at general surgeons, dedicated breast surgeons, and plastic surgeons. There is a focus for surgeons just beginning their use of NSM as well as a review of patient selection criteria, operative approaches, reconstruction options, and management of complications. The chapters are written by experts in the performance and reconstruction of NSM. Chapters are supplemented with appropriate illustrations and photos of NSM and TSSM techniques and reconstructions.

We hope that our textbook will become a valuable resource for surgeons, including those in training, who have a focus on state-of-the-art breast cancer surgery.

Orange, CA, USA — Jay K. Harness
Washington, DC, USA — Shawna C. Willey

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1 The Evolution of Nipple-Sparing Mastectomy (NSM)

Jay K. Harness

The evolution of the management of all aspects of breast cancer is breathtaking. We have evolved from more radical treatments to less extensive and personalized treatments with vastly improved outcomes.

The surgical management of breast cancer has also evolved dramatically over the decades from the disfiguring Halsted radical mastectomy to breast conservation, and now nipple-sparing mastectomy (NSM).

The nipple–areolar complex (NAC) defines the breast, and *it makes a breast a breast*. Historically, the standard of care was to discard the NAC because of possible involvement with cancer, a site for possible recurrent cancer, and the fear that we could not keep the NAC alive because of thinly created mastectomy skin flaps. The psychological benefits of restructuring or preserving the NAC have been clearly demonstrated [1, 2].

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The Psychological Benefits of Preserving the Nipple

The emotional benefits of breast reconstruction include: (1) Reduction of a patient's preoccupation with her breast cancer, (2) Facilitation of wardrobe flexibility restricted by wearing an external prosthesis, (3) Elevation of mood and less anxiety, (4) Enhancement of body image, and (5) Improvement of sexual responsiveness. Including the nipple (reconstructed or natural) as part of breast reconstruction gives a patient a sense of completeness, not present with breast contour reconstruction alone [3]. The sense of completeness allows a patient to experience herself as "like herself," meaning close to her preoperative state [1].

Didier and colleagues showed in their study of NSM patients a very high level of satisfaction for having preserved their nipples, and less feelings of being mutilated by their mastectomies. They also found that NSM had impacted positively on patient satisfaction with cosmetic results, with femininity and body image, especially related to nakedness [2].

Historical Background

The concept that preserving the NAC is less mutilating than a total mastectomy can be documented to as early as 1882 [4]. However, the

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modern era of NSM really began with the report by Bromley S. Freeman, MD in 1962 [5]. The nipple-sparing mastectomies performed by Dr. Freeman at the Mayo Clinic preserved the glandular tissue beneath the NAC in order to protect the blood supply to the NAC. The term, "subcutaneous mastectomy" (SCM) is what his NSM was called, and continues to be known as today. The procedure was *not* for women with cancer, but those with painful and extensive fibrocystic changes of the breast. A 10-year follow-up of 1500 Mayo Clinic SCM patients for benign disease found a subsequent 0.4 % incidence of breast cancer [6]. This demonstrated the preventive or prophylactic effect of a near-total mastectomy on the development of expected subsequent breast cancers.

The initial report of the use of SCM for breast cancer treatment was in 1984 in the *British Journal of Surgery* by Hinton et al. [7]. Hinton reported on 98 patients undergoing SCM, with two patients having bilateral mastectomies, making a total of 100 SCMs. The series began in 1974. He compared the SCM group with a parallel group of women undergoing simple mastectomies. The majority of patients in both groups had early-stage (I, II) breast cancer. There was no statistical difference between the SCM and simple mastectomy groups when comparing local recurrence (LR), disease-free survival (DFS), and overall survival (OS) [7]. The surgery community pushed back hard against Hinton's concept, despite the fact that he reported that the SCM group achieved local recurrence and early survival rates equivalent to those for modified radical mastectomy [7].

Another British report was published 6 years later in 1990 by C.C.R. Bishop and colleagues [8]. Their procedure was unique. They performed total mastectomies, including axillary clearances, with preservation of the nipple, together with the skin of one-half of the breast. The other half of the breast and the mastectomy site was then reconstructed with the latissimus dorsi flap and a silicone implant. From 1982 to 1988, a total of 87 women underwent total mastectomy and immediate reconstruction with their unique approach. In Group I, 63 women had their procedures for tumor recurrence after prior partial mastectomy and radiation therapy. There were no recurrences in the preserved nipples at a mean follow-up of 3.9 years. In Group II, 24 women had their procedures as primary treatment of their early-stage breast cancers with three nipple recurrences (12 %) at a mean follow-up of 3.8 years [8].

Cautious Beginnings

Despite the pushback against Hinton's concept of SCM for breast cancer treatment, institutions in Japan, the United States, Germany, and Croatia began performing NSMs for both prevention and treatment from 1985 to 1998 [9–16].

The most pivotal early publication on the results of NSM was in 2003 by Gerber and colleagues from Rostock, Germany [12]. They reported on 61 patients who underwent skin-sparing mastectomy (SSM) with NAC conservation, 51 patients who had SSM without NAC conservation, and 134 patients who had a standard modified radical mastectomy (MRM). The SSM patients, with or without NAC conservation, were younger, averaging around 49 years of age. With a mean follow-up of 59 months, only one patient had a recurrence in the preserved NAC. The minimum distance from tumor to NAC was 2 cm in those who underwent SSM with NAC conservation [12].

In 2009, Gerber then reported on the same group of patients, now with a mean follow-up of 101 months [13]. There was no difference in local regional recurrence rates or deaths in all three groups. There were no additional recurrences in the NAC-preserved SSM group, other than the one case originally reported in 2003. Their conclusion was that preservation of the NAC was oncologically safe [13].

The first American group to publish on NSM for cancer was Dr. Joseph P. Crowe and colleagues from the Cleveland Clinic [17]. Their 2004 publication reported on 54 NSMs attempted among 44 patients. Six NAC core specimens found neoplastic involvement on frozen section analysis, resulting in conversion to total mastectomies. Forty-five of the 48 completed NSMs maintained postoperative viability of the NAC; three NACs had partial necrosis. This small series covered the time period from September 2001 to June 2003 [17].

A follow-up paper from Crowe and colleagues reported on their experience with 110 consecutive patients undergoing 149 NSMs from 2001 to 2007 [18]. There were no NAC recurrences in their series. They primarily utilized lateral incisions for the performance of their NSMs. The incidents of NAC neoplastic involvement at the time of mastectomy remained at 11 % in the larger series, which was the same as their initial report in 2004 [17, 18]. Sixty-four of the 154 NSMs were for prevention, and 85 were for breast cancer treatment. Exclusion criteria for performing NSMs included patients whose tumors were larger than 3.5 cm, centrally located tumors, lymph node involvement, inflammatory breast cancer, clinical involvement of the NAC, and patients who underwent neoadjuvant chemotherapy [18].

Areolar Preservation

Contributing to the interest in NSM was a series of papers by Dr. Rachel M. Simmons and coworkers on areolar-sparing mastectomy, published between 2002 and 2004 [19–21]. Their initial report in 2002 was a retrospective analysis of 217 mastectomy patients conducted to determine the frequency of malignant nipple or areolar involvement with tumor. They also analyzed the association between nipple and/or areolar involvement and prognostic factors, including tumor size, pathologic stage, nuclear-grade, axillary nodal status, and tumor location. The overall frequency of malignant nipple involvement was 10.6 %. In a subgroup of patients with tumors less than 2 cm, peripheral tumors, and two positive nodes or less, the incidence of nipple involvement was 6.7 % [19]. When the nipple and areola involvement were analyzed separately, only 2 of 217 patients (0.9 %) had involvement of the areola. All patients with areolar involvement had Stage III breast cancers that were centrally located. They concluded that the preservation of the areola with skin-sparing mastectomy, in selected patients, warranted further study.

In 2003, Simmons and her coworkers reported on a small series of 12 patients who underwent 17 areola-sparing mastectomies (ASM) [20]. The study period was only 20 months. Ten mastectomies were for prophylaxis, four for ductal carcinoma in-situ (DCIS), and three were for peripheral infiltrating carcinomas, less than 2 cm in size. In 2004, they reported on the 2-year follow-up. They had no recurrences, one postoperative infection, and excellent cosmetic results. They concluded that ASM would be offered to selected patients, including those desiring surgical breast cancer prophylaxis, as well as those with DCIS or small peripheral infiltrating ductal carcinomas [21].

Increasing Interest in Nipple-Sparing Mastectomy

Starting in the late 1990s, multiple academic institutions in the United States, Italy, and other locations around the world began to seriously consider NSM as an alternative to SSM. From 2000 to 2010, multiple reports from these academic institutions began to appear in the surgical literature, summarizing their individual institutional experiences [10–13, 17, 18, 22–34]. There were multiple issues that these reports analyzed. In general, the issues focused on patient selection, operative techniques, complications, oncologic safety, and cosmetic outcomes. Most of the institutional series were small, with short-term follow-ups averaging around a mean of 20 months.

In these initial series, much of the patient selection focused on patients wanting prophylactic mastectomies for risk-reduction. Several series were predominantly preventative mastectomies as a safe way to venture into the arena of NSM.

With breast cancer patients, various safe criteria were created for patient selection. Clearly, no patients would be eligible for NSM with clinical involvement of the NAC or bloody nipple discharge. Past literature analyzing NAC involvement with cancer in mastectomy specimens found the incidence of nipple–areolar involvement ranging from 5.9 to 50 % [10, 29]. Factors that have been associated with occult nipple involvement have been tumor size, subareolar location, tumor-to-nipple distance, positive axillary nodal status, multicentric tumors, and angiolymphatic invasion [29]. As a result, most institutions chose conservative inclusion criteria for selecting patients for NSM.

A good example of this approach is the initial criteria used by Dr. Scott Spear and colleagues. Tumor size less than 3 cm, tumor location greater than 2 cm from the NAC, clinically negative axillary nodes, no skin involvement, no inflammatory cancer, or Paget's disease were key components of their selection criteria. In addition, preoperative MRI to exclude nipple involvement and possible preoperative ultrasound-guided core biopsy of the nipple base could also be used to rule out occult involvement of the nipple. With their initial criteria, they also excluded excessively large and ptotic breasts [11].

In these early institutional reports, various types of mastectomy incisions for NSM emerged. Incision designs included: radial (lateral or 6 o'clock axis), inframammary, circumareolar, NAC-crossing, lateral/inferolateral, mastopexy-type incision, and omega/areolar incisions [11, 22, 25].

The major complication that concerned everyone was partial or full loss of the NAC. What also emerged from the early literature was that there was a "learning curve" needed for incision selection and the tedious performance of NSM. As experience grew, complication rates fell [25]. The early literature also suggested that lateral (3 and 9 o'clock), vertical (6 o'clock), and inframammary incisions had lower ischemic complications with the NAC ranging from 0 to 5 % [11, 22, 25].

The oncologic safety of preserving the NAC in cancer patients is difficult to evaluate in the early institutional series because of the short mean follow-up times. Most series reported no NAC recurrences, and low regional recurrence rates were comparable to SSM, with reconstruction [11, 25, 30]. Three series with long-term follow-up of over 5 years have reported NAC recurrence rates of 3.7 %, 1.2 % and 0 %, respectively [9, 14, 15]. If the results of all series on NSM are combined, the NAC recurrence rate averages around 0.6 %.

Why would NAC recurrences rates be so low? One important reason could be the fact that terminal ductal lobular units (TDLUs) are demonstrated in only 25 % of nipples. More importantly, the TDLUs are always found at the base of the nipple, not within the nipple proper [22]. As a result, it is likely not important to core out the nipple as part of the NSM operative technique.

Cosmetic outcomes reported by these early institutional reports found that the majority of patients had excellent to good outcomes at least 70 % of the time [12, 13, 22, 25, 28, 29].

European Institute of Oncology of Milan (EIO)

Nipple-Sparing Mastectomy Series

The largest series of NSMs in the literature comes from the EIO in Milan, Italy [26–28, 30]. Their experience requires special mention. In their past description of the technique used for the performance of an NSM, they leave a thin layer of breast tissue beneath the NAC. In other words, their technique is really a SCM. To compensate for leaving breast tissue behind the NAC, they have utilized intraoperative radiation therapy to sterilize the residual breast tissue [28]. At the time of the so-called nipple-sparing mastectomy, they are delivering 16 Gy of radiation therapy directly to the NAC. It is now informally understood that they have recently abandoned this approach, and now no longer leave breast tissue on the underside of the areola, or perform intraoperative radiation therapy.

In 2012, Dr. Petit and his colleagues from the EIO, reported on a unique form of NAC recurrence in 861 patients who had undergone their NSMs. There were seven cases (0.8 %) of Paget's disease diagnosed with an average latency patency period from NSM to recurrence of 32 months (range, 12–49) [35]. My group has also reported an identical case of Paget's recurrence in the areola 34 months after an areolar-sparing mastectomy [36].

The etiology of Paget's local recurrence in the NAC is unclear. The Milan Group believes that extensive DCIS, negative hormone receptors, over-expression of HER2/neu, and high pathological grade tend to be associated with more Paget's disease local recurrence [35]. Subsequent local resection of the NACs was curative for the seven cases from Milan, and the one case from my institution.

Increasing Mastectomy Rates

Reviewing the evolution of NSM would be incomplete without also reviewing a parallel phenomenon taking place over the same time period. Women with early stage breast cancer were increasingly choosing mastectomy as their primary surgical treatment, as well as also choosing contralateral prophylactic mastectomy (CPM), in addition to their therapeutic mastectomy [37–42].

Recent published reviews of both the Surveillance Epidemiology and End Results (SEER) database and the American College of Surgeons National Cancer Database (NCD) confirm these trends [37, 39, 40, 43]. The trend has also been confirmed by a review of the New York State Cancer Registry from 1995 to 2005 [38].

For both DCIS and invasive cancers, patients are increasingly considering mastectomy, despite the fact that they are excellent candidates for breast-conserving surgery (BCS). What are the factors driving this phenomena?

One factor is worry about in-breast recurrence after BCS. For both DCIS and invasive cancers in gene-negative patients, the local in-breast recurrence rates are estimated to be 0.8–1.2 % per year [41, 43]. Women often feel that a "bigger operation" (mastectomy) may offer a better chance for survival, despite the fact that years of clinical trial results refute that belief.

In the reports analyzing the increasing mastectomy trends, other factors are discussed that appear to contribute to the decision for mastectomy over BCS. These include: utilization of preoperative breast MRI; white race; higher household income and education levels; younger age; greater peace of mind; avoidance of radiation therapy; and fear [41, 43]. A physician recommendation for BCS or mastectomy in early stage breast cancer also plays a role. In the latest report on mastectomy trends by Kummerow and colleagues, more than 80 % of women reported that their physicians made a specific recommendation for either BCS or mastectomy. Less than 50 % of women reported being asked by their physicians whether they preferred BCS or mastectomy [43].

Kummerow also noted that the observed increase in overall mastectomy rates from 1998 to 2011 was largely attributed to a rise in bilateral mastectomy for unilateral early stage disease from 5.4 % of mastectomies in 1998 to 29.7 % in 2011 [43]. There was also a concurrent increase in reconstruction procedures from 36.9 to 57.2 % during the same time period [43].

Kummerow's observations are a good lead-in to a discussion about increased use of contralateral prophylactic mastectomy (CPM). Tuttle and coworkers report in 2007 brought to light what most breast surgeons were already observing; namely, a marked increase in the performance of CPMs. The CPM rate was 3.3 % for all surgically treated patients, and 7.7 % for patients undergoing initial primary mastectomy [37]. The overall CPM rates significantly increased from 1.8 % in 1998 to 4.5 % in 2003. The CPM rate for patients undergoing mastectomy increased from 4.2 % in 1998 to 11.0 % in 2003 [37]. The use of CPM in the United States more than doubled with the 6-year period of their study.

What factors are driving the increasing rate of CPM? One factor is the fear of a subsequent contralateral breast cancer. The annual incidence of subsequent contralateral invasive breast cancer has been stable for many years, estimated to be approximately 0.5–0.75 % per year [37]. For women with a diagnosis of DCIS, the estimated risk of developing either a contralateral invasive cancer or recurrent DCIS is approximately 0.6 % per year [39].

If a patient needs or chooses a unilateral mastectomy as her primary surgical treatment, a CPM may be chosen for better cosmetic symmetry and reduction of fear of subsequent contralateral cancer [40]. A family history, gene status, surveillance of the breast, anxiety, and the use of preoperative MRI are commonly cited reasons why patients are increasingly choosing CPM [37–40, 42]. In addition, rates of bilateral mastectomy are higher in hospitals where immediate breast reconstruction are available, indicating a possible strong influence on women choosing bilateral mastectomy [44]. Improved reconstruction techniques, including NSM, are also likely drivers of women choosing primary and contralateral prophylactic mastectomies [37–44]. As with unilateral mastectomy, patients electing CPM are better educated, white, younger, and more affluent [37–40].

The Nipple Is Just Another Margin

During the evolution and adoption of NSM, much debate has centered around the NAC. Is it involved with microscopic cancer? What characteristics of the tumor (e.g., size, positive nodal status, tumor-to-nipple distance, grade, multicentric, etc.) predict occult involvement of the NAC? What incisions and surgical techniques have the highest viability of the NAC? What are the short- and long-term recurrence rates in the NAC? As individual surgeons and institutions have gained experience with NSM, answers to these questions are emerging.

In the more up-to-date literature on NSM, the reported incidence of occult NAC involvement ranges from 2.7 to 8 % [45–47]. These low numbers likely represent better patient selection by physical examination, digital mammography, high-frequency ultrasound, and breast MRI. These up-to-date reports do *not* show a correlation with occult NAC tumor involvement with tumor size, nodal status, grade, tumor-to-nipple distance, or other factors.

It has been feared that NAC preservation would potentially increase local regional recurrence rates. However, the oncologic outcomes after NSM have recurrence rates similar to those of SSM, showing that NSM does not appear to compromise oncologic safety [11, 15, 48–50].

All reports on the technique of performing NSM (also called by some authors "total skin-sparing mastectomy") mandate obtaining a biopsy of the base of the nipple. All current techniques recommend complete resection of *all* subareolar breast tissue at the time of the initial mastectomy, or at the time of the second-stage reconstruction. There is debate if the biopsy of the base of the nipple should be evaluated by frozen section, or by the processed permanent pathology. In the multiple reports on the results of NSM, authors argue both for and against frozen section or touch prep analysis of the nipple base at the time of mastectomy, versus waiting for the permanent pathology report [15, 30, 45, 50–52]. Those who favor permanent pathologic assessment do so because of the possibility of false-negative results, and also differentiating ADH from low-grade DCIS on frozen section. In addition, there is now also interest in re-excising the nipple base at the time of expander-implant exchange if the permanent pathology report indicated a positive nipple-based margin. Often, the re-excision of the nipple base (including coring out the inside of the nipple) or removal of the NAC demonstrates no additional cancer [47, 52].

In conclusion, "the nipple is just another margin" [54].

More Positive Articles on Nipple-Sparing Mastectomy

Increasing numbers of articles have been published from 2011 to the present on institutional experiences with NSM, including meta-analyses of overall survival (OS), disease-free survival (DFS), and local recurrence (LR) with NSM [45, 46, 49–67]. All of these articles combined have found no significant differences in DFS, LR, or OS when comparing NSM with SSM or MRM. The articles demonstrate the increasing acceptability of NSM as a prophylactic procedure, as well as for therapeutic purposes.

There is also a trend with NSM toward increasing eligibility. The absolute contraindications to NSM are generally agreed upon. They include: clinical or imaging evidence of NAC involvement, inflammatory breast cancer, cancers associated with a bloody nipple discharge, and locally advanced breast cancers with dermal involvement [46, 53, 64]. Relative contraindications to NSM include: active smoking, scleroderma, large ptotic breasts, BMI (greater than 30), prior whole breast radiation therapy, and insulin-dependent diabetes [46, 53, 64]. Lymph-node positive patients and those who have undergone neoadjuvant chemotherapy may also be candidates for NSM [59].

What about BRCA 1/2 mutation carriers? Are they eligible for NSM? There have been few large-scale studies that have examined the outcomes of BRCA 1/2 carriers who have undergone NSM. The largest series reported in the literature to date is from Yao and colleagues [66]. Nipple-sparing mastectomy was performed in 397 breasts in 201 BRCA 1/2 carriers in Evanston, Illinois, Chicago, Illinois and Boston, Massachusetts. With a mean follow-up of 32.6 months (1–76 months), there have been four cancer events, three in cancer patients and one in a risk-reduction patient. There have been no recurrences in the NAC [66]. The authors concluded that longer follow-up of these patients is needed to determine specific local regional recurrence rates, but their results suggest that BRCA 1/2 patients are eligible for NSM for both prevention and treatment of breast cancer [66].

At the Annual Meeting of The American Society of Breast Surgeons, held from April 13–17, 2016, there was an oral presentation by Dr. James Jakub on the results of a multi-institutional study of BRCA positive patients undergoing prophylactic NSM. The retrospective study was from nine academic medical centers. A total of 551 risking-reducing mastectomies were performed in 348 patients, with a medial follow-up of 34 months. None of the patients who underwent a bilateral risk-reducing NSM developed breast cancer at any site. The conclusion of the presentation was that NSM is highly preventative against breast cancer in a BRCA population [68]. The report is being submitted for publication.

The guidelines of the National Comprehensive Cancer Network (NCCN) are an important benchmark followed by most comprehensive cancer programs in the United States. In the NCCN Guidelines Version, 1.2016- Breast Cancer Updates, the following language appears (BINV-H (2 of 2)): "Evidence of nipple involvement such as Paget's disease or other nipple discharge associated with malignancy, and/or imaging findings suggestive of malignant involvement of the nipple or subareolar tissues contraindicates nipple preservation" [69]. In other words, these are virtually the same criteria used by nearly all series on nipple-sparing mastectomy to exclude patients from undergoing NSM.

Conclusions

The evolution of nipple-sparing mastectomy as a standard form of mastectomy is nearly complete. The contemporary nipple-sparing mastectomy is *NOT* a subcutaneous mastectomy. Longer-term follow-up data is needed, but the initial experience with this procedure for more than three decades is very favorable. What has emerged over time are recommendations for NSM eligibility, workable operative techniques with acceptably low complication rates, very good to excellent cosmetic outcomes, and a clear understanding that *the NAC is just another margin*.

Patients undergoing NSM should be evaluated and followed by a multidisciplinary team of specialists, including experienced breast and plastic surgeons. It is important to recall that no breast surgeon can claim that he or she removes 1000 % of all microscopic breast tissue when performing any type of mastectomy, including NSM. Therefore, long-term follow-up is essential for all NSM patients. Surgeons are also encouraged to support and enroll patients in the American Society of Breast Surgeons' Nipple-Sparing Mastectomy Registry (see Chap. 23).

It is likely that future reports will continue to validate nipple-sparing mastectomy as an oncologically safe and an esthetically improved way of performing preventative and therapeutic mastectomies in properly selected patients. Stay tuned!

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2 Nipple and Breast Anatomy

Jennifer Rusby and Riaz Agha

Introduction

Knowing the anatomy of the breast is fundamental to surgical management of breast disease. In an era when Halsted's radical mastectomy was the standard treatment for breast cancer (and some benign conditions), anatomy mattered little [1]. Now, with better oncological outcomes and greater aesthetic expectations from patients, a sound knowledge of anatomy becomes essential to optimise removal of the affected or at-risk breast tissue while carefully preserving the surrounding structures to minimise morbidity and enhance post-operative aesthetics.

Embryology and Development

The breast parenchyma develops from a single ectodermal bud in-growth into mesodermal tissue in the mammary ridge or milk line. All but the two breast buds overlying the 4th intercostal space regress, leaving bilateral nipple–areola complexes overlying primitive duct structures [2]. Failure to regress leaves an accessory nipple which may lie anywhere along the milk line between the clavicle and the inguinal region.

At puberty, increased circulating oestrogen results in growth of ducts, lobules, connective tissue and fat to form the adult breast [3]. Glandular increase is due to growth and division of ducts, and (type 1) lobule formation occurs within 1–2 years of the first menstrual period. Full differentiation takes many years and may never be attained without pregnancy [2]. Thereafter, with each menstrual cycle there is slightly more mammary development with new budding of structures and type 2 lobule formation continuing until about age 35. It is not until pregnancy that profound changes occur in the composition of the breast which affect its outward appearance in terms of size and shape, as well as its microscopic structure. In early pregnancy, proliferation of distal elements of the ductal tree results in acini and the epithelial cells within these acini increase in number and size to form type 3 and 4 lobules. In the second half of pregnancy, the formation of true differentiated secretory units occurs and the luminae become distended with colostrum. Post-lactational regression occurs due to cell autolysis and regeneration of periductal and perilobular connective tissue. A further regression occurs at the menopause, in both parous and nulliparous women, leaving predominantly type 1 lobules containing terminal-ductal lobular units (TDLUs).

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Surface Anatomy

The breast extends from the 2nd to the 6th rib and the lateral mammary fold usually lies at the anterior axillary line, but may extend posteriorly to reach the latissimus dorsi muscle. Medially breast tissue usually reaches the lateral border of the sternum, but may encroach to the midline. Depending on the degree of ptosis, much of the breast volume may rest inferior to the infra-mammary fold. Ptosis is classified according to Regnault [4]:

- *First degree:* The nipple is at the level of the infra-mammary fold (Pitanguy's point) and above the lower pole breast tissue.
- *Second degree:* The nipple is below the infra-mammary fold but higher than most of the lower pole breast tissue and skin.
- *Third degree:* The nipple is below the infra-mammary fold and at the lower contour of the breast and skin brassiere.
- *Pseudoptosis:* The nipple is at or above the infra-mammary fold, but the majority of the breast tissue rests below it.

The primary intention of nipple-sparing mastectomy, which is invariably associated with immediate breast reconstruction, is oncological local control in women with breast cancer and breast cancer risk-reduction in those at high risk, whilst optimising aesthetics. Secondary but important concerns are to match the contralateral, unaffected breast as nearly as possible, or to enhance the breast aesthetic by producing a template reconstruction to which the contralateral, unaffected breast can be adjusted to match. In risk-reducing cases, the secondary aim is bilateral aesthetically-pleasing reconstructed breasts.

When bilateral reconstruction is undertaken, or contralateral symmetrisation is anticipated, the surface anatomy takes on a new importance. The surgeon and patient must have a clear and shared vision of the anticipated post-reconstruction desired shape and appearance. Recent work has given an element of objectivity to "the ideal breast" and may serve as a useful starting point for the discussion about the intended breast shape and nipple position [5]. The ideal breast has an upper to lower pole ratio of 45:55, the nipple points upwards at an angle of approximately 20° from the nipple meridian, and the upper pole slope is linear or slightly concave and the lower pole is convex [5]. The integration of objective surface imaging including 3D-surface imaging into evaluation of aesthetic outcome after breast reconstruction surgery is likely to lead to further guidance in the future [6, 7].

Structure of the Breast

Skin and Subcutaneous Fat

The breast is covered by normal skin, except at the areola which will be discussed in more detail later. Preservation of a healthy skin envelope is essential for a favourable outcome from skin- and nipple-sparing mastectomy. The skin is associated with a variable thickness of subcutaneous fat. The interface between deep dermis and subcutaneous fat is not smooth but punctuated by columns of fat projecting into dermal "caves". This gives a characteristic punctate appearance on mammography and more prominently so on tomosynthesis [8]. It is thought that Camper's fascia (which itself is predominantly adipose) separates subcutaneous fat from fat surrounding the glandular tissue and that this is the "oncoplastic plane" sought by surgeons aiming to remove breast and maintain skin-flap viability [9]. Anecdotally, the visibility of the plane and the thickness of the subcutaneous layer of fat varies from patient to patient and by quadrant within a single patient. Histological studies have attempted to investigate this further. Beer et al looked for a superficial fascial layer in breast reduction specimens, but found that it was absent in 44 % of specimens [10]. It also appeared to be very superficial with a distance from the layer to the deep dermis of 0.2–0.4 mm. This would make a skin flap too thin to be viable and this may not be the fascial plane seen at operation.

Larson et al. examined skin, again from reduction mammoplasty specimens, to identify a zone of subcutaneous fat which is free of breast tissue [11]. They reported the thicknesses of the subcutaneous layer between the dermis and the breast

Fig. 2.1 Plate VI Figure 2 Mammary ducts injected with *red*, *yellow*, *black*, *green*, and *brown*. (From Cooper A. On the anatomy of the breast. London: Longman; 1840 with permission)

parenchyma to range from 0 to 29 mm (median 10 mm). There was no correlation with body mass index or age of the patient, breast specimen weight or dermis-to-breast thickness of the contralateral breast. The difficulties in correlating histopathological findings with clinical appearance means that an optimal mastectomy skin flap thickness cannot be recommended [12]. Furthermore, examination of mammograms reveals a wide variation in the depth of subcutaneous fat, again unrelated to body mass index or breast density.

Some surgeons are using mammographic images to help tailor the skin flap thickness, and even to plan the optimal reconstruction (two-stage submuscular expander then implant for thin skin flaps vs. one-stage with ADM for intermediate thickness vs. one-stage with titanium mesh for much thicker skin flaps).

Glandular Tissue

The gland itself is made up of ducts and lobules, merging at terminal ductal lobular units, thought to be the site of development of both ductal and lobular breast cancers. While the large ducts remain relatively unchanged during life, the lobules undergo enormous transformation in preparation for breast feeding, followed by involution, as described above. Breast ducts branch within the parenchyma to form a network, though in a roughly segmental fashion (Fig. 2.1). The number of duct systems is variable, but likely to be between 5 and 50, since this is the number of ducts seen in the nipple–areola complex [13, 14]. Of these, it is possible to cannulate approximately nine per breast, hence the illustrations of Cooper and more recent authors [15].

There is general consensus that duct systems are anatomically distinct [16], though they may lie in overlapping planes and with interlocking borders. However, Ohtake et al. prepared three-dimensional reconstructions from 2 mm slices through 20 quadrantectomy specimens and identified ductal anastomoses in several cases. In one specimen, intraductal tumour extended widely from the primary invasive carcinoma through a branch connecting adjacent ductal-lobular systems [17].

Several authors have called for a more in depth understanding of the macroscopic anatomy of the whole breast [16]. To date, a full anatomical description has not been undertaken. The variation seen in the external appearance of the breast is likely to be paralleled by substantial variation in the number and arrangement of duct systems. Concerns that using large parts of surgical specimens for research might compromise clinical care, the laborious nature of the work to produce 3D reconstructions, and the difficulty of relating the ductal architecture to radiological or surgical intervention have meant that this area has not attracted much research activity.

Supporting Structures

The breast tissue is supported by fascia, fibrocollagenous septa and the suspensory ligaments of Cooper. The latter arise from the clavicle, clavipectoral fascia and the retromammary fascia and branch out through the breast tissue to the dermis of the skin. Wueringer and Tschabitscher have described an internal breast septum running transversely across the lower pole of the breast, enhancing our understanding of the inferior pedicle blood supply [18]. It is well-vascularised and anatomically consistent and has therefore been utilised in reduction mammoplasty [19]. The infra-mammary fold deserves particular attention. This is formed where the superficial and deep layers of superficial fascia unite at the inferior border of the breast. If disrupted during the course of skin- or nipple-sparing mastectomy it should be recreated during breast reconstruction to help produce a natural-looking breast.

Blood Supply

The blood supply to the breast is derived from six sources: perforating branches of the internal mammary artery, the highest thoracic artery, the anterior and posterior branches of the intercostal arteries, the thoracoacromial artery and the lateral thoracic artery either of which can give off the superficial thoracic artery which also supplies the breast [20]. Van Deventer et al. have subsequently questioned the nomenclature [21], but there is agreement that the breast is supplied by several sources and with variation between individuals. Venous drainage maps to the main branches of arterial supply but there is, in addition, an extensive superficial network of veins. Although there is variation between individuals, the two sides are usually symmetrical.

Amanti et al. [22] recently studied the blood supply of the breast using MRI and identified three perforating branches other than the named branches of the internal thoracic artery (pericardiophrenic, anterior mediastinal and sternal and anterior intercostal branches). The superior perforating branch emerges from the pectoralis major muscle at the second to third intercostal spaces, an intermediate one, known as “major”, at the level of the third to fourth intercostal spaces, while the lower branch emerges in correspondence with the fifth to sixth intercostal spaces. They report that these perforating vessels supply blood to the pectoralis major muscle, to the breast skin envelope, and to the mammary gland. Whilst care must be taken to avoid leaving breast tissue, these perforating vessels can often be seen at the medial border of the breast and preserved.

Nerve Supply

In a manner similar to the blood supply, the nerve supply to the breast comes from several sources, namely the lateral and anterior cutaneous branches of the second to the sixth intercostal nerves, and from the supraclavicular nerves, leading to discrepancies in the literature as to the exact supply of the nipple. This is likely to be variable between individuals. Laterally, branches from the third, fourth and/or fifth, and medially branches from the second to fifth intercostal nerves may be found passing along the superficial fascia to contribute to a plexus in the subdermal tissue of the areola. Branches from the sixth intercostal nerve supply the lower part of the breast. A deep branch from the anterior division of the fourth lateral cutaneous nerve passes through the inferolateral part of the breast to reach the subareolar neural plexus. Together, these convey sensation from the skin of the breast and the sympathetic nerves to the blood vessels and smooth muscle in the skin and nipple.

Lymphatics

In his paper of 1874, Sappey demonstrated that the lymphatics of the breast drain predominantly to the axillary lymph nodes [23]. He noted the appearance of a subareolar plexus of lymphatics which led to the notion that lymphatic spread from a tumour to the axilla is via the subareaolar plexus. While Suami et al. also identified a dense network of lymphatic capillaries and pre-collectors in the dermis of the areola region, they concluded that the flow of lymph from most of the breast (even the infero-medial periphery) was direct to the axilla through the superficial lymphatic system, rather than via the subareolar plexus [24]. Furthermore, they identified that the superficial lymphatics have a "wavy" path, sometimes lying in the subdermal plane, sometimes passing deeper, through the breast tissue. They found no evidence of direct anastomosis between the superficial collecting lymphatics and the collectors associated with perforating arterial branches, but stated that this does not exclude a connection of small-calibre lymphatic vessels which could not be demonstrated radiologically. The presence of two draining systems (the superficial, and the perforating) offers a mechanism for anatomical false negative sentinel lymph node biopsy, and for metastasis of breast cancer to internal mammary nodes.

Obstruction of the lymphatics by extensive lymphovascular or nodal involvement gives rise to the edema and erythema mimicking acute inflammation, hence the name "inflammatory carcinoma". Anchoring of the skin by Cooper's ligaments gives rise to the characteristic dimpling known as peau d'orange. Inflammatory breast cancer has been seen as a contraindication to skin- and nipple-sparing mastectomy even after neoadjuvant systemic therapy, though this may be challenged as pathological complete response rates continue to rise.

Nipple and Areola

The nipple, like the breast, can vary in size, shape and position. The skin of the areola is usually more pigmented than the surrounding skin and Montgomery's tubercles (a group of three to six blind-ending ducts always associated with large sebaceous glands are present [25]). Contraction of underlying smooth muscle results in rugae. The nipple is formed of ducts surrounded by a connective tissue scaffold, rich in smooth muscle, and the necessary blood and lymphatic vessels.

Embryologically the ducts arise from the nipple and grow into the supporting mesodermal scaffold more proximally, but functionally, the flow of milk is from within the breast distally to the nipple. The number of ducts in a cross section of the nipple varies dramatically, from 5 to 50 on histological cross-section. In one series [14] the median was 23 with an interquartile range of 19–28. The ducts varied in size, many having a crenelated appearance suggesting the potential for expansion to form lactiferous sinuses as reported by Cooper [26]. Most remained very narrow (0.06 mm diameter) at 1.5 mm from the tip, increasing to 0.7 mm at 3 mm below the tip and many shared common orifices. These findings may explain why studies requiring cannulation or ultrasound visualisation of ducts report far fewer ducts than are present in histological studies.

The dominant blood supply to the nipple is via the internal thoracic artery. Clinically, vessels are often seen at the areolar border in the upper inner quadrant, concordant with the findings of O'Dey [20], that the internal thoracic vessels had a curved course with superior convexity and arrive at the supero-medial border of the nipple–areola complex. O'Dey also reported that the lateral thoracic artery supplied up to three separate branches to the nipple–areola complex during its descending course, and that these passed through deep breast tissue before ascending towards the superolateral edge of the nipple–areola complex [20].

Microscopic studies also suggest a dual blood supply, part arising through the deep parenchyma, and part via the subdermal plexus (Fig. 2.2). Thus, as the deep blood supply is removed during a skin- and nipple-sparing mastectomy, careful attention must be paid to preserving the subdermal plexus of vessels to ensure the viability of skin flaps and nipple is maintained. Nakajima et al. showed parallel vessels ascending within the nipple before branching in the upper third [27]. This can be seen in figure 2.1 in that paper, and in the image from Cooper's book reproduced below (Fig. 2.3).

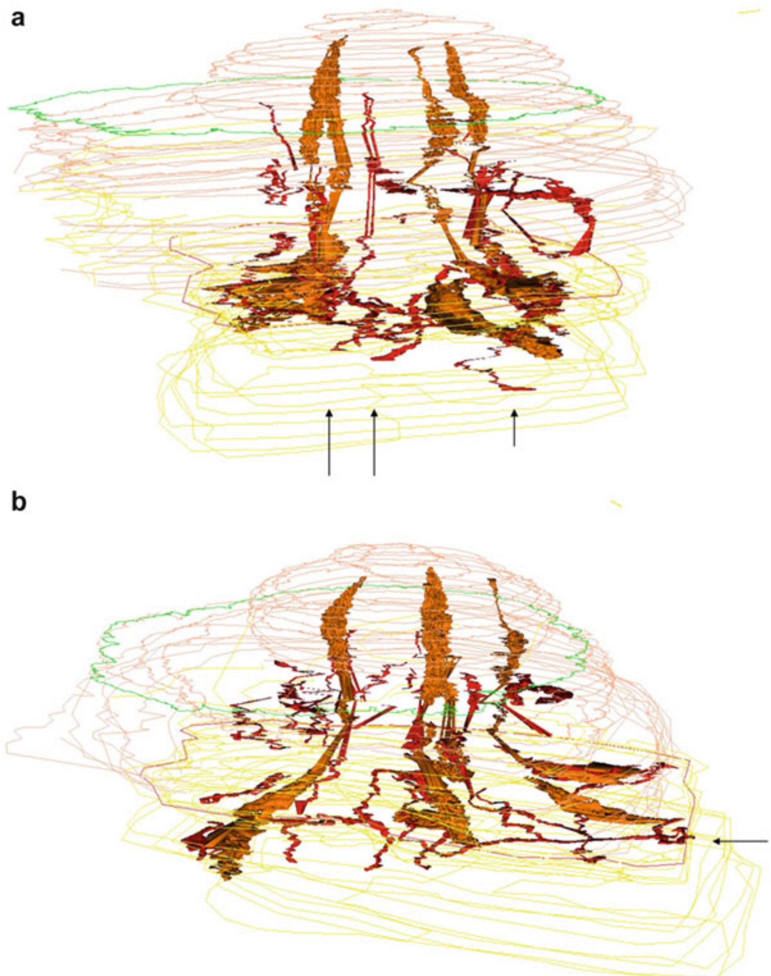

Fig. 2.2 Three-dimensional reconstructions illustrating the deep and superficial blood supply to the nipple (1). Skin shown in *pink*, subcutaneous fat in *yellow*, ducts in *orange*, the level of the nipple–areola junction in *green*, and vessels in *red. Arrows* indicate incoming arteries. (**a**) illustrates 3 vessels reaching the nipple-areola complex from deep tissue and part (**b**) illustrates a vessel running in the subdermal plane to reach the nipple. (From Rusby J. An anatomical study of the skin, nipple and areola of the breast. Towards a scientific basis for nipple-sparing mastectomy. University of Oxford DM Thesis; 2009 with permission)

Fig. 2.3 Plate II, 14: The arteries of the nipple (twice magnified), terminating in veins in the papilla. (From Cooper A. On the anatomy of the breast. London: Longman; 1840 with permission)

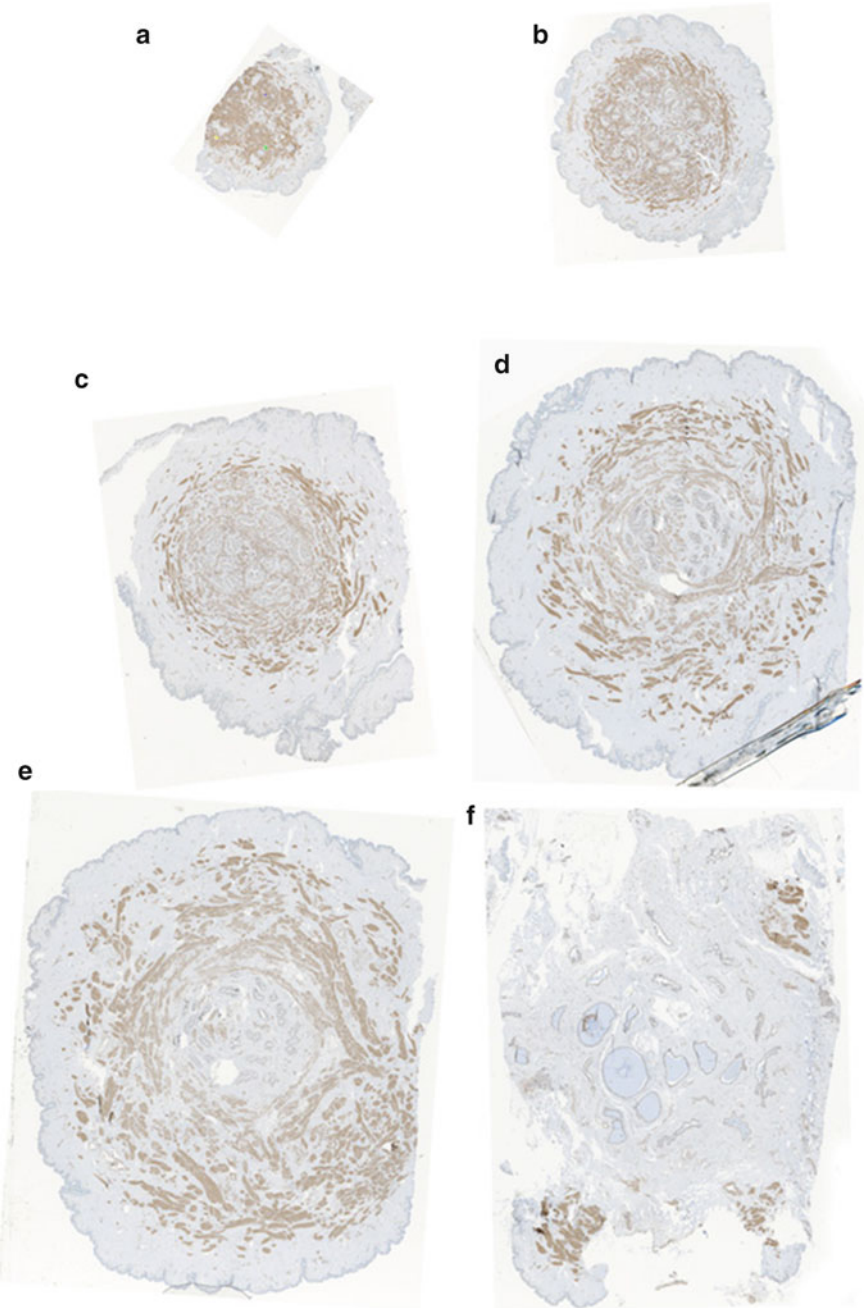

Fig. 2.4 (**a**–**f**) Interval sections through a nipple stained with antibody to SMA. (From Rusby J. An anatomical study of the skin, nipple and areola of the breast. Towards a scientific basis for nipple-sparing mastectomy. University of Oxford DM Thesis; 2009 with permission)

Staining of sections of the nipple with anti-SMA antibody (highlighting smooth muscle) reveals that most of the volume is accounted for by smooth muscle. Towards the tip of the nipple, the fibres are arranged concentrically around individual ducts while at the base of the nipple, the larger fibres are concentrically around the whole duct bundle (Figs. 2.4 and 2.5). The function of

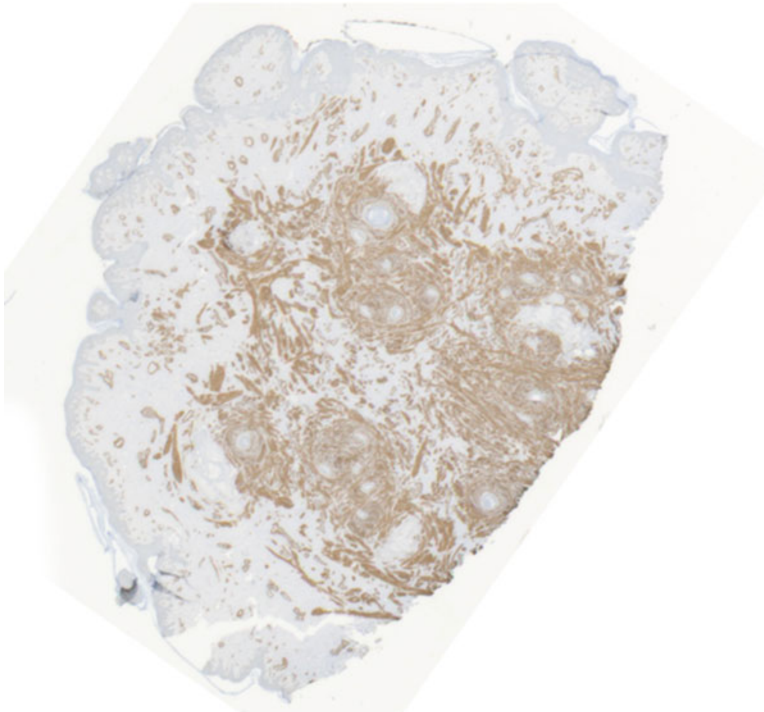

Fig. 2.5 Enlarged image of Fig. 2.4a, showing how, near the nipple tip, muscle fibres encircle individual ducts, in contrast to the base of the papilla (Fig. 2.4e) where muscle fibres encircle the duct bundle as a whole. (From Rusby J. An anatomical study of the skin, nipple and areola of the breast. Towards a scientific basis for nipple-sparing mastectomy. University of Oxford DM Thesis; 2009 with permission)

these muscle fibres is unknown, though presumably result in erection of the nipple in sexual arousal and for breast feeding, and possibly even acting as a sphincter to control the flow of milk. Anecdotally, after nipple-sparing mastectomy, many patients report that the nipple retains an erectile reaction to cold and touch, though most report minimal sensation.

Summary

It is vital to have a thorough knowledge of the breast and nipple–areola complex anatomy in breast surgery in general and nipple-sparing mastectomy in particular. Clinically, it can be helpful to consider the breast in three distinct areas: the footprint, the gland and the skin envelope [28]. Assessing and documenting the patient's current status in these areas and having knowledge of "ideal" breast aesthetics together with an understanding of the patient's goals, desires and past history will help when planning any breast surgery.

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3 Patient Selection and Breast Imaging

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There is increasing interest in identifying appropriate candidates for nipple-sparing mastectomy (NSM) as data accumulate demonstrating the oncologic safety and cosmetic and psychological benefits [1] of this approach. This chapter will review oncologic and technical considerations in patient selection for NSM, as well as recommendations for preoperative work-up to maximize the likelihood of successful nipple–areola complex (NAC) conservation.

Patient Selection: Oncologic Considerations

Oncologic criteria for NSM should be designed to minimize the need for unplanned nipple excision and to reduce the risk of NAC recurrences. Several clinical and pathological characteristics have been shown to correlate with increased likelihood of occult nipple involvement (Table 3.1); however, in the absence of pathology demonstrating nipple margin involvement with tumor, none has been shown to correlate with increased risk of NAC recurrence. Apart from the few accepted absolute contraindications to NSM (Table 3.1), other relative risk factors do not preclude an attempt at NSM in a patient who is highly motivated to preserve her NAC. Of course, such patients should be fully informed regarding the risks of NSM, including partial or complete NAC necrosis, and unplanned NAC excision, either during the mastectomy or as a second procedure. Indeed, as discussed at the end of this section, a number of institutions have accepted "liberalized" criteria for NSM with outcomes that are acceptable to many patients and clinicians.

Absolute Contraindications to NSM

Generally accepted absolute contraindications to NSM include extensive tumor involvement of the skin, inflammatory breast cancer, Paget's disease of the nipple, and clinical [2–4] and/or imaging evidence of direct NAC involvement [5]. Some authors advocate for routine intraoperative frozen section of subareolar tissue or a nipple core specimen [6, 7]. Detection of invasive or noninvasive cancer in frozen or permanent section analysis of subareolar or nipple core tissue is generally considered an indication for NAC excision, although alternative approaches such as margin re-excision or radiation of the NAC have been reported [8]. Some institutional protocols do allow for NSM in patients with initial skin

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Table 3.1 Contraindications to nipple-sparing mastectomy, risk factors for nipple–areola complex involvement, and risk factors for technical complications

Absolute contraindications to nipple-sparing mastectomy
Extensive tumor involvement of the skin (that does not resolve with neoadjuvant chemotherapy, if administered)
Inflammatory breast cancer
Paget's disease of the nipple
Clinically suspicious nipple
Imaging evidence of direct nipple–areola complex involvement
Positive intraoperative frozen section of subareolar or nipple core specimen (if performed)
Risk factors for NAC involvement
Large tumor size
Central/retroareolar tumor location
Tumor-to-nipple distance <2 cm
Multicentricity
Extensive intraductal component
Micropapillary carcinoma
Axillary lymph node metastasis
HER2 positive disease
ER or PR negative disease
Lymphovascular invasion
High tumor grade
Risk factors for technical complications or poor cosmetic results
Prior or planned postoperative breast radiation
Current smoking
Obesity
Very large or ptotic breasts

involvement that shows excellent response to neoadjuvant chemotherapy [9, 10]; however, applicability to patients with initial direct NAC involvement or inflammatory breast cancer has not been reported.

Tumor Size

There is conflicting evidence about the relationship between tumor size and prevalence of occult nipple involvement. Mallon and colleagues have published a comprehensive review of clinicopathologic factors and their association with nipple involvement [11]. Their review is somewhat limited by inclusion of several studies from an era when more women presented with locally advanced disease, as well as studies that did not exclude women for clinical and/or radiographic evidence of direct nipple involvement. Nonetheless, their review is useful as perhaps the most complete analysis to date of risk factors for NAC involvement.

Mallon's meta-analysis of 16 studies examining tumor size found that the incidence of nipple involvement was 9.8 % for tumors smaller than 2 cm, 13.3 % for tumors 2–5 cm, and 31.8 % for tumors greater than 5 cm ($p < 0.05$) [11]. However, some studies have suggested that this relationship is mitigated by adjustment for potential confounding factors such as tumor-to-nipple distance or subareolar location [5, 12].

Tumor Location

At least six multivariate analyses in large groups of patients have identified central or retroareolar tumor location as a risk factor for occult nipple involvement [13–18]. Mallon's meta-analysis of data from five of these studies found that 35.2 % of central/retroareolar tumors had nipple involvement, compared to 9.7 % of peripheral tumors ($p < 0.05$) [11]. Retroareolar tumors can be close to or far from the NAC, which may influence the risk of NAC involvement associated with this factor.

Tumor-to-Nipple Distance

In the relevant literature, tumor-to-nipple distance is probably the most uniformly reported clinicopathologic risk factor for nipple involvement [15, 16, 18–32]. Studies have variously reported tumor-to-nipple distances of 2–4 cm as a threshold value below which the prevalence of nipple involvement is significantly increased [20, 21, 23, 25, 27, 33]. However, a recent report of a large, prospectively collected database ($n = 392$) found that, although tumor-to-nipple distance (assessed by mammogram, ultrasound, or MRI) was associated with nipple involvement on univariate analysis, on multivariate analysis only imaging or clinical evidence of direct NAC involvement remained independently associated with positive nipple pathology [5].

Multicentricity/Multifocality

Mallon's meta-analysis of six studies found a higher incidence of occult nipple involvement in multicentric versus unicentric tumors (29.6 % vs. 12.4 %, $p<0.05$) [11]. However, these data should be applied with caution in modern-era patients in whom mammographically occult multicentricity is detected on MRI. In pooled data from two studies, there was no association between multifocality and occult nipple involvement [11].

Tumor Histology

Mallon's analysis of 14 studies found that in most there was no correlation between histologic type and occult nipple involvement [11]. Two reports showed a higher incidence of occult nipple involvement in infiltrating ductal carcinomas with extensive intraductal component [20, 21], and a third report showed a higher prevalence of occult nipple involvement in micropapillary tumors [15].

Nodal Status

The superficial lymphatic plexus of the breast is found in the dermis and subcutaneous region and drains primarily to the ipsilateral axillary lymph nodes [34, 35]. Thus, there is a theoretical possibility of a correlation between occult nipple involvement and axillary nodal metastasis. Mallon's meta-analysis of 16 studies found a higher incidence of occult nipple involvement in cases of lymph node-positive disease (24.4 %), compared to lymph node-negative disease (10 %, $p<0.05$) [11]. Furthermore, four studies found increasing likelihood of nipple involvement with heavier nodal disease burden [13, 14, 21, 27]. A more recent, large study ($n=466$) not included in the meta-analysis found an association between axillary nodal metastasis and nipple involvement, but this relationship was attenuated by multivariate analysis accounting for other clinicopathologic factors, including tumor size and lymphovascular invasion, which are themselves associated with nodal positivity [18].

Prognostic/Predictive Tumor Markers

Pooled analysis of four studies showed a higher prevalence of NAC involvement in patients with HER2 positive disease (19.7 %), compared to HER2 negative disease (10.1 %, $p=0.0001$) [11]. Six studies correlating estrogen receptor (ER)/progesterone receptor (PR) status to NAC involvement showed disparate results. One of these six studies had a sample size ($n=2028$) exceeding that of the other five studies combined [15]. Meta-analysis of these six studies reflects the findings of this largest study, showing a weak but significant association between both ER negativity and PR negativity and occult nipple involvement [11]. While no rationale was proposed for these associations, it is consistent with the more aggressive tumor biology of HER2 positive and hormone receptor negative disease.

Lymphovascular Invasion and Tumor Grade

Mallon's meta-analysis of seven studies found that the incidence of nipple involvement was higher for tumors with lymphovascular invasion, compared to those without lymphovascular invasion (35.6 % vs. 12.4 %, $p<0.05$). His analysis of 11 studies found that increasing grade was associated with increasing likelihood of NAC involvement: the incidence of NAC involvement for grades 1, 2, and 3 tumors were 8.7, 12.6, and 17.2 %, respectively ($p<0.05$) [11].

BRCA Mutation Carrier Status

Terminal duct lobular units, from which both ductal and lobular breast cancers are thought to arise, are found in 9–26 % of NACs from total or skin-sparing mastectomy specimens [36–38].

This has led to concern that NSM may be associated with increased risk of recurrent or de novo cancer, particularly in BRCA mutation carriers.

In the largest reported series of NSM in BRCA mutation carriers, Yao and colleagues retrospectively reviewed results of 397 NSM in 201 BRCA mutation carriers (62.2 % BRCA1, 37.8 % BRCA2). Of 150 patients who underwent NSM for risk reduction, four (2.7 %) had an incidentally discovered cancer, and in none was the NAC margin involved. At a mean follow-up of 32.6 months, three of 51 cancer patients experienced a local recurrence (5.8 %), and 1 risk-reduction patient experienced a new breast cancer diagnosis (0.7 %); none of these involved the NAC [39]. Several other studies have reported on therapeutic or risk-reducing NSM in smaller numbers of BRCA-positive patients (range, $n=6–89$) over relatively short follow-up times (mean/median, range 10.4–51 months). No new breast cancers occurred after risk-reducing NSM [40–44]. The only study reporting a local recurrence (a case of Paget's disease in the retained NAC) included women without BRCA mutations, and it was unclear if this recurrence occurred in a BRCA mutation carrier [40].

Longer follow-up is available in two earlier studies of BRCA mutation carriers who underwent risk-reducing subcutaneous mastectomy [45, 46]. Subcutaneous mastectomy preserves a margin of breast tissue below the NAC, whereas modern NSM removes most of the breast tissue under the NAC and within the nipple. Nevertheless, in these studies rates of de novo cancer in the NAC were also very low [45, 46]. Rebbeck and colleagues evaluated l05 BRCA 1 or 2 mutation carriers who underwent bilateral risk-reducing mastectomy, at least 30 % of which were subcutaneous. At a mean 6.4 years of follow-up, two women (1.9 %), both of whom underwent subcutaneous mastectomy, had a new breast cancer diagnosis [45]. Hartmann and associates evaluated 26 BRCA 1 or 2 mutation carriers (18 known deleterious mutations, eight variants of uncertain significance) who underwent risk-reducing mastectomy, of which 23 were subcutaneous. There were no new breast cancer diagnoses at a median of 13.4 years of follow-up [46].

Based on these data, there is increasing acceptance of therapeutic or risk-reducing NSM in BRCA mutation carriers. However, appropriate counseling and compliance with long-term clinical follow-up are required, and long-term follow-up data are necessary to confirm the safety of this option for BRCA mutation carriers.

"Liberalized" Oncologic Criteria

The rationale for more liberalized oncologic criteria is that, while there are strong associations between certain clinicopathologic features and occult nipple involvement, there is, nonetheless, a high false positive rate for many of these risk factors. A small study ($n=58$) of patients who underwent total mastectomy found that clinical criteria of tumor size <4 cm and tumor-to-nipple distance of ≥2 cm had a false positive rate of 44.4 % for predicting nipple involvement on final pathology [47]. A larger study of a prospectively maintained database of total, skin-sparing, and nipple-sparing mastectomies ($n=392$) found that, although tumor size and tumor-to-nipple distance were associated with nipple involvement on pathology, on multivariate analysis only clinical or imaging evidence of NAC involvement persisted as independent predictors of nipple involvement on pathology [5].

In recent years, a number of institutions have reported their experience with more liberalized oncologic criteria for NSM candidacy (Table 3.2). Six institutions' experience is reviewed here. The first two analyses summarize outcomes of NSM after liberalized criteria were adopted [3, 4]. Two others report on broadening inclusion criteria and parallel changes in patient outcomes over time [7, 48]. The final two report on outcomes of NSM in a subgroup of patients with locally advanced disease [10, 49].

Paepke and associates report on the outcomes of 109 NSM in 96 patients; 94 NSM were performed for malignancy. Exclusions from NSM were for extensive tumor involvement of the skin, inflammatory breast cancer, a clinically suspicious nipple, or imaging suspicion of NAC involvement. In 14 of 109 breasts (12.8 %), intraoperative frozen section of the subareolar

Table 3.2 Studies reporting results of "liberalized" oncologic criteria for nipple-sparing mastectomy (NSM)

Reference	Study population	Exclusion criteria; Cohort characteristics	Oncologic outcomes	Surgical outcomes
Paepke et al. [3]	All NSM, 2003–2006 (109 NSM, 94 for malignancy)	Exclusions: Extensive tumor involvement of skin, inflammatory breast cancer, clinically suspicious nipple, imaging suspicion of NAC involvement.	12.8 % (14/109) subareolar frozen section positive; 13 NAC excised intraoperatively. No recurrences in NAC (median follow-up, 34 months).	NAC necrosis requiring surgical intervention, 1 % (1 of 97 conserved NACs).
Fortunato et al. [4]	All NSM, 2003–2012 (138 NSM, 122 for malignancy, 124 after 2009)	Exclusions, since 2009: tumor-to-NAC distance <1 cm, bloody nipple discharge, large or ptotic breasts, clinical involvement of the NAC, Paget's disease, inflammatory breast cancer.	16 % ($n=19$) NAC excision based on pathology of retroareolar tissue (margin <2 mm); 11 NACs had residual cancer on pathology. One local recurrence, none in the NAC (median follow-up 26 months).	Total NAC necrosis, 4 % ($n=6$). Mild NAC desquamation, 10 % ($n=14$). Partial mastectomy flap skin necrosis, 4 % ($n=6$).
Coopey et al. [48]	All NSM, 2007–2012 (645 NSM, 315 for malignancy)	Exclusions, early period: tumor size ≥2 cm, tumor-to-nipple distance <2 cm. Exclusions, final period: clinical or imaging evidence of NAC involvement, locally advanced breast cancer with skin involvement, inflammatory breast cancer, bloody nipple discharge.	3.7 % ($n=24$) had NAC removed for positive subareolar margin; decreasing positive subareolar margin over time as criteria were liberalized (6.5 % vs. 2.7 %, $p=0.027$). Local recurrences in 2.6 %, with none in NAC (mean follow-up, 22.1 months).	Total nipple necrosis, 1.7 % ($n=11$).
Krajewski et al. [7]	All NSM, 2009–6/2014 (566 NSM, 218 for malignancy)	Exclusions, early period: tumor diameter >2 cm, tumor-to-nipple distance ≤2 cm, inflammatory breast cancer, cancer extension into the NAC; relative contraindications: obesity, large/ptotic breasts, prior radiation. Exclusions, final period: adherence to early exclusion criteria became less stringent over time; noted increasing rates in this period of high BMI, bra cup size C or larger, prior radiation, tumor-to-NAC distance ≤2 cm, receipt of neoadjuvant chemotherapy.	2.8 % of cancer patients had nipple excision for positive pathology ($n=6$: 5 atypia, 1 DCIS). Five locoregional recurrences, none in NAC (median follow-up, 19 months).	Fewer 30-day complications, late vs. early period (18.7 % vs. 41.4 %, $p<0.0001$). Trend towards decreased nipple loss, late vs. early period (2.2 % vs. 5.7 %, $p=0.10$).
Burdge et al. [49]	Skin-sparing mastectomy and NSM for locally advanced disease, 2001–2012 (39 patients had NSM, 21 patients had skin-sparing mastectomy)	Exclusion criteria: locally advanced disease with skin involvement, inflammatory breast cancer, collagen-vascular disease, and known smoking within the previous 6 months. Characteristics: 38 of 39 NSM patients received neoadjuvant chemotherapy; 39 of 39 NSM patients received post-mastectomy radiation to the affected breast. Average tumor size among NSM was 3.4 ± 2.2 cm.	Following NSM, 10.3 % experienced locoregional recurrence, none in NAC (mean follow-up 25.3 ± 18.8 months).	For NSM and skin-sparing mastectomy: wound/tissue necrosis, 16.7%; implant removal, 5%; capsular contracture, 10%.
Peled et al. [50]	NSM for locally advanced disease, 2005–2013 (139 NSM)	Exclusions: NAC involvement on exam or imaging, significant ptosis, large breast size, initial skin involvement (unresponsive to neoadjuvant chemotherapy, if administered). Characteristics: 18 % stage IIB, 82 % stage III, 77 % received neoadjuvant chemotherapy, 20 % received adjuvant chemotherapy, 63 % received post-mastectomy radiation.	5 % locoregional recurrences, none in the NAC (mean follow-up, 41 months).	NAC necrosis, 1.4 % ($n=2$). Mastectomy skin flap necrosis, 3.6 % ($n=5$). Implant loss, 11 % of expander-implant reconstructions ($n=14$). Infection requiring IV antibiotics, 12 % ($n=17$).

NAC nipple–areola complex

margin was positive for tumor involvement, and in 13 of these cases the NAC was excised, converting to a skin-sparing mastectomy. Although most instances (81.8 %) of NAC excision for positive histology were in patients with retroareolar tumors, nipple conservation was achieved in the majority of patients with retroareolar tumors. At a median follow up of 34 months, there were no recurrences in the NAC. One of 97 conserved NACs experienced necrosis requiring surgical intervention [3].

Similarly, Fortunato and colleagues reported their experience with 138 NSM (122 for malignancy) in 121 patients. Of these, 124 cases were performed after 2009, when a liberal policy of considering NSM for all patients with a minimal tumor-to-NAC distance of 1 cm, no bloody nipple discharge, no large or ptotic breasts, and no absolute contraindications (clinical involvement of the NAC, Paget's disease, inflammatory breast cancer) was adopted. Sixteen percent ($n = 19$) of patients underwent NAC excision based on retroareolar margin <2 mm on pathology; of these 19 excised NACs, 11 (58 %) had residual cancer on pathology. At a median follow up of 26 months, there was one local recurrence, which was outside of the NAC. There were 6 cases (4 %) of total NAC necrosis, 14 cases (10 %) of mild NAC desquamation, and 6 cases (4 %) of partial mastectomy skin flap necrosis [4]. Of note, this is the only report of liberalized oncologic criteria reviewed here that retained a tumor-to-NAC distance criterion as a contraindication to NSM.

Two studies examined how institutional criteria for NSM candidacy and outcomes after NSM evolved in parallel over time. Both report improved technical outcomes over time and no NAC recurrences despite broadening indications for NSM [7, 48].

Coopey and colleagues assessed trends in eligibility and outcomes over time for 645 NSM performed in 370 patients at the Massachusetts General Hospital from 2007 to 2012. Three hundred fifteen NSM were for malignancy (48.8 %). Initial criteria for therapeutic NSM were tumor size <2 cm and tumor-to-nipple distance ≥2 cm. However, with time these exclusions were eliminated, and final exclusion criteria included only clinical or imaging evidence of NAC involvement, locally advanced breast cancer with skin involvement, inflammatory breast cancer, or bloody nipple discharge. Despite this liberalization of criteria and the fact that more NSM in the later years were done for cancer, the authors noted a decreasing incidence of positive subareolar margins over time (6.5 % in 2007–2010 vs. 2.7 % in 2011–2012, $p = 0.027$), which they attributed to improved patient selection with increasing surgeon experience. At a mean follow-up of 22.1 months, local recurrence occurred in 2.6 % of breasts operated on for cancer, and no recurrences involved the NAC. Total nipple necrosis occurred in 1.7 % of breasts, and this rate was stable across time periods ($p = 0.45$) despite higher body mass index (BMI) and higher breast volumes in the later time period [48].

Krajewski and associates at the Mayo Clinic reported on their experience over time with 341 patients who underwent 566 NSM (218 NSM were for malignancy). Early criteria for NSM included risk reduction or cancers 2 cm or less in diameter and located over 2 cm from the NAC; inflammatory breast cancer and cancer extension into the NAC were exclusion criteria. Obesity, large/ptotic breasts, and prior radiation were initially relative contraindications. Over time (2009–2010 vs. 2013–2016/2014), there were significant increases in mean BMI and proportion with bra cup size C or larger, prior radiation, tumor within 2 cm of the NAC, and neoadjuvant chemotherapy. Of 19 nipple excisions in patients with a preoperative diagnosis of cancer, six were for positive pathology (five atypia, one DCIS). No factors, including tumor-to-nipple distance, multifocality/multicentricity, or performance of preoperative MRI were associated with nipple excision. At a median 19-month follow-up, there were five locoregional recurrences, and none were within the NAC. Between the earlier and later time periods, there were declining rates of 30-day postoperative complications (41.4 % vs. 18.7 %, $p < 0.001$), postoperative complications requiring treatment (15 % vs. 3 %, $p = 0.0001$), and a trend towards decreased nipple loss (5.7 % vs. 2.2 %, $p = 0.10$) [7].

Finally, two studies report their outcomes after NSM for a subgroup of patients with locally advanced disease. Again, the oncologic outcomes were excellent, with no cases of NAC recurrence [10, 49].

Burdge and associates at the University of Arkansas retrospectively reviewed skin-sparing and nipple-sparing mastectomy procedures performed from 2001 to 2012 for locally advanced disease. Exclusions were for skin involvement, inflammatory breast cancer, collagen-vascular disease, and smoking within the previous 6 months. Twenty-one patients who underwent skin-sparing mastectomy and 39 patients who underwent NSM were included. Of 39 patients treated with NSM, 38 received neoadjuvant chemotherapy, and all underwent post-mastectomy radiation to the affected breast. Mean pretreatment tumor size for patients undergoing NSM was 3.4 cm (±2.2 cm). In the skin-sparing and nipple-sparing groups combined, wound/tissue necrosis occurred in 16.7 %, implant removal occurred in 5 %, and capsular contracture occurred in 10 %. Over a mean follow-up of 25.3 ± 18.8 months, 10.3 % of patients treated with NSM experienced locoregional recurrence, and no recurrences were within the NAC [49].

Peled and associates at the University of California, San Francisco reported on prospectively recorded outcomes of 139 NSM performed from 2005 to 2013 for locally advanced disease (stage IIB, 18 %; stage III, 82 %). This group's selection criteria have evolved over time, and current criteria require MRI only for tumors that are close to the NAC on mammogram or clinical exam, and exclude patients from NSM based only on NAC involvement on exam or imaging, significant ptosis, or large breast size [9, 10]. Patients with initial skin involvement that responds to neoadjuvant chemotherapy are offered NSM. In this study, 97 % of included patients received chemotherapy (77 % neoadjuvant, 20 % adjuvant), and 63 % received postmastectomy radiation therapy. Reconstruction was with expander-implant (92 %), pedicled TRAM flap (7 %), or DIEP flap (1 %). With a mean follow-up of 41 months, 5 % of patients had locoregional recurrences, 15 % experienced distant recurrence, and 2 % had simultaneous local and distant recurrences. There were no recurrences in the NAC. Surgical complications included NAC necrosis (1.4 %), mastectomy skin flap necrosis (3.6 %), implant loss (11 % of expander-implant reconstructions), and severe infection requiring IV antibiotics (12 %). Mastectomy skin flap necrosis and implant loss were seen only in patients who received post-mastectomy radiation [10]. In a separate publication, the same group reported that axillary lymph node dissection was an independent risk factor for implant loss, probably due to impaired lymphatic drainage of the breast, and suggested that patients who require axillary lymph node dissection be encouraged to undergo lumpectomy or mastectomy with autologous reconstruction whenever feasible [50].

In summary, despite the broadening indications for which NSM has been offered, including patients with locally advanced disease, tumor proximity to the NAC on preoperative imaging, and deleterious BRCA 1/2 mutations, the rate of NAC recurrence remains exceedingly low. There is increasing evidence that the NAC can be treated as any other skin margin, and can be safely retained in patients without clinical, imaging, or pathology evidence of NAC involvement with very low risk of local recurrence.

Patient Selection: Technical Considerations

Whereas oncologic criteria have been developed to minimize NAC excisions and NAC recurrences, technical considerations should be designed to minimize complications such as skin flap necrosis, nipple necrosis, implant loss, wound infection, and poor cosmetic outcome.

Breast Size and Ptosis

Many surgeons consider patients with excessively large and/or ptotic breasts as suboptimal candidates for NSM [6, 43], due to the theoretical risks of both skin flap or NAC necrosis and poor cosmesis from malposition of the NAC on the reconstructed breast mound [51]. Indeed, several studies have shown an association between high specimen weight and increased risk of complications [52–55]. Spear and colleagues suggest that aesthetic outcomes are poor for patients with estimated breast size over 500 g [6]; however, most authors have not suggested absolute criteria for breast size or degree of ptosis relative to NSM candidacy.

In fact, several authors have reported successful NSM in patients with large and/or ptotic breasts. Schneider has reported favorable results in 19 patients with large, ptotic breasts (cup size C, sternal notch to nipple distance >24 cm, and grade 2–3 breast ptosis; included patients had to meet all three criteria) who underwent NSM and free flap reconstruction [56]. She reports that her group has yet to identify an upper limit of breast size or sternal notch to nipple distance above which NSM is contraindicated. The Massachusetts General Hospital reports that nipple necrosis rates remained low (1.5 %), even as NSM were performed in larger and more ptotic breasts in recent years [48]. Some authors have proposed modified NSM techniques in such patients [6, 51, 57–59]. This topic is addressed in detail in a separate chapter.

Although the large, ptotic breast certainly is not an absolute contraindication to NSM, we recommend that the breast surgeon/plastic surgeon team's early experience with NSM be in women with small breasts (A or B cup, or <500 g) with no ptosis or mild ptosis. With increasing experience, however, many surgeons doubtless will achieve excellent results with more extended criteria.

Prior Breast Surgery

Several studies have shown NSM to be an appropriate option in patients with a history of prior breast surgery. Huston and colleagues compared 122 NSM in patients with prior lumpectomy to 196 NSM in patients without prior lumpectomy; all NSM were performed through inframammary incisions. They found no significant difference between the groups in NAC ischemic complications (24.6 % with prior lumpectomy, 17.9 % without prior lumpectomy, $p=0.1477$) [60], although the overall incidence of NAC ischemia was higher than reported in most series. Two groups have reported on small numbers of NSM ($n=13$, $n=21$) performed in breasts with prior mammoplasty, mastopexy, or augmentation via circumareolar or Wise-pattern incisions. One group used the prior incisions, whereas the other advocated for inframammary incisions to minimize nipple ischemia; both groups reported no ischemic complications [61, 62]. Peled and associates reported successful NSM in patients with prior circumareolar incisions, using a criterion of 6 months intervening time, without increased vascular compromise [9]. The same group also reported successful NSM with implant-based reconstruction in 51 breasts (34 women) with prior augmentation mammoplasty, with complication rates comparable to those achieved in patients without prior augmentation [63]. Another small series ($n=17$) of patients with prior breast augmentation undergoing NSM and implant or autologous reconstruction reported low rates of postoperative complications [64].

Prior or Anticipated Breast Radiation

Prior breast radiation is associated with increased risk of ischemic complications after NSM [65], and both prior radiation and planned postmastectomy radiation have been considered relative contraindications to NSM [66]. However, several recent studies challenge this exclusion criterion.

Sbitany and colleagues studied 903 NSM with immediate expander/implant-based reconstruction and found that, compared to no radiation ($n=727$), prior radiation ($n=63$) and post-mastectomy radiation ($n=113$) were associated with higher risks of infection requiring oral antibiotics (13.1 % vs. 27.0 % vs. 26.5 %; $p=0.004$, $p<0.001$, respectively), infection requiring intravenous antibiotics (7.3 % vs. 20.6 % vs. 22.1 %; $p=0.001$, $p<0.001$, respectively), and expander/implant loss (5.1 % vs. 20.6 % vs. 17.7 %; $p<0.001$, $p<0.001$, respectively). Unlike other studies, the authors did not demonstrate an increased risk of NAC necrosis in irradiated breasts, although there was a higher risk of skin necrosis requiring debridement in breasts undergoing postmastectomy radiation (no radiation, 3.7 %; postmastectomy radiation, 11.5 %; $p=0.001$) [67]. In a separate analysis of data from the same institution, Peled et al. identified inframammary incision placement (compared to periareolar incision) as a risk factor for incisional breakdown leading to implant loss after post-mastectomy radiation, a phenomenon attributed to increased tension on the inframammary incision [68].

A study by Tang and associates of 982 NSM with autologous (2.8 %), expander/implant (33.6 %), or direct implant (63.5 %) reconstruction found that, compared to no radiation therapy ($n=818$), both prior radiation ($n=67$) and postmastectomy radiation ($n=97$) were associated with increased overall complications (10.2 % vs. 21.7 % vs. 17.5 %; $p=0.003$, $p=0.03$, respectively) and nipple loss (0.92 vs. 4.3 vs. 4.1 %; $p=0.04$, 0.02, respectively). Compared to no radiation, postmastectomy radiation was associated with increased rate of reconstruction failure (2.2 % vs. 8.2 %, $p=0.003$), although previous radiation was not (2.2 % vs. 2.9 %, $p=0.47$). Although radiation therapy was associated with complications, rates of reconstruction failure and NAC necrosis were low enough that the authors did not consider prior or anticipated radiation in isolation a contraindication to NSM. However, in irradiated breasts, the rate of complications with 0, 1, 2, or ≥3 additional risk factors (age >55 years, breast volume ≥800 cm^3, smoking, or periareolar incision) were 13.4 %, 17.5 %, 50.0 %, and 66.7 % ($p<0.001$), suggesting that caution is advised in irradiated patients with multiple additional risk factors. Multivariate analysis did not show an association between type of reconstruction and complications requiring surgical revision. In this analysis, contrary to the findings in Peled et al., circumareolar incisions were found to increase the risk of complications in irradiated breasts [69].

Another retrospective study from Alperovich and colleagues compared 475 NSM in nonirradiated breasts to 26 NSM in previously irradiated breasts (with a mean radiation-to-mastectomy time of 12 years). Reconstruction was with tissue expanders ($n=14$), microvascular free flaps ($n=8$), direct implants ($n=2$), latissimus flap with implant ($n=1$), or rotational perforator flap ($n=1$). Rates of mastectomy flap necrosis (11.5 %, $p=0.46$), complete NAC necrosis (3.8 %, $p=0.47$), partial NAC necrosis (3.8 %, $p=1.00$), and implant explantation (7.7 %, $p=0.06$) in the previously irradiated group did not differ significantly from rates in the nonirradiated group (rates not reported). The authors concluded that NSM with implant-based or autologous reconstruction is an appropriate alternative for patients with prior radiation [70].

In summary, patients with a history of prior radiation or anticipated need for postmastectomy radiation who undergo mastectomy with immediate reconstruction are at increased risk of complications, regardless of management of the nipple [71]. However, risks specific to conservation of the NAC, e.g. nipple necrosis, although reported in some studies to be higher than in non-irradiated patients [69], are nonetheless acceptably low (<5 %) in the studies reviewed here. Therefore, while patients should be counseled about the associated increased risks, prior or anticipated radiation in isolation should not be considered a contraindication to NSM.

Comorbidities

Data regarding smoking [52, 54, 60, 65], diabetes mellitus [52, 53, 60, 72], and advanced age [52, 53, 60, 73] as potential risk factors for NAC necrosis are conflicting. This may be due in part to the retrospective nature of the studies, making it impossible to control for confounding variables such as smoking cessation, amount of smoking, glycemic control, or duration of disease. Certainly, given the evidence for active or recent cigarette smoking as a risk factor for ischemic complications after total or skin-sparing mastectomy [74–76], it is reasonable to infer that smoking increases the risk of complications after NSM.

Several studies have shown an association between obesity and complications after NSM [52–54, 65, 72], perhaps in part due to the correlation between obesity and large breast size (discussed above). Both the Massachusetts General Hospital and Mayo Clinic have reported that, as the mean body mass index (BMI) of patients undergoing NSM at their institutions has increased over time, there were concomitant stable [48] or decreasing [7] rates of nipple loss due to ischemia, probably due to improvements in surgical technique.

In summary, prior or postoperative breast radiation, current smoking, and obesity are all documented risk factors for technical complications after NSM. Very large or ptotic breasts present an additional technical challenge to the performance of NSM. These constitute relative contraindications, and NSM should be avoided in such patients in an institution's early experience with the technique. However, with increasing experience, NSM may be an appropriate option in the presence of one or more of these risk factors in an informed patient who is highly motivated to preserve her NAC. Consideration also should be given to a woman's overall health and tumor stage/biology, as complications leading to need for additional surgery or delay in adjuvant therapy may be unacceptable in certain high-risk patients.

Preoperative Evaluation of the Nipple–Areola Complex

Preoperative evaluation of the NAC begins with a thorough physical exam. Asymmetry of the NAC relative to the contralateral breast, nipple retraction, changes in NAC skin character, and ulceration or eczematous changes of the NAC are all suggestive of malignant involvement [77]. In addition to supine examination, the patient should be positioned upright with arms above the head, which can accentuate NAC retraction [77].

Regardless of surgical treatment, preoperative imaging of breast cancer patients should include mammogram, and in cases of invasive disease, breast ultrasound. Techniques to increase the accuracy of mammography for retroareolar findings include positioning the nipple in profile in at least one mammographic view and, in cases of retroareolar density or suspicious microcalcifications, spot compression, and magnification views [78]. Ultrasonographic evaluation of the NAC can be optimized by use of a standoff pad and abundant gel to bring superficial lesions into the focal zone of the ultrasound beam, and use of a warm room and warm ultrasound gel to minimize muscle contraction within the nipple and areola [78]. Two techniques described by Stavros, the 2-handed compression technique and the rolled-nipple technique, may increase the utility of ultrasound in evaluation of the NAC [79].

Mammogram is less sensitive for retroareolar tumors, compared to tumors in other areas of the breast [78, 80]. This has led to interest in the use of MRI evaluation prior to NSM. MRI findings suggestive of malignant involvement of the NAC include bulkiness; asymmetry or asymmetric enhancement (compared to the contralateral breast); nodular or irregular enhancement along the posterior nipple border; retroareolar mass; tumor continuity with the NAC; and early, delayed, or persistent enhancement of the NAC [78, 81] (Fig. 3.1).

Several studies have examined the utility of preoperative MRI to predict NAC involvement. Friedman and colleagues correlated the findings on blinded MRI review with surgical pathology. In their analysis of 35 breast cancers, MRI detected all eight cases with nipple or retroareolar involvement, and also discriminated between nipple and retroareolar involvement; there was one false-positive MRI suggesting retroareolar involvement in a patient with negative nipple pathology [82]. Moon and colleagues identified 51 breast cancers within 2 cm of the NAC on ultrasound; for these cases they performed blinded review of MRIs and mammograms and correlated these findings with NAC pathology. They found that NAC enhancement on MRI was 93.8 % sensitive and 85.7 % specific to identify NAC involvement on pathology. Conversely, mammographic findings did not correlate significantly with NAC pathology [83]. Cho and associates evaluated specifically the utility of 3-T MRI to identify NAC involvement by tumor. Among 403 patients, 43 had surgically confirmed NAC involvement. The finding of one suspicious feature on MRI was 60.5 % sensitive and 87.5 % specific for identifying NAC involvement on pathology [81]. Sakamoto and colleagues retrospectively reviewed MRIs of 81 breasts in 78 breast cancer patients whose NACs were surgically removed; they found that unilateral enhancement was strongly associated with positive NAC pathology, compared to no or bilateral enhancement (17/33 vs. 0/48, $p<0.001$) [84]. Importantly, however, none of these studies excluded patients for clinical suspicion of NAC involvement, and three explicitly included patients with nipple retraction or clinical evidence of Paget's disease [81, 82, 84]. In assessing the utility of MRI to

Fig. 3.1 Breast MRI showing suspicious findings in the left nipple: nipple inversion, asymmetric nipple enhancement, and enhancing subareolar mass involving the posterior nipple margin. The right nipple demonstrates normal nipple enhancement pattern

detect nipple involvement, it is critical that patients with clinical evidence of NAC involvement be excluded, since another small study (77 breasts) found that, although tumor-to-NAC distance <2 cm on MRI was predictive of positive NAC pathology, MRI was not superior to a thorough clinical evaluation to predict NAC involvement [29].

Several studies have also identified tumor-to-NAC distance on MRI as predictive of malignant NAC involvement on pathology. Ponzone and colleagues prospectively collected clinical, imaging, and pathological data from 112 consecutive patients undergoing NSM for breast cancer, of which 31 (27.7 %) had NAC involvement on pathology. On multivariate analysis, MRI tumor-to-NAC distance was an independent predictor of NAC involvement, and negative intraoperative pathology coupled with an MRI tumor-to-NAC distance ≥5 mm provided optimal discrimination between involved and uninvolved NACs [28]. However, the high proportion of patients in this study with NAC involvement at the time of NSM is unusual and makes interpretation of these study results difficult. Byon and associates retrospectively reviewed 466 mastectomies, of which 7.7 % had clinically occult nipple involvement. On multivariate analysis, both tumor size and tumor-to-nipple distance on MRI were predictive of NAC involvement [18]. However, these studies did not compare MRI to other imaging modalities. Again, this missing information is critical since a few studies have suggested that MRI may overestimate tumor size (compared to the pathological tumor size) [85–87], and another small study suggested that ultrasound is more accurate than MRI for predicting intraductal extension towards the nipple [88].

Perhaps most importantly, several reports of MRI for predicting NAC involvement have suggested a clinically significant rate of false positive findings ranging from 11.7 to 14.3 % [81, 83, 89]. This raises concern that preoperative MRI may over diagnose NAC involvement, leading to unnecessary exclusion of eligible patients from an attempt at nipple preservation. Although the data supporting this claim are limited, a much more robust body of literature supports the related impression that routine preoperative MRI is associated with unnecessary mastectomy in early-stage breast cancer [90–93].

For this reason, we and others [7, 9, 43, 48] do not advocate for mandatory MRI prior to NSM. At our institution, MRI is offered selectively at the surgeon's discretion to NSM candidates with tumor proximity to the NAC (without direct involvement) on mammogram or clinical breast exam, dense breasts on mammogram, known deleterious germline mutations, or otherwise deemed to be at high risk for occult nipple involvement based on clinicopathologic criteria (Table 3.1). For such patients, a shared decision-making model is employed, and MRI is presented as an option, with a thorough discussion of the risks and benefits.

Regarding other supplemental imaging modalities, of the role of tomosynthesis/3-D mammography or nuclear medicine breast imaging (scintimammography) in evaluation of the NAC prior to NSM has not been defined. It is possible that 3-D mammography, given its improved ability to detect small lesions [94], will contribute to better definition of the retroareolar space, but this benefit has not been demonstrated to date. Lack of spatial resolution in nuclear medicine breast imaging will likely limit this modality's usefulness in preoperative work-up for NSM.

In addition to imaging work-up, at least two techniques for preoperative histologic assessment of retroareolar specimens have been proposed. A British group reported their experience with preoperative ultrasound-guided mammotome biopsy of ducts beneath the NAC in a small series of patients scheduled for NSM. Among 33 women with invasive or in situ breast cancer scheduled for 36 NSM (three prophylactic), seven breasts (20 %) had a positive mammotome biopsy. The histopathology of the mastectomy specimens correlated 100 % with the mammotome biopsy results [95]. Review of the literature did not identify larger studies of this technique, nor suggest that this practice has been widely incorporated into institutional protocols. Routine mammotome biopsy is not utilized at our institution in preoperative work-up of the NSM candidate.

Another group reported on nipple delay procedure, combined with subareolar biopsy and sentinel node biopsy, as a means of both ischemic preconditioning of the NAC and histologic evaluation of retroareolar tissue prior to NSM. Patients were selected for a nipple delay procedure based on presence of risk factors for nipple necrosis: breast ptosis (NAC position below the inframammary fold, or suprasternal notch to nipple distance of 26 cm or more), preexisting breast scars, or history of active cigarette smoking. Risk factors for malignant involvement of the NAC were not considered in patient selection. Nipple delay was performed 7–21 days prior to mastectomy in 31 NACs of 20 patients. Two NACs were excised at the time of mastectomy due to positive subareolar histology from the prior biopsy, and a third was excised for symmetry. Of the 28 remaining delayed NACs, all survived the post-mastectomy course [59].

In summary, preoperative evaluation of the NAC should begin with careful physical examination. Mammogram and ultrasound, with careful attention to technique, can often detect subareolar tumor involvement. MRI is probably the most sensitive imaging modality for defining NAC involvement, but should be used selectively due to concern that false positive results may unnecessarily preclude appropriate candidates from NSM. Subareolar mammotome biopsy and nipple delay procedure with subareolar biopsy have both been proposed as methods to obtain preoperative subareolar pathology, although neither technique has been widely adopted to date.

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4 The Inframammary Approach to Nipple-Sparing Mastectomy: The Georgetown University Hospital Experience

Scott L. Spear, Ryan Mathis, Frank P. Albino, and Troy A. Pittman

Introduction

In the last decade or two, a revolution of sorts has occurred across the face of medicine and surgery. It could generally be described as a realization that treating the whole patient is as or more important than treating the disease or tumor. This revolution has many faces, which have in common the belief that collateral damage from treatments or surgery often can and should be avoided. Another way of describing this in terms of surgery is that what remains after surgery is equally if not more important than what is removed. Although there was an understandable reactionary resistance to this notion, its time has undeniably arrived and it is indisputably here to stay. General examples of this long overdue phenomenon to name a few include endoscopic surgery, robotic surgery, tumor-specific chemotherapy, the CyberKnife, and in the case of this chapter, nipple-sparing mastectomy.

The field of breast reconstruction has followed a parallel course, going from a virtually nonexistent specialty prior to 1980 to a federally mandated woman's right 20 years later. Milestones in breast reconstruction over the last 35 years have in part included: immediate submuscular implant reconstruction, the latissimus flap, the TRAM flap, shaped integrated-valve textured tissue expanders, free flaps, shaped implants, perforator flaps, oncoplastic surgery, acellular dermal matrices, and intraoperative laser angiography. Although the coincident more aggressive use of adjuvant chemotherapy and radiation therapy have made breast reconstruction more challenging, the acceptance first of skin-sparing mastectomies followed soon thereafter by nipple-sparing mastectomy has been a much appreciated blessing. The enthusiasm and momentum for increasingly conservative ablative measures culminating in total skin-sparing or nipple areolar complex (NAC)-sparing mastectomies have been tempered to some extent by the need to ensure and document an equivalent oncologic procedure without a sacrifice of surgical safety or esthetic results. This has required a need to explore and modify various techniques and has resulted in the development of some new innovative approaches to both the mastectomy and reconstruction while constantly checking that we were maintaining an acceptable safety profile. As the

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notion of "nipple-sparing" mastectomy has gained traction, it has presented new challenges and questions including, who are appropriate oncologic candidates? What, if any, are the tumor-specific contraindications? What incision or incisions assure the best esthetic outcome while minimizing complications? Is the risk of local recurrence increased? What mastectomy techniques are best? Is there a need for new technologies or instrumentation? Despite these questions and challenges, we think it is safe to say that "nipple-sparing" mastectomy is here to stay and has been demonstrated to be oncologically sound and a huge advance cosmetically. Today in the properly selected patient, NSM represents the optimal balance between safety, esthetics and oncologic treatment.

Undoubtedly, nipple preservation has raised the bar for the quality of esthetic results after breast reconstruction. Despite our theoretical enthusiasm for this concept, we understandably began cautiously in its implementation. So to begin with, at Georgetown University Hospital, we started with NSM in prophylactic cases, notably in patients with a BRCA gene mutation. From a technical perspective we picked women with C cup or smaller breasts and began mostly with lateral radial incisions with 90–180° extensions around the edge of the areola. This allowed our teams to have similar access to the breast as when performing a skin-sparing mastectomy through a transverse incision. It also allowed easy access to perform a marginal retroareolar biopsy and subsequent excision of the nipple in the case of the rare finding of occult disease at the base of the nipple. This conservative approach was especially important as we evolved to NSM for breasts with cancer and similarly as we extended this technique to larger breasts. In both circumstances, the lateral radial incision allowed easier access and more confident complete tumor removal. And incidentally, it did not complicate the reconstruction.

Our evolution to the inframammary incision as well as exploring therapeutic NSM in the patient with breast cancer occurred more or less simultaneously. As we had more experience with the radial incision, we observed a disturbing tendency for peri-incisional necrosis, peri-areolar necrosis, nipple malposition, and poor scarring. This phenomenon was confirmed in the hands of other NSM pioneers. This led to NSM through the more remote and more challenging inframammary fold incision. It began with smaller breasts and was eventually expanded to larger breasts of D cup size and some ptosis. The larger and more ptotic breasts necessitated longer incisions and extending the incision around to the lateral mammary fold as well. In some cases adding a radial axillary incision to facilitate dissection in the upper quadrants and axilla is necessary. With the added confidence obtained in risk reduction cases, the same techniques were employed in women with breast cancer, with the key difference being the requirement for adequate excision with disease free margins.

Based on current literature [1, 2] and our operative experience at Georgetown University Hospital, we previously put forth a purposely conservative algorithm for therapeutic nipple-sparing mastectomy

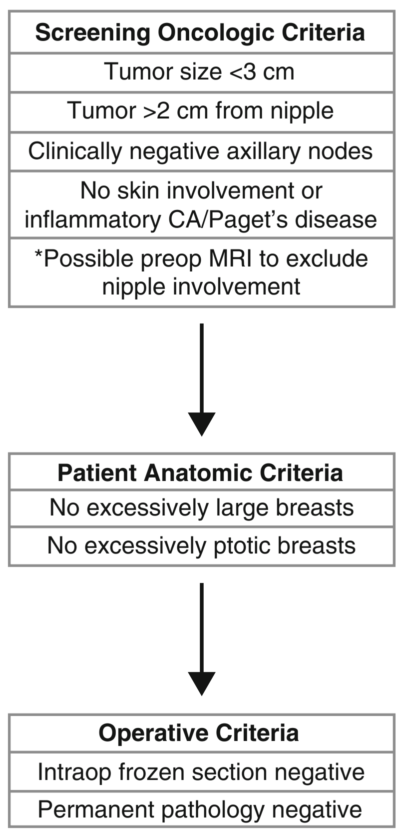

Fig. 4.1 Algorithm for therapeutic nipple-sparing mastectomy at Georgetown University Hospital [3]

(Fig. 4.1) [3, 4]. Our published preoperative oncologic criteria included no clinical involvement of the nipple, tumor size less than 3 cm, tumor location greater than 2 cm from the nipple (which is ambiguous and could also be interpreted as 2 cm from the areola), no skin or inflammatory cancer/Paget's disease and clinically negative nodes including possible staging MRI to exclude nipple involvement.

Our experience with NSM at Georgetown continues to evolve, including our increasing preference for inframammary incision placement, and a preference for permanent rather than frozen section pathologic confirmation of tumor free or clean retroareolar margins. With increasing false-positive frozen sections, we now send the tissue for permanent section only. Traditional teaching has been that if either the frozen section or permanent sample come back positive the nipple areolar complex must then be resected [3, 4].

With great technical success and oncologic safety implementing these criteria, efforts moved towards maximization of esthetic outcomes and patient satisfaction.

Early Experience with Lateral Incisions

As discussed previously our initial incision of choice for NSM was lateral radial incisions with the option of 90–180° extensions around the edge of the areola which allowed adequate access to perform a retroareolar biopsy as well as adequate oncologic resection.

However, unlike a skin-sparing mastectomy where the NAC is actively reconstructed in a staged fashion, a nipple-sparing mastectomy retains the original NAC position passively and its final position is ironically less controllable. We found the risk of nipple malposition is increased by a lateral breast incision and especially radiation. No matter what incision is used, any incision and any mastectomy preferentially tightens the skin above the nipple and further elevates the NAC, and this was exacerbated using a lateral radial incision (Fig. 4.2).

In our experience and in the experience at many other centers, the lateral breast incision with peri-areolar extension also compromises the blood supply to the nipple by bisecting the breast, directly decreasing flow through the subdermal plexus to the NAC [5]. The blood supply of the breast post-mastectomy is provided predominantly by the second intercostal perforator and the subdermal plexus. If the second intercostal perforator is violated, skin flap and NAC survival is reliant upon the collateral flow from the subdermal plexus. In light of this, it is thought that the inframammary (IMF) approach to a nipple-sparing mastectomy is superior to lateral incision in terms of blood supply to the NAC because it preserves the subdermal plexus around the entire perimeter of the nipple areolar complex. This translates clinically into a higher incidence of nipple necrosis using the lateral incision with peri-areolar extension as compared to the inframammary approach [5, 6].

Evolution of NSM: The Inframammary Approach

Patient selection for the IMF incision is critical in order to minimize the risk of wound dehiscence and delayed healing. Prior surgical scars and the expected length of the skin flaps must be assessed to determine if this surgical approach to the NSM is warranted. Specifically, patients with preoperative ptosis are at risk of postoperative delayed healing as they will have long mastectomy flaps. As the flap length increases, the likelihood of adequate tissue perfusion along the incision decreases. The relationship between flap length and thickness will help to predict success or surgical complication and should be considered preoperatively and then again assessed intra-operatively at the conclusion of the mastectomy using indocyanine green laser angiography or other accurate imaging system. Technical limitation of the IMF incision, namely difficulty visualizing and subsequently removing the superior-lateral glandular tissue, can be overcome with a combination of retraction and hand-guided dissection or when necessary a counter incision hidden in the axilla. Various techniques can

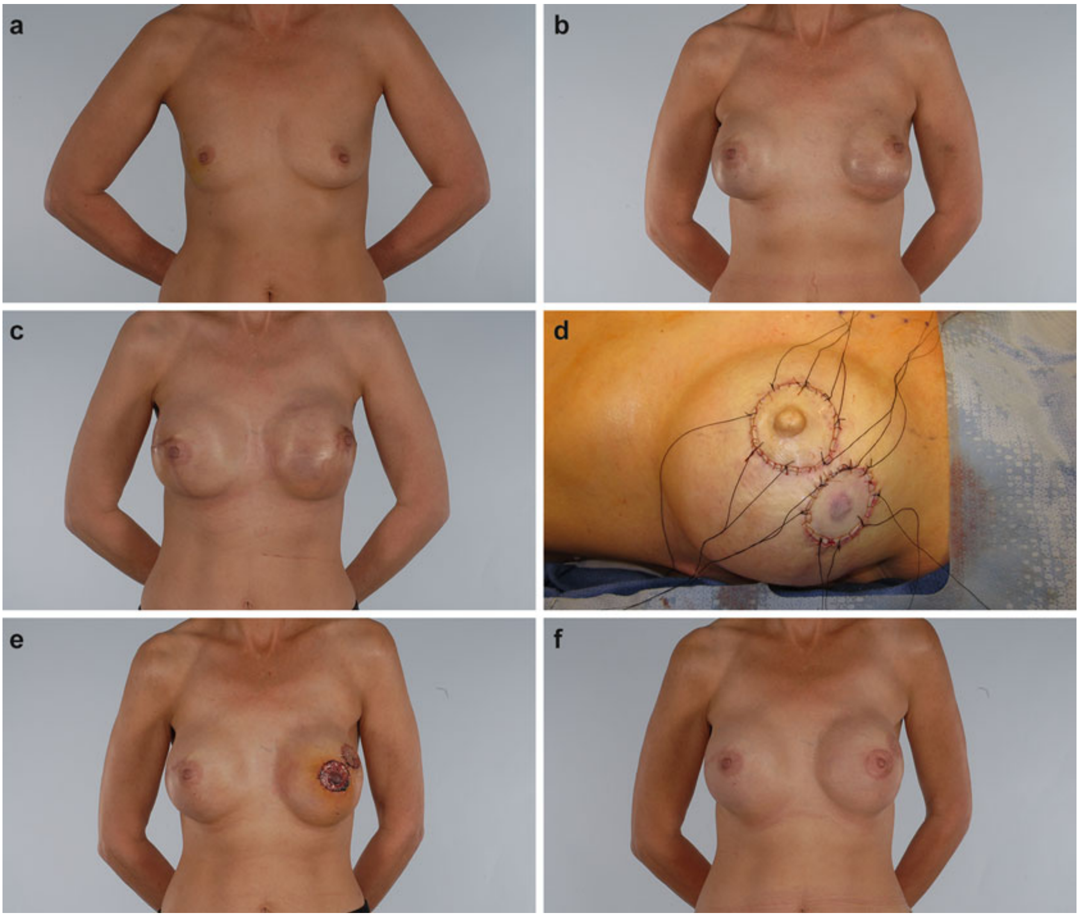

Fig. 4.2 Fifty-three-year-old female with invasive right breast cancer (**a**) elected to undergo bilateral nipple-sparing mastectomy through a lateral incision with superior, peri-areolar extension. She had an immediate reconstruction at the time of her mastectomies with 300 cc tissue expanders, filled to 150 mL intra-operatively, and acellular dermal matrix. The expanders were filled to a volume of 310 mL over the next several weeks and at 4 months underwent an implant exchange using high profile, smooth round 450 cc gel implants. Immediately postoperatively (**b**) the left nipple was noted to be displaced superiorly and laterally. This nipple malposition persisted at 6 months (**c**) at which point she elected to have an excision and grafting of the NAC to a more favorable location (**d**, **e**). This result is maintained at 1 year (**f**)

facilitate surgery through the more remote IMF incision. In particular scalpel or scissor dissection without constant internal direct visualization works well as compared to trying cautery at a distance in a dark hole. Bipolar as compared to monopolar cautery is kinder to the tissues and the blood supply. And the availability of better lighted retractors such as the Invuity (Invuity Inc., San Francisco, CA) has made things easier as well, and allows for direct visualization of the superior-lateral parenchyma to ensure the mastectomy is complete and uniform over this region (Fig. 4.3).

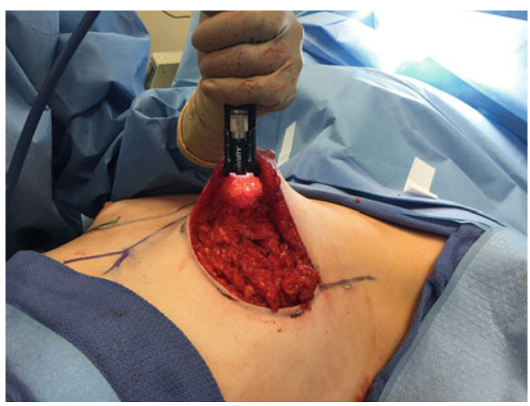

Fig. 4.3 Retraction using a lighted retractor during nipple-sparing mastectomy through an IMF incision

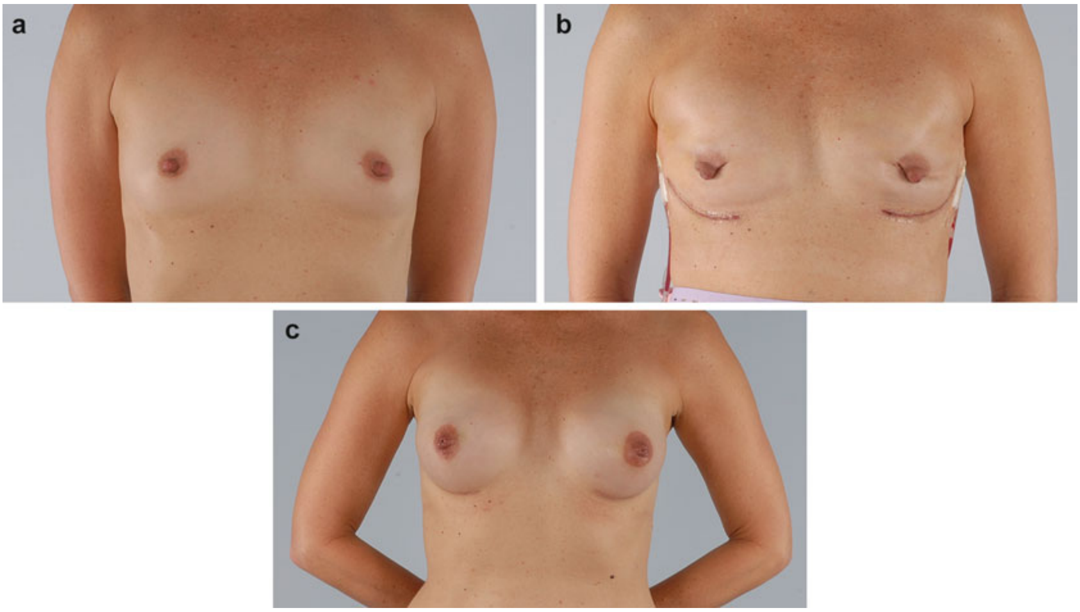

Fig. 4.4 Forty-nine-year-old female (**a**) with a strong family history of breast and ovarian cancer elected to undergo bilateral nipple-sparing mastectomies and immediate breast reconstruction using tissue expanders and acellular dermal matrices through an IMF incision. Three hundred and fifty milliliter tissue expanders were initially filled to 150 mL at the time of surgery. (**b**) Following complete expansion, she presented 3 months later for exchange to oval base, high projecting 370 cc shaped silicone implants. The 1-year result is shown here (**c**)

The IMF incision has gradually evolved into our preferred approach to NSM as our surgical team has gotten more familiar and comfortable with remote mastectomy incisions and given its decreased risk of partial or complete nipple necrosis (Fig. 4.4). When necrosis does occur using the IMF approach, it rarely involves the nipple and tends to occur instead on the hidden lower pole of the breast or at the edge of the flap which makes it easier to manage and also allows the damage to be kept more out of sight. Attempts to further improve outcomes have led us to extend this incision laterally for some select patients. In cases of predicted difficulty gaining access to the superior-lateral breast by the breast surgeon during the mastectomy, unfavorably medial preoperative NAC position, or need to better define the lateral breast the IMF incision can be extended laterally while still allowing for an inconspicuous scar (Fig. 4.5). In select cases, an extended lateral incision also allows access to the axillary lymph node basin avoiding a counter-incision.

Operative Technique

Thoughtful and precise preoperative markings are necessary in order to execute a successful NSM and immediate reconstruction. Landmark identification must be highlighted with the patient in a standing position in order to correctly identify the breast footprint and in particular the true inframammary fold which may be ill-defined or mobile in the deflated or multiparous breast, In some cases where the original fold sits abnormally high and close to the nipple (N-IMF distance pre-op measured at 7 cm or less), it may be wise to plan the incision at a nipple to fold distance of 8 or 9 cm in order to accommodate the anticipated reconstructed breast size (Fig. 4.6). Immediately prior to surgery, the planned IMF incision is infiltrated with local anesthetic and epinephrine solution. The incision is sharply made and double-prong skin hooks are used to help develop a plane between the gland and subcutaneous skin flaps. The dissection proceeds by first separating the breast from the skin flaps or

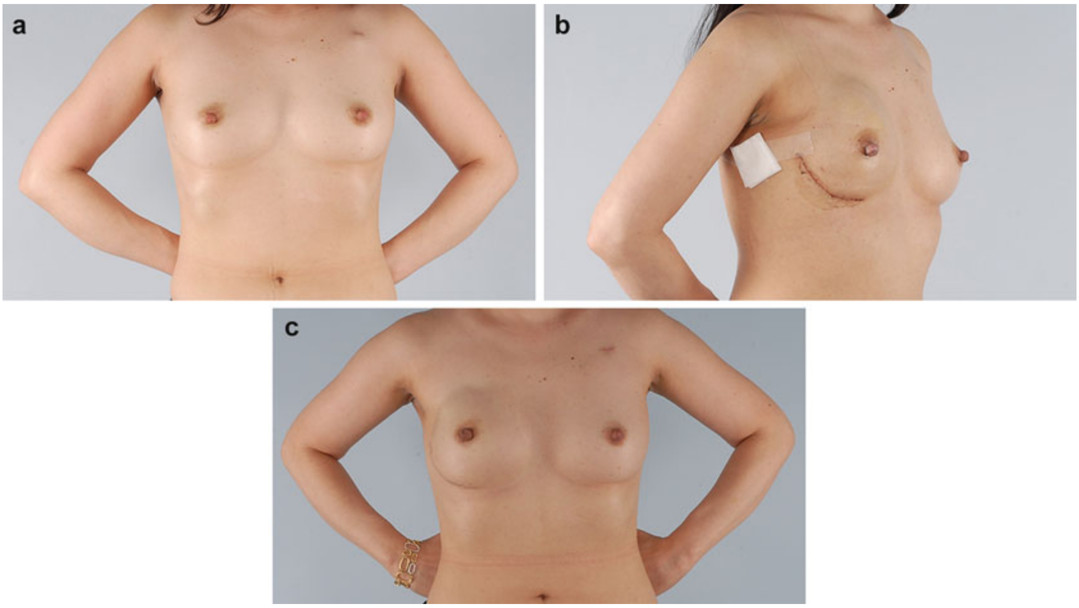

Fig. 4.5 Forty-two-year-old female with newly diagnosed invasive right breast cancer (**a**) seeks prosthetic reconstruction. An extended lateral IMF incision was utilized for the NSM in order to obtain easier access to the axillary tail and immediate reconstruction using a tissue expander (275 mL initially filled to 125 mL) and acellular dermal matrix. (**b**) Note the sentinel lymph node biopsy was also performed through this incision. Three months later, she underwent an implant exchange with 390 cc moderate plus projecting shaped gel implants. Six-month results are shown (**c**)

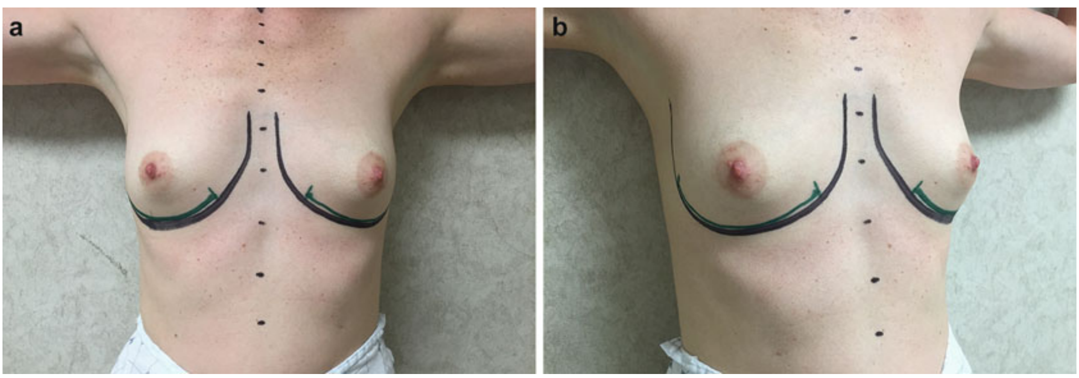

Fig. 4.6 Preoperative Markings (**a**, **b**). Note the *green* markings indicate the surgical incision

from the pectoralis major; however, most commonly the plane between the gland and skin flaps is approached first. In this case, dissection is carried out sequentially from the IMF using sharp scissors, keeping electrocautery (preferably using the less traumatic bipolar variety or the less thermally destructive PEAK® PlasmaBlade System—Medtronic, Minneapolis MN) to a minimum and reserved only for planned vessel cautery in an effort to balance hemostasis and flap perfusion. As the nipple areolar complex is encountered it is separated from the underlying breast with a sharp scalpel just deep to the dermis. Exposing the subareolar region, the nipple papilla is discovered and a retroareolar biopsy is taken at a point of duct confluence (Fig. 4.7). We do not recommend nor do we perform a nipple coring procedure as we deem this both unnecessary and specifically

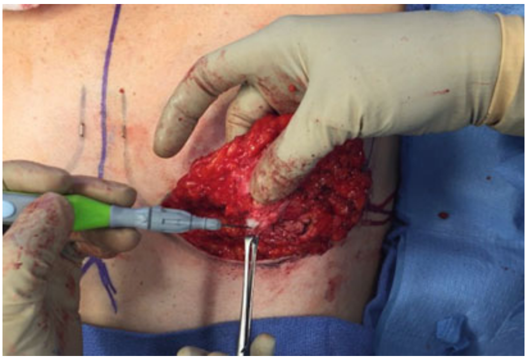

Fig. 4.7 Intra-operative image demonstrating the retro-areolar biopsy site

contrary to the goal of retaining a realistic facsimile of a nipple including some projection. This specimen is sent for permanent pathology sectioning. The remaining skin flap is then raised superiorly using meticulous scissor dissection aided by gentle, intermittent illuminating breast retraction. It is imperative to keep dissection true to the breast footprint and not to artificially extend the dissection beyond breast tissue simply to encounter the clavicle superiorly and the latissimus laterally. While these may serve as obvious limits of the breast not all women have breast tissue extending to these structures. Once circumferentially released, the gland is then reflected caudally as the breast is dissected from the pectoralis major using electrocautery in a superolateral to inferomedial direction or vice versa depending on which seems most practical [3].

Retroareolar Biopsy

In every case of NSM, a retroareolar biopsy should be performed in order to maintain the oncologic safety of this ablative procedure. At the base of the NAC the nipple is separated with the skin flap from the underlying gland using a scalpel. It is critical to re-identify the correct plane between the subcutaneous adipose tissue and glandular tissue once the NAC is completely separated from the gland in order to successfully proceed with the mastectomy moving cranially. The confluence of ducts is then marked on the gland with a silk suture for the pathologist and a thin biopsy is taken from the entire base of the nipple from the mastectomy skin flap. This biopsy is sent for permanent sections and if the result comes back positive the NAC is again biopsied in a staged fashion or it is sacrificed in a later procedure [6, 7]. In our original case series of 50 therapeutic nipple-sparing mastectomies we had no positive frozen sections. We did however have two permanent sections that came back with close margins. Of these two, one was treated with complete excision of the NAC and the other elected for only excision of the nipple with reconstruction at a later time with nipple sharing from the contralateral nipple [6]. With the utilization of this technique it has been advocated that NSM can be done on all patients who fit criteria where total mastectomy is indicated [7].

Staged Retroareolar Biopsy

Historically, positive frozen or permanent retroareolar biopsies have resulted in complete NAC excision due to the high correlation between positive retroareolar biopsy and NAC tumor involvement. However, we have found that of our nine patients in which we found positive retroareolar biopsies only two had definitive disease found after removal of the NAC. This information led to the development of a staged biopsy technique which is performed at the time of the second procedure if the permanent pathology from the retroareolar biopsy demonstrated tumor involvement. This staged biopsy is performed by tattooing four points on the areola through the external mastectomy flap using methylene blue and an 18-G needle. If the needle completely penetrates the flap it will tattoo the internal portion of the flap, marking the extension of the retroareolar region. This marked region of tissue is then excised using a blade or low temperature electrocautery and sent to pathology (Fig. 4.8) [8]. If the staged retroareolar biopsy is positive we remove the NAC; however, this staged technique has allowed us to save the NAC on patients with negative staged retroareolar biopsies who would have historically undergone resection.

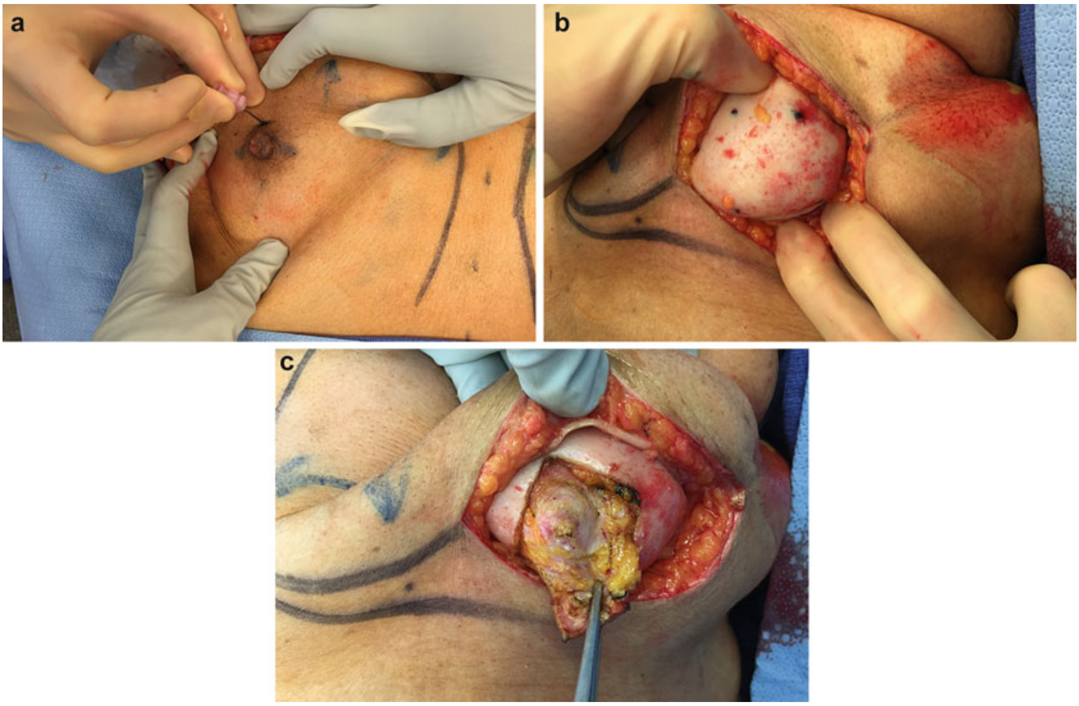

Fig. 4.8 Technique for staged retroareolar biopsy. NAC is marked with 18-G needle dipped in methylene blue (**a**). The blue dye is transposed to the internal portion of the flap to act as a guide for biopsy (**b**). The additional specimen is removed (**c**)

Breast Reconstruction Through the IMF

Immediate, prosthetic breast reconstruction following nipple-sparing mastectomy may be achieved in either a single or two-staged process. Although direct to implant reconstruction may be associated with a higher complication rate in particular cases, other evidence demonstrates that it can be done safely in the properly selected patient population [9]. Basta et al. propose that the most important selection criteria remains intraoperative surgeon assessment of mastectomy skin flap quality and viability. In spite of this data, pooled analysis comparing outcomes for a staged reconstruction with tissue expanders and direct to implant reconstruction following nipple-sparing mastectomy specifically has shown complication rates of 52.8 and 16.7 % respectively. Nipple necrosis rates were higher in the two-staged tissue expander group with a necrosis rate of 4.7 % compared with a 4.1 % nipple necrosis rate in the direct to implant group [10]. This is likely due to some degree of selection bias, but should not be fully discredited. One technique we employ is the use of SPY laser angiography (Novadaq—Mississauga, ON) to assist in assessment of mastectomy flap viability and to assist in determining if someone is a direct to implant candidate. It is critical to ensure that the breast surgeon is aware of the plan to use intraoperative laser angiography to ensure she/he does not use tumescence with epinephrine at the time of the mastectomy. Following the completion of the mastectomy, 5 mL of indocyanine green dye is administered intravenously followed by a 10 mL saline flush and SPY angiography is performed over the next several minutes. Focusing on one mastectomy flap at a time, tissue perfusion, notably the timing of arterial inflow, is visualized using this technology. In our experience regions of ischemia are marked on the skin flaps following 90 s of angiography. These regions are then subsequently investigated quantitatively assigning relative perfusion units (RPUs), referencing the abdomen or sternum as the reference part representing a region of perfusion unaffected by the operative field. While we do not endorse a specific cut off value that demands debridement, we are particularly concerned for the viability of areas with RPUs less than 20. In cases of these regions of poor perfusion, we correlate these numbers with how the flaps appear clinically. When technically feasible and where the compromised tissue is deemed expendable, these areas are excised if the clinical examination warrants such measures. Alternatively, a delayed reconstruction, unfilled tissue expander, or hyperbaric oxygen therapy may be pursued.

Tissue expander reconstruction subpectorally via the IMF incision is routinely employed for immediate breast reconstruction. Most commonly this is performed as a partial submuscular coverage using ADM as a hammock to extend the inferior edge of the pectoralis major muscle while still providing support to the underlying implant. A tabbed expander is particularly useful in these cases to prevent device rotation, making sure to suture at least two of the three device tabs. Ensuring the expander is situated along the appropriate inferomedial breast contour, the ADM is draped over the device and secured to the chest wall to further support the expander and provide extended coverage. Reconstruction may also be achieved in the pre-pectoral plane. Far from novel, the subcutaneous or pre-pectoralis device position has reemerged recently with notable support given the preservation and lack of disturbance of the pectoralis major muscle, ease of performance, exceptional surgical outcomes, avoidance of animation deformities, and the reduced postoperative pain all with the help of ADM support and coverage in lieu of partial muscle coverage. Patients who have robust mastectomy flap perfusion, demonstrate sufficient skin or mild to absent skin redundancy, and wish to keep the same general breast size are excellent candidates for direct to implant breast reconstruction. Although often touted as a “single stage” reconstruction, patients who are deemed good candidates for direct to implant breast reconstruction still undergo breast revision procedures in at least 3.2 % of cases [11]. Still, for patients who need to complete their reconstruction for adjuvant therapy or for those who are opposed to multiple operations, direct to implant breast reconstruction is a valuable tool. At worst, direct to implant reconstruction can be looked at as using the implant as a temporary device rather than an expander. Notably, the complication rate for direct to implant reconstruction is lower when completed through an inframammary incision compared to lateral or radial breast incisions likely due to the preservation of the collateral blood flow to the nipple from the subdermal plexus [10]

Conclusion

The evolution of nipple-sparing mastectomy specifically at Georgetown University Hospital, and in general around the globe, mirrors the evolution of breast cancer treatment from radical tumor ablation with little concern for esthetics to sufficient or adequate local tumor ablation with serious concern for esthetic outcomes and the overall well-being of the patient. Nipple preservation has dramatically raised the bar for esthetic outcomes for breast reconstruction following mastectomy. The inframammary approach to NSM has evolved into the procedure of choice for the breast cancer team at Georgetown University Hospital for the properly selected patient. Looking forward, matching patient anatomy, oncologic treatment goals, and personal preferences with reconstruction timing, device selection, and implant location should allow us to continue to improve surgical outcomes and patient satisfaction.

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5 The Inframammary Approach to Nipple-Sparing Mastectomy: The UCSF Experience

Anne Warren Peled and Michael D. Alvarado

Introduction

Total skin-sparing and nipple-sparing mastectomy (NSM) techniques with preservation of the entire breast skin envelope at the time of mastectomy have become increasingly popular. Several longer-term studies have documented oncologic safety of the technique, with local-regional recurrence rates similar to those after other mastectomy techniques. As surgeons have become more experienced with NSM, ischemic complications such as nipple or mastectomy skin flap necrosis have decreased to low rates.

Incision Selection

Several different incision types have been described for NSM, including peri-areolar, inframammary (IMF), vertical, lateral, free nipple grafting, and others. When our group at University of California, San Francisco (UCSF) began performing NSM in 2001, we utilized a variety of incision types [1]. However, we refined our practice several years later after reviewing complication rates and finding that incisions crossing the nipple or encompassing greater than 30% of the nipple–areolar complex (NAC) diameter, as well as free nipple grafting, were associated with higher rates of nipple necrosis [2]. By 2011, nearly all NSM cases were performed with either a limited superior-areolar/mastopexy incision or IMF incision [3].

Selection of a superior-areolar or IMF incision is determined by a number of factors, primarily related to patient breast size and shape (Table 5.1). Ideal candidates for an IMF incision are women with small-to-medium-sized breasts and Grade I or II ptosis. Using an IMF incision in women with larger breasts can make it challenging to adequately visualize and access the axillary tail. Additionally, women with significant ptosis will likely benefit from repositioning of the NAC, which is best performed through a superior-areolar incision with crescenteric excision of skin superior to the NAC and subsequent elevation of the NAC upon closure of the incision.

Special Considerations

Autologous Flap Reconstruction

In our experience performing NSM in conjunction with immediate autologous reconstruction, we have found that peri-areolar incisions can lead to higher rates of nipple necrosis as compared to

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Table 5.1 Criteria for NSM incision selection

Inframammary incision preferred
Small-/medium-sized breasts
Minimal ptosis
Small NAC diameter
Prior circumareolar incisions
Consideration for other incisions
Moderate/severe ptosis requiring NAC repositioning
High likelihood of post-mastectomy XRT

IMF incisions [4]. Given the compromised esthetic outcomes that can result from NAC necrosis [5], we have developed alternative strategies when performing autologous reconstruction following NSM, including using IMF incisions and performing two-stage reconstruction with initial expander placement.

Prior Breast Surgery (Reduction Mammoplasty/Mastopexy, Lumpectomy)

NSM incision selection in patients with prior breast surgery, particularly those with periareolar or circumareolar incisions, can be challenging due to concerns for skin flap and nipple perfusion following mastectomy. However, use of the IMF incision is often a good choice in these patients, as it avoids any further disruption to the dermal blood supply to the NAC. Performing NSM in this population requires careful preservation of the periareolar dermis in order to maximize NAC viability through the subdermal plexus circumferentially supplying the NAC after NSM [6]. Our group and others have found that NSM can be safely performed through IMF incisions following prior breast surgery, with low rates of ischemic complications [7–10].

Anticipated Post-mastectomy Radiation Therapy

In our experience, we have found that use of the IMF incision should be avoided in women with a high likelihood of post-mastectomy radiation therapy due to higher complication rates, particularly wound breakdown and subsequent expander-implant loss [11]. This is likely related to a number of factors. From a mechanical standpoint, incisions along the most dependent portion of the breast are more susceptible to downward pressure from the expander-implant sitting just above the at-risk, irradiated incision. Additionally, when incisional breakdown does occur, expander-implant salvage can be more challenging with IMF incisions, which are directly over the thinnest portion of the pectoralis muscle or the interface between acellular dermal matrix and the chest wall. With periareolar incisions, the expander-implant is well covered by a thick layer of pectoralis muscle just deep to the incision, which likely provides improved expander-implant protection, supporting the higher rates of salvage after incisional breakdown seen in patients with peri-areolar incisions in our practice. Further, with periareolar incisions, it is much easier to close both the capsule and pectoralis muscle, thus leaving well-vascularized tissue beneath the healing TSSM incision, which can help with expander-implant salvage if superficial incisional breakdown does occur.

Technique

Preoperative Markings

Standard preoperative markings for NSM through an IMF incision include the sternal notch, midline, bilateral inframammary folds, and the planned incision (Fig. 5.1). The incision should be made 5–7 mm above the IMF itself in order to be well concealed underneath the breast postoperatively. For adequate exposure, the incision is ideally a minimum of 7 cm in length; as the subsequent scar is hidden from view when looking straight towards the breasts, the longer incision is well accepted by patients postoperatively and helps significantly during the procedure.

Operative Technique

Mastectomy skin flaps are created using electrocautery throughout the breast except for underneath the NAC, where sharp dissection is used. Use of lighted retractors is beneficial for

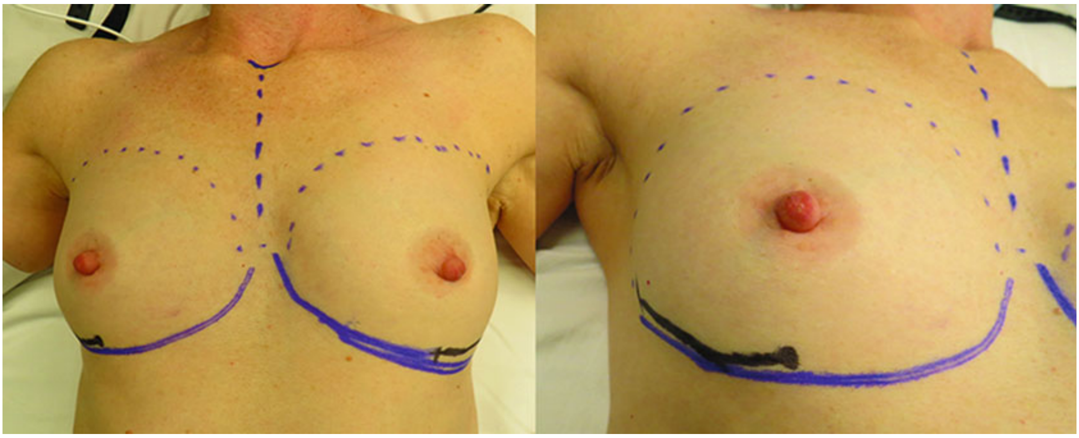

Fig. 5.1 Preoperative markings for NSM via an IMF incision

Fig. 5.2 Initiating inferior flap

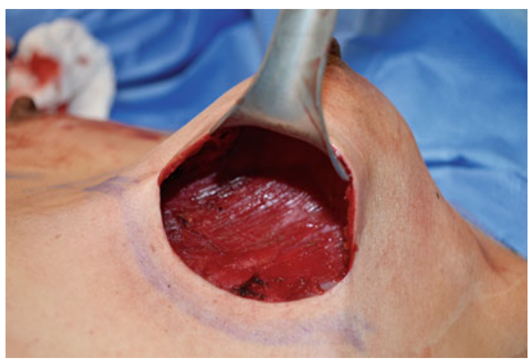

Fig. 5.3 Removing breast tissue off muscle from an inferior approach

adequate exposure, particularly during resection of the axillary tail. Care should be taken when beginning the flap as the surgeon moves in a cranial fashion. This "inferior" portion of the envelope is at the greatest risk for ischemic complications (Fig. 5.2). Starting the flap with adequate retraction is essential for avoiding a "thin" flap. Once the entire breast has been separated from the skin and the tail is removed from the clavipectoral fascia, the breast can be taken off the pectoralis either from cranial to caudal or by starting at the incision and lifting the breast from below (Fig. 5.3). Depending on distance from the incision to the border of the clavicle, sometimes it is easier to elevate the breast from below. Care must be taken to not get between the pectoralis major and minor, but if done properly this method requires less retraction and lifting on the skin envelope for exposure. Following removal of the mastectomy specimen, the specimen is oriented, with care to mark the tissue just deep to the NAC for focused pathological analysis upon permanent sectioning. The mastectomy skin flap is then inverted at the NAC skin and any residual nipple tissue is sharply excised and sent as a separate specimen (Fig. 5.4).

The vast majority of NSM reconstructions at UCSF are implant-based, with a small number of microsurgical reconstructions performed. Based on our early experience demonstrating high rates of ischemic complications with immediate permanent implant placement [2], all prosthetic reconstructions done after NSM are two-stage procedures. This involves subpectoral placement of a textured,

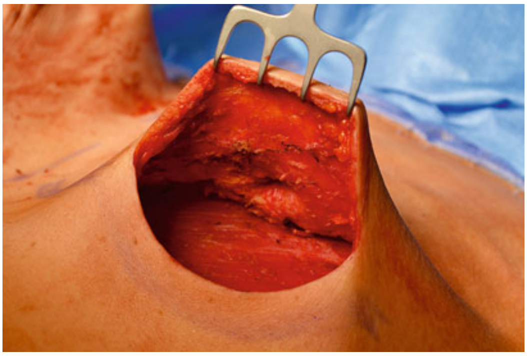

Fig. 5.4 Anterior flap revealing cored out nipple

integrated valve tissue expander with detachment of the pectoralis major at its inferior origin and use of an inferolateral sling of acellular dermal matrix to complete the pocket for the expander (Fig. 5.5). One closed-suction drain is placed into the mastectomy space. At the completion of the case, dressings are placed over the breast mound and around the nipple in such a way as to centralize the NAC over the breast skin and minimize subsequent NAC asymmetry or malposition.

Postoperative Management

All patients having expander-implant reconstruction receive prophylactic antibiotics while surgical drains are in place, which are removed at 10–14 days postoperatively based on drain output. Tissue expansion is typically started 2 weeks postoperatively and continues on a weekly basis until adequate volume is achieved. Standard practice is to minimally overfill the tissue expanders by approximately 10 % of recommended volume. If adjuvant chemotherapy is recommended, this is initiated 2 weeks after the completion of tissue expansion. If post-mastectomy radiation therapy is indicated, patients first undergo complete expansion followed by irradiation without deflation of the tissue expander. Expander-implant exchange is performed a minimum of 6 months after radiation therapy is complete.

Outcomes

Several studies looking at type of incision and complication rates have come from the group at Massachusetts General Hospital. Similar to our experience at UCSF, while their group was initially using several types of NSM incisions, including periareolar or lateral radial incisions, they subsequently adjusted their technique based on their outcomes data and are now performing most of their NSM procedures through inferolateral IMF incisions. This change in technique resulted from their consistent findings that peri-areolar incisions are independently associated with higher rates of complications [12]. In 2015, Tang et al. [13] reported a 16 % rate of complications requiring surgical revisions in patients with peri-areolar incisions compared to an 11 % rate in patients with other types of incisions (majority inferolateral IMF incisions), with an odds ratio of 1.7 on multivariate analysis.

The group at Mayo Clinic in Rochester has also assessed institutional trends over time in NSM incisions and found that the distribution of incision type changed significantly from their early experience with the technique [14]. In the early years using NSM, over 65 % of cases had peri-areolar incisions, with only 26 % of cases done through an IMF incision; however, by 2014, these numbers had changed significantly, with peri-areolar incisions accounting for less than 16 % of cases and IMF increasing to nearly half of all NSM cases. This shift in incision type was associated with lower rates of complications, including nipple necrosis.

Other groups have also found improved outcomes using IMF incisions as compared to peri-areolar ones. Carlson et al [15] reported 19 % NAC rates in patients with IMF incisions versus 60 % of patients with peri-areolar incisions, which has led them to favor IMF incisions for the vast majority of their cases. Similar results have been found in smaller series, including several studies demonstrating reduction in ischemic complications when selecting IMF or lateral incisions instead of periareolar ones [16–18]. Much of the benefit from avoiding peri-areolar incisions is thought to come from

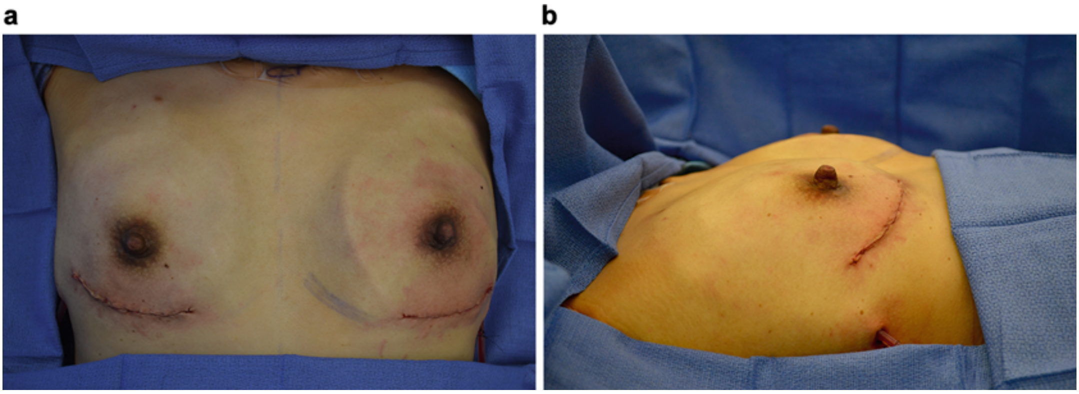

Fig. 5.5 (**a**) Immediate post-op photo with bilateral tissue expander. (**b**) Immediate post-op lateral view

preserving the subdermal plexus, which has been demonstrated with near-infrared fluorescence imaging to be disrupted in animal models with periareolar incisions as compared to radial ones [19]. Use of the IMF incision may be particularly important with patients whose NAC blood supply predominantly comes from the underlying breast tissue, as these patients are more reliant on the subdermal plexus for NAC perfusion once the underlying breast tissue has been removed [20].

In our group's analysis of risk factors for ischemic complications following NSM and immediate reconstruction [21], patients undergoing NSM through a superior peri-areolar incision were nearly five times more likely to have nipple necrosis on multivariate analysis; however, superior peri-areolar incisions tend to be used more often in women with larger breasts, which has been shown to be an independent risk factor for reconstructive complications.

Conclusions

In summary, the IMF approach to NSM offers many advantages, primarily reducing the risk of nipple necrosis by minimizing disruption of the peri-areolar blood supply. Although the approach can be challenging in patients with larger breasts or significant ptosis, it can be used in the majority of patients undergoing NSM with good clinical and esthetic outcomes.

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6 The Vertical Infra-Areolar Approach to Nipple Skin-Sparing or Total Skin-Sparing Mastectomy

Amy Rivere, Pallavi Archana Kumbla, and V. Suzanne Klimberg

Introduction

Halstead first described and published on the technique of the radical mastectomy in 1894, which remained the standard treatment for breast cancer for nearly 70 years [1]. The breast cancer management paradigm shifted with the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study in 1971. This study randomly assigned patients to radical mastectomy (standard of care at that time) versus total mastectomy with loco-regional irradiation or total mastectomy without targeted axillary therapy. Shortly afterwards, in 1973, breast conservation surgery for women with Stage I or II breast cancer measuring ≤4 cm was evaluated in the NSABP B-06 trial to determine its safety and efficacy [2]. Follow-up of these practice-changing studies revealed that radical surgical procedures have not improved survival or diminished local or systemic recurrence [3]. Extensive surgical intervention for breast cancer continued to diminish after the development of sentinel lymph node biopsy rather than axillary lymph node dissection in patients with early-stage breast cancer [4].

In addition to treating patients with a diagnosed breast cancer, multidisciplinary teams are now faced with decisions on how to treat patients who are at high risk for the development of breast cancer over their lifetime. Genetically tested mutations, strong family history, cancer syndromes, and biopsy proven high risk lesions are all potential indications for surgical intervention.

The subcutaneous mastectomy with preservation of the nipple-areola complex (NAC) was initially developed as a prophylactic mastectomy for patients who were high risk for the development of breast cancer. In 1999, Hartmann et al. reported on 575 prophylactic subcutaneous mastectomies performed in women with a family history of breast cancer [5]. There was a 0.2 % (1/575) breast cancer occurrence in the nipple-areola complex following subcutaneous mastectomy and 1 % (6/575) breast cancer occurrences on the chest wall with a median follow-up of 14 years. This provided evidence that the risk of developing

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breast cancer was small even when the nipple–areola complex was left behind [5].

Gerber and colleagues first described skin-sparing mastectomy with the preservation of the nipple–areola complex. The procedure was essentially a subcutaneous mastectomy, eventually resulting in several case reports in the literature of nipple recurrence [6]. A variation on the technique was performed by Petit and colleagues, but with the addition of intraoperative or postoperative radiation therapy to decrease the risk of recurrence in the preserved nipple. Regardless of the oncologic benefit of adding radiation to this method, patients had higher rates of nipple necrosis and resection [7].

In an attempt to reduce the risk of retroareolar recurrence in nipple sparing mastectomies, Petit and Veronesi studied 1001 patients who underwent subcutaneous mastectomies with conservation of the nipple–areola complex [8]. Eight-hundred of these patients then underwent intraoperative radiotherapy and 201 underwent delayed brachytherapy following surgery. After median follow-up of 20 months, 35 cases (3.5 %) of total nipple–areola complex necrosis and 55 (5.5 %) cases of partial necrosis of the nipple–areola complex were reported. Removal of the NAC was required in 50 patients (5 %). There were 14 (1.4 %) local recurrences, none of which were located in the NAC [8] (Table 6.1).

Procedures continued to evolve into total skin-sparing or nipple skin-sparing mastectomy, defined as a mastectomy that removes the breast and nipple–areolar complex while preserving the entire skin envelope of the breast, including the skin overlying the nipple–areolar complex [9]. The glandular tissue beneath the nipple–areolar complex is removed with the mastectomy specimen taking care to leave only the skin of the nipple and areola in place.

The progression of the nipple skin-sparing mastectomy described by Sufi et al. in 2000, and termed the "envelope mastectomy," provides the earliest report of nipple skin-sparing or total skin-sparing mastectomy without leaving the nipple–areola complex intact [10]. The original reported incision was a lazy S in the mid axillary line allowing for the mastectomy, nodal clearance, and latissimus dorsi flap all through one incision. Twelve patients were included in the original study with short-term follow-up of 8.5 months in which there were no recurrences and 92 % cosmesis satisfaction score [10].

A similar procedure termed, nipple-sparing mastectomy (NSM) with immediate reconstruction, preferably with a lateral incision, by Crowe et al in 2004, included 54 NSMs on 44 patients [11]. They excluded patients who had undergone neoadjuvant chemotherapy, had inflammatory breast cancer, Paget's disease of the nipple, patients whose tumor was greater than 3.5 cm, or centrally located tumors. Intraoperative frozen sections of nipple core biopsies were performed with six specimens positive for invasive cancer, all of which were converted to total mastectomies without preservation of the nipple. Of the 48 NSMs completed, three had partial loss of the nipple–areolar complex, all occurring early in the experience, and all three of these had medial incisions. There was no long-term follow-up mentioned [11].

We coined the term total skin-sparing mastectomy (TSSM) in 2005, in our review of 50 TSSMs performed on 31 patients. An inframammary

Table 6.1 Results of follow-up studies evaluating the NAC recurrence after mastectomy with preservation of the NAC

Author	Year	N	F/U months	NAC excision (%)	Recurrence	Recurrence in NAC	RR (%)
Kissin	1987	20				1	5
Bishop	1990	24	46.8	45.5		3	12
Gerber	2003	61	59	4		1	1.6
Petit	2005	300		12	2	0	0
Gerber	2009	60	101		7		11.7
Paepke	2009	109	34	12	2	0	1.8

Recurrence in the NAC is low even in these instances where the NAC was preserved incision was preferred centered at the mid-clavicular line. Six of the 50 TSSMs required resection of the nipple–areola skin, four due to tumor involvement and two due to skin necrosis. The average cosmetic score was 8.5 on a scale of 1–10 and there were no recurrences after a mean follow-up of 7.9 ± 5.4 months [9].

In addition to oncologic safety of saving the nipple, patients reported improved satisfaction, body image, and psychological adjustment when the nipple–areola complex was preserved during mastectomy [12,13].

A systematic review of total skin-sparing mastectomy (TSSM) evaluating oncologic outcomes and postoperative complications was published in 2013 by Piper et al. [14]. The authors performed a Medline and Cochrane database review resulting in 27 papers. Techniques that allowed tissue to remain below the nipple without removal of the nipple–areola complex were excluded. In terms of oncologic outcomes, 159 (6.4 %) of nipple core biopsies sent for frozen section were positive for tumor leading to resection of the nipple–areola complex, and ultimately a skin-sparing mastectomy. To assess local-regional recurrence, 11 papers were included, all having at least 24 month follow-up, totaling 1467 patients. Overall, forty (2.7 %) of these had recurrences. Of the four studies that included > 5 years of follow-up, the recurrence was 24 of 547 (4.4 %). In terms of postoperative complications, 2 % had complete nipple–areola complex loss due to necrosis and 8.8 % had some degree of loss. Mastectomy skin flap loss, either partial or full thickness, was reported as 9.5 % overall. Of the TSSMs, 81 % underwent 2-stage reconstructions with expanders followed by implants with an overall implant loss rate of 3.9 % [14]. This systematic review demonstrates the oncologic safety as well as an acceptable complication rate of the TSSM [14].

Basis for Oncologic Safety

When considering anatomic application to oncologic principle, most breast tumors develop in the terminal ductal lobular units, which is especially relevant in prophylactic mastectomy. Stolier et al. found that 91 % (29 of 32) nipples examined had no terminal ductal lobular units within the nipple papilla. Terminal ductal lobular units were sparse in the three specimens that identified their presence, and all were located at the base of the papilla [15].

A prospective study published by Benediktsson et al. included 216 patients who had either already undergone a partial mastectomy with findings of positive margins or multicentricity, or had features not amenable to partial mastectomy including tumor size >3 cm or multifocal carcinoma [16]. The surgical technique described leaves a 5 mm thick plate of glandular tissue spanning a 2 cm diameter beneath the nipple to preserve nipple–areola blood supply. All patients had intraoperative frozen sections performed requiring 11 removals of the nipple–areola complex for malignancy. This study represents patients with advanced disease undergoing a nipple-sparing technique including lymph node metastasis in 40.3 % with 29 patients having carcinoma in situ, 72 patients with Stage I disease, 82 patients with Stage II disease, and 33 patients with Stage III disease. Median follow-up was 13 years with all patients followed at least 11.6 years or until death. Disease-free survival was 51.3 % and overall survival was 76.4 % with the frequency of locoregional recurrence of 8.5 % among irradiated and 28.4 % among non-irradiated patients ($p = 0.025$). Patients that were further monitored after locoregional recurrence were found to have 5-year freedom from a second locoregional recurrence or distant metastasis of 60 % and overall survival of 82 % [16]. This prospective data provides a basis for oncologic safety of the TSSM even with inclusion of locally advanced breast cancer patients.

A recently published systematic review from Huang included 42 studies evaluating the oncologic safety of nipple skin-sparing mastectomy in which it is emphasized that there is need for uniform preoperative selection and standardization of both surgical technique as well as pathological examination of nipple-sparing mastectomy specimens [17]. Locoregional recurrence ranged broadly from 0-24 % among studies, but the majority demonstrated no significant difference in local recurrence, distant metastasis, or overall survival between traditional mastectomy and nipple-sparing mastectomy for the treatment of breast cancer. NAC recurrence rates were between 0 and 3.7 %. They were found to have a good prognosis with removal of the NAC with a 93 % disease-free survival rate at 5 years following the NAC recurrence. It was noted that patients with early local recurrence, defined as <3 years after surgery had 68 % overall survival and late local recurrence had 86 % overall survival ($p=0.03$). This large review supports the oncologic safety of nipple-sparing mastectomy, even with the inclusion of studies performing subcutaneous mastectomy as a nipple-sparing technique [17].

Indications for TSSM

Initially, indications for TSSM were small tumors, tumors that were not close to the nipple and those that were not multicentric. With increasing data on the oncologic safety of the TSSM, the inclusion criteria for patients offered TSSM has broadened. We now include those with locally advanced breast cancer, those undergoing neoadjuvant treatments, those requiring radiation, and those who are BRCA gene mutation positive.

Absolute contraindications to TSSM are patients with involvement of the skin, involvement of the nipple–areola complex, inflammatory breast cancer, and known smokers. Consideration of breast size and ptosis should also be included in the decision to offer TSSM in relation to cosmesis. Nipple-sparing mastectomy in patients with significantly ptotic breasts may be difficult to reconstruct and may lack cosmetic appeal. There have now been a variety of methods of tissue rearrangement techniques to improve cosmetic appeal of the nipple-sparing mastectomy technique in patients with large or ptotic breasts.

Incision Choice

Blood supply is an important factor in prevention of nipple ischemia and necrosis, and can be interrupted depending on incision choice. The blood supply to the nipple is derived medially from the internal mammary perforators, and superiorly from the thoracoacromial artery, the vessels to the serratus anterior, and the lateral thoracic artery. Laterally, the blood supply originates from the terminal branches of the 3rd-8th intercostal perforators, and the inferior supply arises from branches of the superior epigastric artery. Unnecessary damage to the peripheral blood supply of the breast envelope may occur if the dissection is carried too far beneath the inframammary fold, lateral to the latissimus dorsi muscle, or over the sternum; therefore, these areas should be avoided [18]. Approximately 60 % of the total breast blood supply is from the robust perforators off of the internal mammary artery, which may explain the increased rate of nipple necrosis when using a medial incision [11].

In depth anatomical evaluation of the nipple was performed by Rusby et al. noting that vascular structures were incorporated in the duct bundle of the nipple, but the majority could be salvaged even when taking a nipple core biopsy (Fig. 6.1) [19, 20]. They noted that when leaving a 2 mm rim of nipple tissue after taking the duct bundle, 50 % of vessels were salvaged while removing 96 % complete duct excision. When leaving a 3 mm rim of nipple tissue after taking the duct bundle, 66 % of vessels were preserved while removing 87 % of ductal structures. Similar vessel densities were found in nipples that had been previously irradiated and those that had not been exposed to radiation. The unknown variables remaining are whether or not the vessels within the nipple exposed to irradiation have normal vasodilatory potential in the face of threatening ischemia to the nipple and how much the nipple is affected by venous congestion after a nipple-sparing mastectomy [19].

The TSSM can be accomplished through a variety of incisions as we have previously published [21]. Our initial experience with TSSM utilized incision variability, including the inframammary incision, radial and axillary incisions, and incisions through previous scars, but we now find preference in the vertical infra-areolar incision due to consideration of cosmetic result and blood supply to the nipple. A previous incision may be used if adequate exposure is possible to

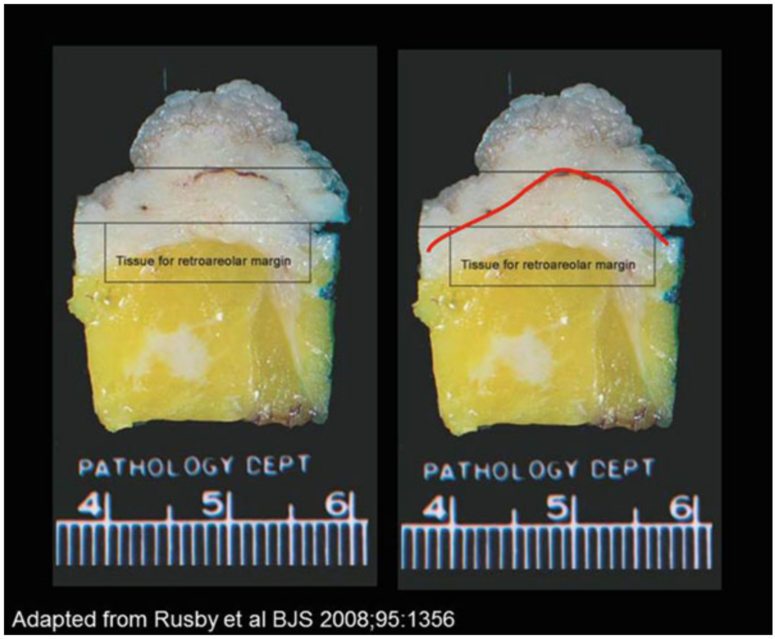

Fig. 6.1 The skin is indicated by the *red line* (adapted from Rusby), the desired plane of dissection to remove the nipple–areola complex from the nipple–areola

obtain through the same incision. In patients who will require removal of the nipple–areola complex and overlying skin, a lollipop incision with extension towards the inframammary fold was preferred allowing excellent exposure and the best projection for reconstructive purposes. This is true especially for patients with a positive intraoperative nipple core biopsy where the vertical infra-areolar incision can be extended to a lollipop incision to include removal of the involved nipple–areola. An inverted T incision may allow for the best projection of the breasts when encountering patients with pendulous breasts or a significant amount of ptosis.

We have typically avoided the medial incision so as not to disrupt the abundant blood supply to the nipple from the internal mammary perforators as was demonstrated in Crowe's experience [11]. In addition, reconstruction with implants is extremely difficult through a medial incision. The vertical infra-areolar incision is our incision of choice when possible as it does not disrupt the nipple–areola skin, is well hidden on the underside of the breast, and preserves all vascular flow to the nipple resulting in fewer complications than with our initial cohort where the inframammary incision was used more commonly [21].

Stolier and colleagues reported on 82 nipple-sparing mastectomies with 87 % of those performed through a 6 o'clock radial incision [18]. These authors found the inframammary incision to be problematic for access to the internal mammary vessels for autologous reconstruction and found access to the nipple dissection to be more difficult, which is the critical portion of the case for long term outcomes. However, there were no occurrences of flap loss or of nipple–areola complex necrosis in the entire group, regardless of incision [18].

Technique

Intraoperative subareolar injection of unfiltered technetium-99 m sulfur colloid is performed after induction of anesthesia [23]. Klimberg, Rubio, and colleagues found that subareolar injection is as accurate as peri-tumoral injection in localization of the sentinel lymph node [22]. Subareolar injection also avoids the necessity of image guidance for nonpalpable lesions in order to perform peri-tumoral injection as well as the avoidance of radioactive zone overlap in tumors of the upper outer quadrant of the breast [22]. Our results of 775 intraoperative Tc-99 injections support the subareolar injection as an accurate method for sentinel lymph node biopsy. We were successful with localization of the sentinel lymph node in 98.6 % (419/425) cases of subareolar tracer injected alone, 94.8 % (326/344) of those with dual injection of Tc-99 and Lymphazurin, and 100 % (6/6) in those with a dermal injection [23]. We no longer use blue dye in the breast during TSSM due to previous experience with skin flap necrosis and permanent skin staining at the injection site.

However, we have initiated routine use of axillary reverse mapping (ARM) with injection of blue dye below the subcutaneous tissue of the upper, inner arm volar surface in all patients undergoing sentinel lymph node biopsy or axillary dissection. We do exclude patients with renal insufficiency and those with allergies to various makeup products since there is frequently a similar component of blue dye contained in many cosmetic products. Our most recently reported data evaluated 360 patients who underwent sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND). Crossover occurred in 4 % of patients where the sentinel node was also the blue node, and the remaining 96 % of sentinel nodes were hot, but not blue. Blue lymphatics were visualized in 80 of 237 (33.7 %) SLNB procedures and 93 of 123 (75.4 %) ALND procedures. The lymphedema rate from SLNB with ARM was 1.7 % (4/237) and was 2.4 % (3/123) when using ARM for ALND over an average 12 month follow-up period [24,25]. Regardless of whether one is performing ARM or not, we wish to emphasize that we do not recommend injecting blue dye in the skin of the flap to be preserved as there is an increased necrosis rate at the injection site.

Performing the axillary sentinel lymph node biopsy through a remote incision may be challenging but has been demonstrated as feasible in a single institution's retrospective analysis of 52 patients undergoing 87 nipple-sparing mastectomies through inframammary incisions. Sentinel node biopsy was successfully performed in 84 of 87 cases (96.6 %) with a mean of 2.8 nodes removed and no complications related to the node biopsy were encountered after a median 6.5 month follow-up [26].

Outline Breast Mound

Minimizing the length of the incision creates a challenge in identifying anatomical landmarks within the breast envelope during the dissection. Outlining the boundaries of the breast mound with a marking pen prior to incision will assist in identifying the boundaries at the periphery of the breast tissue during the dissection.

Incision

We prefer the inframammary vertical incision extending from the most inferior aspect of the areola at the 6 o'clock position, or limbus, to the inframammary fold. When the patient is in the supine position, the breasts tend to fall laterally creating an angle between the areola and the inframammary fold. It is recommended that the patient should be marked either in the upright position prior to induction of anesthesia, or if supine, the breast should be centered to its natural position prior to marking for the incision. This will prevent an angled scar and will keep the nipple directly above the vertical scar when the patient is in the upright position. The incision may vary in length from 4-8 cm, depending on individual breast size. This incision is well hidden while maximizing centralization of the nipple for cosmesis and it preserves all known blood supply to the nipple, therefore minimizing complications of nipple necrosis. By creating an incision at this location, it allows complete preservation of the superior epigastric vessels, the lateral thoracic vessels, and the internal mammary perforators. We have found this to be the most adequate method to maximize postoperative blood supply to nipple, in turn preventing nipple–areola ischemia and flap necrosis. This can be extended to a circumareolar or lollipop incision for patients requiring removal of the nipple and areola, usually for patients with known involvement of the nipple or those with positive intraoperative nipple core pathology [21].

Dilation of the Skin Flaps

The dilator technique is used beginning with 19 French Pratt cervical dilators advanced through the avascular plane separating mammary tissue from the subcutaneous fatty tissue (Fig. 6.2). We begin our dilation at the lower, outer quadrant of the breast first, moving in a lateral to medial direction inferior to superior around the nipple (Fig. 6.3). We upsize the dilators until we reach approximately 39 French (Fig. 6.4). Then, we begin to create our lower outer quadrant flap by connecting the tracts of the dilated tissue. The dilation method demonstrates the correct thickness of the flap according to body habitus. It leaves interspersed columns of Cooper's Ligaments and vessels that then allow the operator to essentially connect the dots using Metzenbaum scissors or the electro cautery device.

The retractors of choice to begin the dissection are S-retractors or appendiceals, which can easily slide into the tracts that have been formed by the dilators. The dilator tracts create a roadmap through the avascular plane by providing both visual and palpable guidance to the proper plane of dissection (Fig. 6.5). For creation of the skin flaps, the cutting function of the electrocautery device is preferred over coagulation to minimize dissipation of heat to the flaps, therefore minimizing tissue destruction and preserving blood supply.

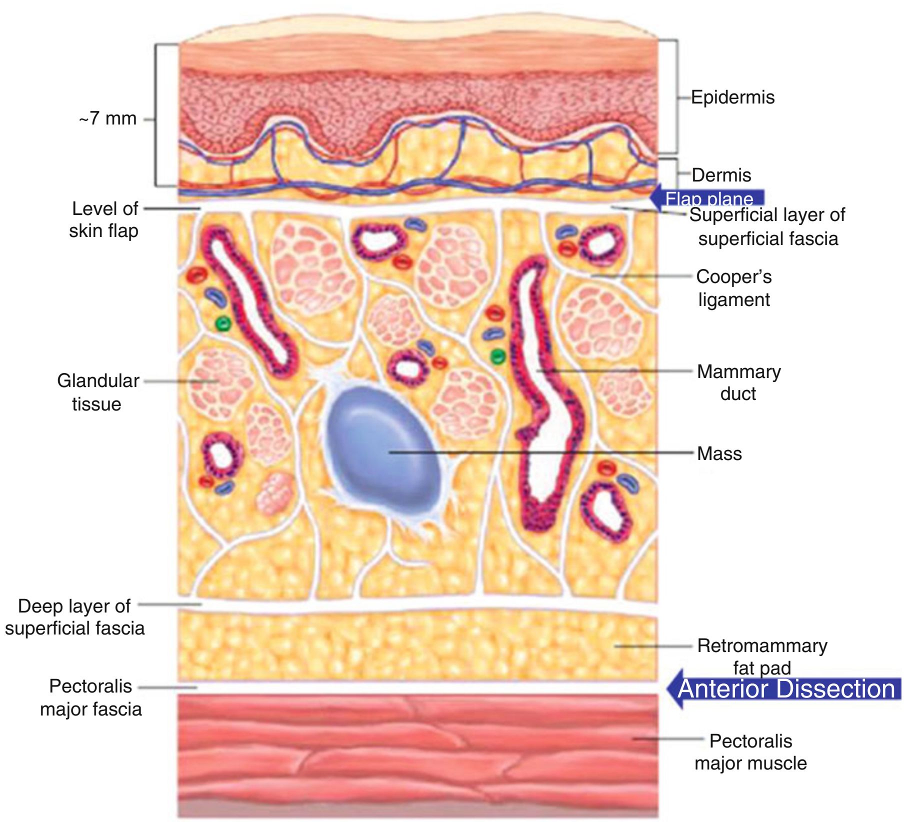

Fig. 6.2 The anatomical dissection planes are demonstrated here with *blue arrows*. The flap plane is an avascular plane separating the breast tissue from the subcutaneous fat and dermis. The anterior dissection plane is the avascular plane of dissection separating the breast tissue from the pectoralis major muscle

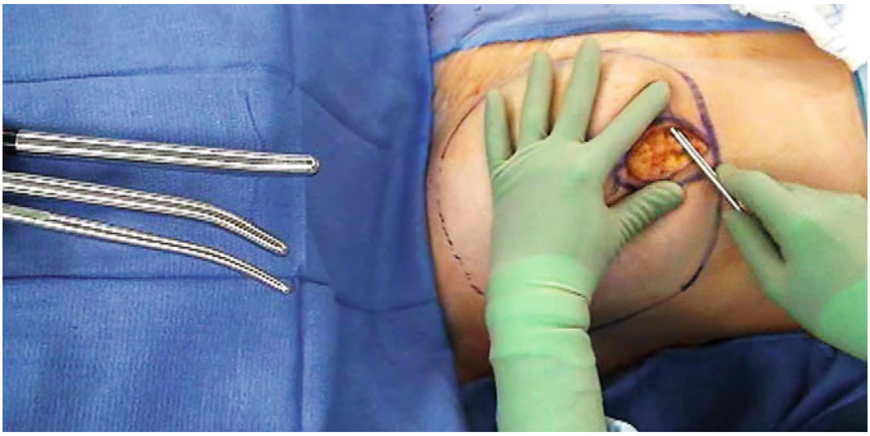

Fig. 6.3 Outlining the breast mound prior to incision and dilation provides an external landmark for the extent of the dissection. Here the vertical infra-areolar incision approach is demonstrated with dilation being performed with a Pratt Cervical Dilator. Notice the progressive sizing of the dilators demonstrated to the *left* of the image. For reference, the patient's head is to the *left* and feet are to the *right* of the image

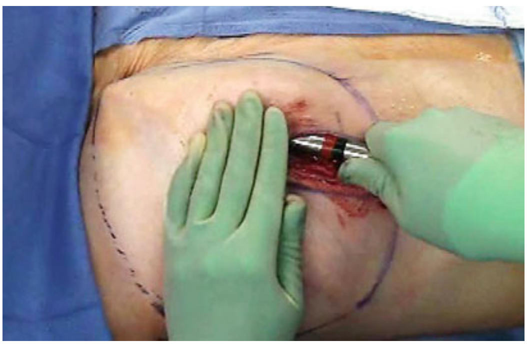

Fig. 6.4 Upsizing of the dilator is demonstrated here. The extent of the dilation stops at the pre-incision skin markings outlining the breast mound. This is done circumferentially while progressively upsizing the dilators through the avascular flap plane

Lower Outer Quadrant Flap Dissection

Keeping to the lower, outer quadrant, we locate the pectoralis major muscle at the most medial aspect of this quadrant and begin our anterior dissection removing the breast in a lateral to medial and inferior to superior direction off of the pectoralis major muscle to complete the anterior dissection (Fig. 6.2). When using the vertical infra-areolar incision, the insertion of the pectoralis muscle is often most easily located just medial to the incision. It is important to travel with the grain of the muscle rather than against it to prevent cautery injury to the muscle fibers (Fig. 6.6a). It is unnecessary to take the pectoralis fascia unless it is involved or abutting tumor.

Anterior Dissection: Removal of the Breast from Chest Wall

This dissection is carried medially to the lateral border of the sternum, superiorly to the second or third rib depending on existence of breast tissue, laterally to the skin flap on a horizontal plane at the level of the pectoralis minor, and inferiorly to the inframammary fold. At this point, the breast should be completely mobilized from the pectoralis muscle (Fig. 6.6b).

Lower Inner Quadrant Skin Flap

Completion of the lower hemisphere of the breast flap is performed by continuing the dissection along the avascular plane that was previously dilated from the 6 o'clock position medially. Caution should be taken when arriving at the most inferior-medial aspect of the breast to preserve the superior epigastric vessels. If there is uncertainty in the anatomic path of this important blood supply to

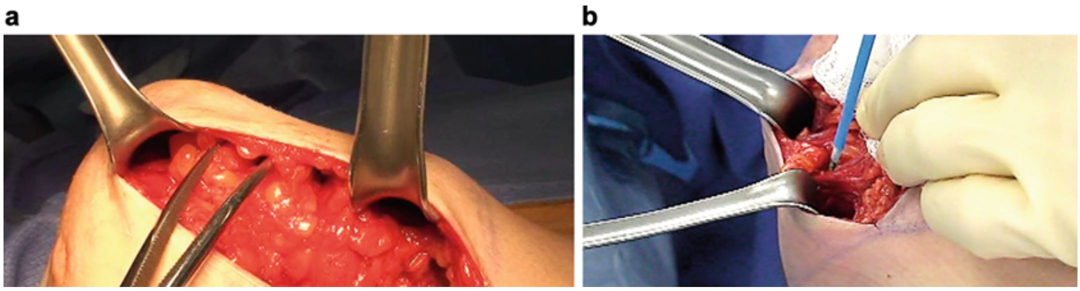

Fig. 6.5 (**a**, **b**) Tracts formed by the dilation technique create a roadmap to the avascular plane between the breast tissue and the subcutaneous fat. This allows for accurate flap thickness by connecting the visible tracts

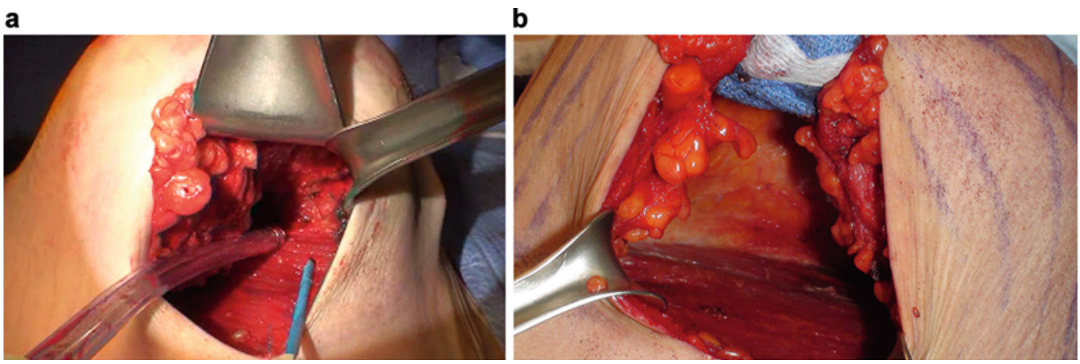

Fig. 6.6 (**a**) Anterior dissection of the breast tissue from the underlying pectoralis fascia. Note the direction of the muscle fibers. (**b**) The breast tissue is completely mobilized from the chest wall

the skin envelope, use of the intraoperative ultrasound Doppler function can be used as well as the SPY (Novadaq Technologies, Inc., British Columbia, Canada) method of locating vascular supply intraoperatively. The SPY device is a specialized infrared camera-computer system used in conjunction with indocyanine green to evaluate the blood flow patterns to the skin and NAC, predicting the nipples at highest risk for ischemia [27].

Nipple–Areolar Complex

The remaining nipple–areolar complex is then addressed to complete the lower hemisphere dissection. Sharp dissection of the nipple–areolar complex from its overlying skin is recommended. A 10 blade scalpel or scissors can be used to liberate the overlying skin and nipple from the nipple–areolar complex (Fig. 6.7). An Allis clamp is then used to grasp a core of tissue from the underside of the nipple while inverting the nipple (Fig. 6.8). The core is then cut sharply at the base of the Allis clamp to send for an intraoperative frozen section or touch preparation (Fig. 6.9). This will allow the pathologist to examine the nipple tissue for any evidence of malignancy. The nipple should be removed if the frozen section of the nipple core biopsy returns positive as well as later if permanent pathology returns positive.

Re-dilation of the Upper Hemisphere

Once the lower hemisphere of the breast, including the nipple–areolar complex, is free from its overlying skin, dilation of the upper hemisphere should be repeated. This should include the breast tissue medially to the lateral border of the sternum, superiorly to the second or third rib, and laterally should include the Tail of Spence, while avoiding the

Fig. 6.7 Sharp dissection of the nipple–areola complex from its overlying skin is to be performed after the inferior hemisphere flaps are completely dissected from the skin envelope

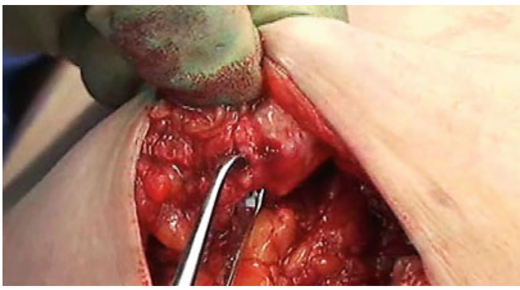

Fig. 6.8 Inversion of the nipple skin after excision of the nipple–areola complex. Note that the dissection immediately resumes the full thickness of the flap at the outer rim of the areola

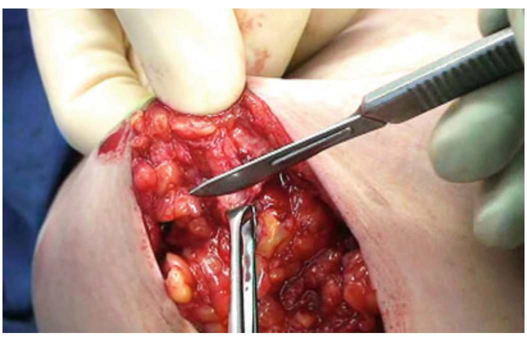

Fig. 6.9 Nipple core biopsy is performed from base of inverted nipple after sharp dissection of the nipple–areola complex from its overlying skin. Grasp desired tissue with an Allis clamp and sharply excise the specimen

axilla. Again, the dilator technique is used beginning with 19 French Pratt dilators advanced through the avascular plane separating mammary tissue from the subcutaneous fat, and upsizing the dilators until we reach adequate visualization of tracts, often up to a 39 French sized dilator. Of course, any smooth dilator can be used while progressing from small to larger sizes to prevent excessive bleeding.

Completion of Upper Hemisphere Skin Flap

Utilizing the vertical infra-areolar incision does create a challenge to reaching the most superior aspect of the breast, especially laterally towards the Tail of Spence. After the dilation is performed thoroughly, the Tail of Spence can be dissected away from the skin of the breast. This area is often the most challenging portion of the dissection due to the increased distance from the incision and limited exposure. We have found several instruments and methods to assist in the visualization and dissection of this region. Wearing a headlight is crucial to obtain adequate visualization through a small incision. For breasts with a short vertical incision due to the limited distance between the limbus and inframammary fold, we have found a sweetheart retractor to be valuable. We also commonly use the St. Mark's retractor to reach a long distance and the C Strang retractor for a broad view. Frequently, the Tail of Spence cannot be completely taken down with the electrocautery. In these instances, we have performed sharp dissection with Jorgensen scissors or long curved Mayo scissors to round the corners of the superior flap. Assuring an adequate dilation is a key factor in developing the dissection plane in this region, in turn providing a safe plane in which sharp dissection can be performed, while minimizing blood loss. Alternatively, one can perform this dissection from the axillary incision made for the SLNB. The breast tissue must then be removed through the incision and marked for pathology assessment.

Preparation for Immediate Reconstruction

If immediate reconstruction is pursued with placement of subpectoral tissue expanders, significant pain in the immediate postoperative period from spasm of the pectoralis muscle may be encountered. A retrospective study by Layeeque and colleagues studied the effect of botulinim toxin (BT) injection on postoperative pain in 48 patients who underwent immediate reconstruction with subpectoral tissue expander placement following mastectomy [28]. They found that immediate postoperative pain was decreased in patients receiving BT compared to controls who did not receive BT. Patients receiving BT also had decreased narcotic requirements in the first 24 h and had a shorter hospital stay. Layeeque and colleagues also found that pain was reduced in the tissue expansion phase leading to a decreased number of expansion sessions as more volume was able to be instilled per session [28]. We routinely utilize 100 units of botulism toxin serotype A (Allergan, Irvine, Ca) reconstituted in 60 mL of normal saline for patients undergoing immediate reconstruction with subpectoral tissue expansion. This is stored at 4 °C until the end of the mastectomy and then 30 mL is injected into the pectoralis major, serratus anterior, and insertion of the rectus abdominis bilaterally which is done by using a 22 gauge needle to inject parallel to the muscle. Care must be taken to not enter the pleural cavity.. We also inject 30 mL of Bupivicaine HCl (0.25 %) without epinephrine (Hospira Inc., Lake Forest, IL) into the pectoralis major, serratus anterior, rectus abdominis insertion, teres major, and latissimus dorsi muscles using a 22 gauge needle parallel to the muscle to decrease postoperative pain.

One-Stage vs. Two-Stage Reconstruction

Important factors in the choice of reconstructive technique following nipple-sparing mastectomy include breast volume, degree of ptosis, areola size, surgeon experience, and tumor related factors such as dimension, location, and proximity to the nipple–areola complex. One-stage direct-to-implant (DTI) breast reconstruction is gaining popularity due to the advent and increased use of acellular dermal matrices in breast reconstruction that prevents pectoralis muscle retraction and implant malposition. The acellular matrix creates an inferior sling that supports the implant and places tension on the pectoralis muscle. Ideal patients are those with smaller breast size who desire to remain a similar size and do not have multiple medical comorbidities that would increase complication risks [29]. In one study by Singh and colleagues, they found that one-stage and two-stage reconstruction options had similar complication risks [30]. However, this option is not ideal for patients who desire to be a larger size or have multiple medical comorbidities such as diabetes mellitus or obesity as excess skin is more sensitive to ischemia. These patients are better served by undergoing a two-stage operation with tissue expansion prior to implant placement. The two-stage approach also allows women to concentrate on their diagnosis and proceed with adjuvant therapy with a less extensive operative procedure [31]. Regardless of which option is selected, both provide excellent cosmetic outcomes (Fig. 6.10).

Fig. 6.10 Postoperative results of the infra-areolar approach to nipple-sparing mastectomy after reconstruction

Summary with Key Points

In summary, there is an abundance of data supporting the oncologic safety of the TSSM or nipple skin-sparing mastectomy and increased complication rates have not been demonstrated in comparison to skin-sparing mastectomies. In addition, the TSSM has superior cosmetic results and allows patients to have a more natural skin envelope for reconstruction. A variety of skin incisions may be used, but considering blood supply to the nipple and the cosmetic outcome, the vertical infra-areolar incision is preferred. Exceptions are made for patients with a prior scar that would allow for adequate exposure to perform the mastectomy, and for patients who will require removal of the nipple–areola, a vertical lollipop incision is best. Patients with known lesions directly beneath the nipple–areola complex, or involvement discovered on intraoperative nipple core biopsy, a vertical infra-areolar incision can easily be extended into a lollipop incision. An inverted T incision may allow for the best projection for reconstructive purposes when encountering patients with a significant amount of ptosis or pendulous breasts.

Patients should be thoroughly informed about the likelihood of sensation loss to the nipple and the surrounding breast skin. They should also have awareness of their own surrounding fatty tissue, especially lateral to the breast as well as in the abdomen. This may be more evident once the breast tissue is removed leading patients to question their swollen abdomen or lateral fatty tissue. Patients should also be informed of the weight of the implants as they may create a sense of heaviness on the chest wall.

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7 Nipple-Sparing Mastectomy in the Large, Ptotic Breast

Arthur H. Salibian, Jay K. Harness, and Donald S. Mowlds

Introduction

Nipple-sparing mastectomy with expander/implant-based reconstruction in selected patients is an accepted method for the treatment of breast cancer. Patients with different breast sizes ranging from small to large and with various degrees of ptosis, may be reconstructed with expander/implant following inframammary nipple-sparing mastectomy [1]. Patients with large or very large, ptotic breasts who are to undergo mastectomy will, however, require a mastopexy if the nipple-areola is to be spared.

Various mastopexy procedures have been described to improve breast shape and correct ptosis in patients undergoing nipple-sparing mastectomy [2–5]. These mastopexy procedures, namely doughnut mastopexy, vertical mastopexy, and bat-wing mastopexy have limitations related to the design of the flap that prevent the excision of large areas of skin to raise the nipple-areola more than 5 cm.

The Wise pattern design [6] for mastopexy that has greater flexibility for skin removal can raise the nipple more than 5 cm. However, if used in conjunction with nipple-sparing mastectomy, the circulation to the corners of the thin medial and lateral mastectomy flaps may be compromised leading to skin necrosis. Furthermore, the narrow, inferiorly based Wise pattern dermal-fat flap may or may not sustain the nipple-areola. When the Wise pattern mastopexy is used in conjunction with nipple-sparing mastectomy for lifts greater than 5 cm, the nipple-areola is excised and grafted in its new location, or reconstructed at a later date [7].

Spear et al. [8] described a three-stage nipple-sparing mastectomy/mastopexy for ptotic breasts. In this staged reconstruction, the mastopexy is performed first as a delay procedure to improve the blood supply to the nipple-areola, followed several months later by the nipple-sparing mastectomy and expander insertion. In the third stage the expander is exchanged for a permanent implant. This three-stage operation, although suitable for relatively smaller breasts, may not be suited for the very large, ptotic breast.

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We have previously reported our preliminary 6-year experience on the management of the large, ptotic breast at the time of nipple-sparing mastectomy using the buttonhole mastopexy technique [9]. In this chapter the buttonhole mastopexy-nipple-sparing mastectomy procedure is discussed, including the management of the ptotic breast after the completion of nipple-sparing mastectomy reconstruction.

Patient Selection

A small percentage of women who are undergoing therapeutic nipple-sparing mastectomy will require a major breast lift because of large breasts. In evaluating patients for mastopexy-nipple-sparing mastectomy, consideration should be given to breast size, degree of ptosis, and the patient's desire to have a mastopexy. Patients with very large breasts (DD cup or larger) are advised to have a buttonhole mastopexy regardless of the degree of ptosis because the skin surface area has to be reduced for proper positioning of the implant with respect to the inframammary fold. Patients with large breasts (D cup) and grade III ptosis who desire to have the ptosis corrected, and do not have concerns about the mastopexy scars, are also candidates for a mastopexy-nipple-sparing mastectomy. Patients with moderate breast size (C cup) with grade III ptosis are advised not to have a mastopexy because the ptosis can be corrected by allowing the skin to physiologically contract over the expander. This converts the ptosis from a grade III to a grade II after the permanent implant insertion.

Contraindications to primary buttonhole mastopexy are related to the location of the tumor with respect to the nipple-areola or the proximity of the tumor to the surface of the skin covering the lower half of the breast. Patients with tumors involving the subareolar breast tissue or tumors close to the areola that preclude leaving a small amount of breast tissue in place to preserve the circulation to the nipple-areola, are not candidates for a primary buttonhole mastopexy. Also, superficial tumors in the lower hemisphere of the breast that require thinning of the inferior pedicle flap carrying the nipple-areola are a contraindication to primary mastopexy because of the increased probability of nipple-areola loss. Deeper tumors in the lower portion of the breast that allow preservation of the full-thickness subcutaneous fat may undergo a primary mastopexy safely.

Candidates for buttonhole mastopexy are informed that a thin layer of breast tissue will be preserved beneath the areola to ensure the viability of the nipple-areola, but that the breast tissue will be completely removed during the second-stage implant exchange. Patients are also told that the pathology of the subareolar breast tissue will be examined, both at the time of mastectomy as well as after its removal in the second stage, to rule out cancer involvement. This temporizing subareolar breast retention procedure is readily accepted by patients.

Buttonhole Mastopexy Technique

Breast markings are made the day prior to surgery to outline the superior skin flap, and the new nipple-areola location. First a curved horizontal line is drawn across the upper border of the areola (diameter 4–4.5 cm) to join the medial and lateral corners of the inframammary fold marking (Fig. 7.1). The horizontal marking also delineates the upper border of the inferior dermal-fat flap carrying the nipple-areola. For very large breasts or extremely ptotic breasts (nipple-to-suprasternal notch distance 34 cm or greater), the new nipple location is marked, raising it 10 cm or more to place it around 20–24 cm from the suprasternal notch. Here it should be mentioned that a 10 cm nipple displacement would result in a lower pole height of 6 cm if the areola diameter were 4 cm. For decreasing nipple displacements, adjustments have to be made in the inframammary marking or in the method of inframammary wound closure to keep the height of the inferior pole 5–7 cm.

For 7–9 cm lifts, the markings are the same, except that the inframammary marking is "notched" centrally in an inverted-V fashion to increase the height of the inferior pole by 1–2 cm. If this modification does not provide the desired

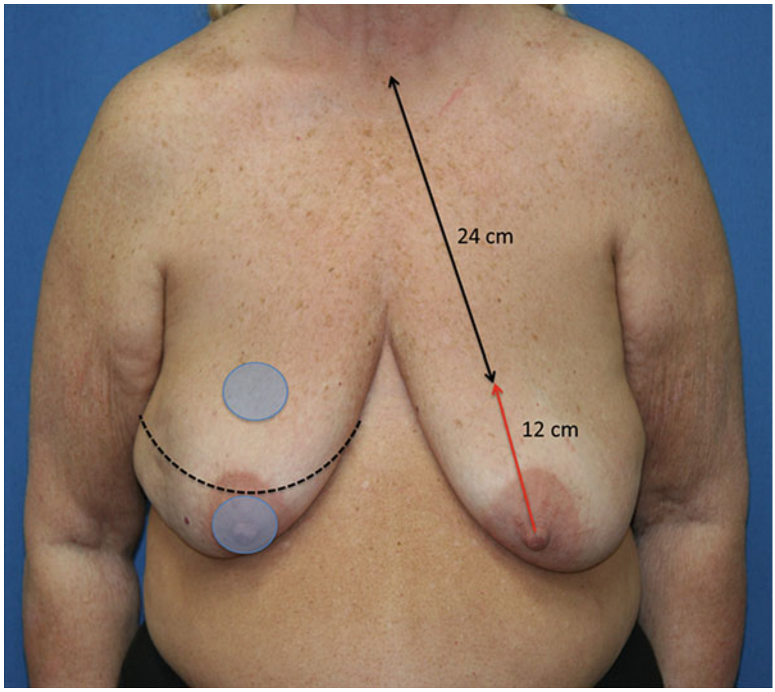

Fig. 7.1 Buttonhole preoperative marking showing the *curved horizontal line* defining the lower border of the upper flap. The upper flap is buttonholed to receive the nipple-areola that is carried on an inferiorly based dermal-fat flap. The nipple-areola is moved up 12 cm for placement at 24 cm from the suprasternal notch (*blue circles*)

5–7 cm height for the inferior pole then the excess skin in the central inframammary fold may be rearranged during the closure, moving it from the horizontal plane to the vertical plane to gain a few cm at the meridian of the breast.

The mastopexy-nipple-sparing mastectomy is an oncologic-plastic team effort, with the plastic surgeon initially assisting the oncologic surgeon on the mastectomy, followed by both surgeons operating simultaneously to perform the sentinel lymph node biopsy or axillary lymphadenectomy, contralateral mastectomy, buttonhole mastopexy, and expander insertion. Prior to raising the mastectomy flaps, the areola is circumscribed keeping its diameter at 4–4.5 cm, and the transverse incision is made as marked preoperatively to raise the upper flap superficial to the anterior mammary fascia. The inferior flap dissection starts medially and laterally because of a well-defined anterior mammary fascial plane, and then proceeds towards the areola. On reaching the areola the dissection is carried through the breast, leaving a 5 mm thick layer of breast tissue attached to the areola. At this point a generous biopsy is obtained from the base of the areola for permanent sections and the periphery of the subareolar tissue tagged with 6–8 medium-size hemoclips for future guidance in the complete removal of the breast tissue at the time of expander implant exchange. As the dissection moves inferiorly towards the inframammary fold, care is taken not to dissect beyond the inframammary fold to avoid damaging the intercostal blood supply to the inferiorly based dermal-fat flap.

After completion of the mastectomy, the entire inferior flap is deepithelialized to create a broad-based 15–20 cm dermal-fat flap carrying the preserved nipple-areola (Fig. 7.2a). The expander (Mentor CPX3, Irvine, CA) is then fixed in place over the pectoralis major muscle using absorbable sutures (Fig. 7.2b) and the upper flap retracted down to cover the dermal-fat flap (Fig. 7.2c) and suture it to the inframammary margin of the deepithelialized flap. Because the upper flap is longer than the inframammary incision, suturing proceeds from both ends, easing the skin towards the meridian of the breast; the scalloping of the skin centrally flattens out postoperatively. Finally, the skin and subcutaneous fat in the predetermined nipple-areola location is cored out (4.5 cm diameter) to exteriorize the nipple-areola and suture it in place (Fig. 7.2d). The wounds are routinely drained with a single fluted drain.

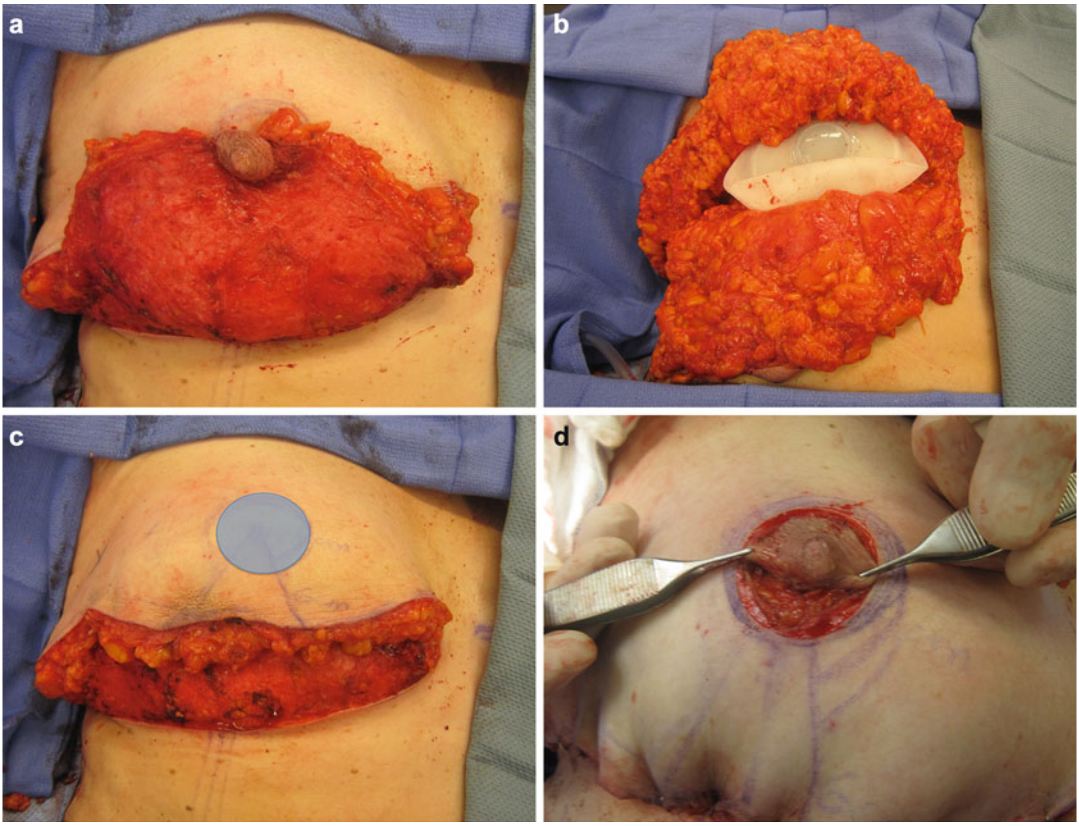

Fig. 7.2 Combined mastopexy-nipple-sparing mastectomy technique. The broad-based inferiorly based dermal-fat flap carries the nipple-areola to its new location (**a**). Tissue expander fixed in place over the pectoralis major muscle. The inferior flap that has been flipped over shows the preserved full-thickness subcutaneous fat (**b**). The superior flap retracted inferiorly to cover the expander. A circular area of full-thickness skin flap (*blue circle*) will be excised to receive the nipple-areola (**c**). Nipple-areola pulled through the buttonhole for suturing in place (**d**)

For 7–9 cm nipple displacements in which the distance between the lower border of the upper flap and the proposed lower border of the areola is less than 5 cm, the buttonhole mastopexy has to be modified to increase the vertical length of the lower pole of the breast. As mentioned earlier, "notching" the inframammary incision at the meridian of the breast will increase the height of the lower pole by 1–2 cm. Another maneuver that increases the inframammary-to-areola distance is shifting the excess skin of the upper flap from the horizontal plane into the vertical plane during the skin closure at the meridian of the breast. This skin shift creates a dog-ear deformity in the vertical plane that is corrected by deepithelializing the excess skin, infolding it, and repairing the skin margins for a final inverted-T suture line. Minor dog-ear deformities that are not corrected primarily may be repaired during the second-stage implant exchange.

Second-Stage Expander Implant Exchange and Removal of Retained Subareolar Breast Tissue

The timing of the second-stage procedure depends on whether the patient is to undergo postoperative radiation therapy or chemotherapy. If radiation therapy is planned, 6 months are allowed before exchanging the implants. Patients having completed chemotherapy wait a month to have the implants exchanged. In the second-stage implant exchange both oncologic and plastic surgeons participate in the first part of the procedure to remove the residual subareolar breast tissue. An 8 cm lateral inframammary incision is made dividing the outer half of the previously deepithelialized inferiorly based pedicle flap to expose the expander and remove it. The nipple-areola is then everted for the oncologic surgeon to excise the retained breast tissue. A 25-G needle passed through the periareolar skin as well as the previously applied hemoclips serve as guides to the peripheral borders of the circular subdermal breast tissue resection. The subareolar specimen is properly oriented and submitted for permanent pathologic examination.

The second part of the procedure involves the capsulotomy, and insertion of the permanent silicone implant. First, radial capsulotomies are performed around the periphery of the areola to smoothen out the transition between the capsule and the undersurface of the areola. A prepectoral peripheral capsulotomy is then made from 7 o'clock to 5 o'clock, undermining the flap subcutaneously for several centimeters. To maintain the integrity of the inframammary fold the inferior border of the capsule is left intact. Additional radial incisions/cross hatching along the periphery of the capsule may be needed to correct any external skin irregularities.

During the second-stage reconstruction the shape of the breast may be improved. If the breast has a square shape because of the broad-based dermal-fat flap, the lateral portion of the flap is trimmed and the excess infra-axillary subcutaneous fat debulked to give the reconstructed breast a more rounded appearance. The medial debulking, if needed, will require a separate medial inframammary incision along the previous scar. Following the contouring of the breast the permanent silicone implant is inserted and the wound closed over a single fluted drain.

Safety of Primary Buttonhole Mastopexy

The primary buttonhole mastopexy as part of the nipple-sparing mastectomy is a safe procedure both from a technical and oncologic standpoint. The Passot buttonhole technique [10] that was originally described for reduction mammoplasty has been adapted for primary mastopexy in patients with large ptotic breasts who are to undergo a nipple-sparing mastectomy. In the modification of the Passot technique, a 15–20 cm wide, inferiorly based, random pattern dermal-fat flap is used to carry the nipple-areola and raise it 7–12 cm, placing it around 20–24 cm from the suprasternal notch. Lifts greater than 12 cm are feasible provided the width-to-height ratio of the inferior pedicle flap does not exceed 1:1 ratio.

In addition to proper flap design, the success of the buttonhole mastopexy depends on the use of a "thick" inferior pedicle dermal-fat flap that retains the full-thickness subcutaneous fat to sustain the blood supply to the apex of the flap. Because the apex of the flap harboring the nipple-areola is the most tenuous portion of the flap, the subareolar breast tissue cannot be thinned down to the dermis. Removing the subareolar breast tissue will invariably result in partial or full-thickness nipple-areola loss. It is imperative therefore to temporarily leave a thin layer of subareolar breast tissue in place during the first stage and remove it in the second stage when the implant is exchanged. Resecting the entire subareolar breast tissue during the second stage does not jeopardize the nipple-areola because of collateral circulation through the surrounding skin. By the same token, dividing the lateral half of the base of the flap to remove the expander and access the undersurface of the areola does not affect the viability of the remaining flap because of the delay phenomenon that enhances the circulation to the dermal-fat flap.

We attribute the success of mastopexy-nipple-sparing mastectomy in selective patients to the thick flaps that preserves the full-thickness subcutaneous fat [11], the flap design that ensures a 300° arc of dermal-fat flap around the areola, and the retention of subareolar breast tissue during the initial mastectomy. The safety of the buttonhole mastopexy is also attested by the fact that it may be used in patients who have previously undergone radiation therapy for breast cancer or for those patients who are to undergo radiotherapy postoperatively.

Planned complete excision of benign retroareolar tissue during the second-stage implant exchange does not compromise the safety of the oncologic surgery as all visible breast tissue, previously reported benign, is eventually excised. Although a 5-year follow-up period is needed for an accurate assessment of local recurrence, there have been no local recurrences in our mastopexy-nipple-sparing mastectomy patients over an average 3-year follow-up period.

Complications

Complications following mastopexy-nipple-sparing mastectomy reconstruction are uncommon if the mastectomy flaps are thick and the subareolar breast tissue is removed in stages. Superficial partial areola loss heals spontaneously leaving light patchy areas of discoloration that do not require tattooing. Deeper and larger areas of skin loss with more noticeable discoloration can be improved with tattooing.

A wound created by full-thickness skin loss but with viable underlying subcutaneous fat is allowed to granulate for skin grafting or left to heal spontaneously with secondary intention. If a full-thickness nipple-areola loss is accompanied with subcutaneous tissue necrosis that exposes the implant, the implant should be removed, the wound debrided, and the defect closed with a rotational flap to minimize the deformity at the apex of the breast. To repair the circular opening in the breast mound, the lateral aspect of the inferior pedicle flap is back-cut, and the flap rotated into the defect for coverage with a skin graft. With the rotational flap repair, the elliptical excision and primary closure of the defect that flattens out the apex of the breast is avoided. Several months after flap healing, an expander is inserted for two-stage implant reconstruction.

A well-known complication of subcutaneous breast reconstruction with implants following subcutaneous mastectomy, commonly performed in the 1980s, was capsular contracture [12]. In mastopexy-nipple-sparing mastectomy reconstruction, grade III–IV capsular contracture after an average 3-year follow-up period is uncommon. Capsular contracture rates may increase over a longer follow-up period. We have not used acellular dermal matrix to improve breast shape, define the inframammary fold, "protect" the implant, or reduce capsular contracture (see Chap. 15).

Aesthetics of Mastopexy-Nipple-Sparing Mastectomy Reconstruction

Patients who have undergone a mastopexy-nipple-sparing mastectomy reconstruction have been satisfied with the result because of the breast lift, the symmetric location of the nipples, the overall breast shape, and acceptable mastopexy scars. The prepectoral location of the permanent implant readily fills the medial upper portion of the breast for better cleavage and avoids the upper pole flatness often seen in subpectoral implantation, a contour irregularity that may have to be corrected with lipofilling [13]. The buttonhole mastopexy, moreover, has the advantage of either maintaining the preoperative breast size, or reducing it, depending on the patient's desire (Fig. 7.3a, b).

Following first-stage masopexy-nipple-sparing reconstruction, the breast may have a square appearance because of the broad-based inferior pedicle flap. The shape of the breast can be improved by debulking the lower lateral and medial corners of the breast during the second stage for a more rounded appearance. In women with wide chests, an excessive lift up to 20–22 cm from the suprasternal notch will give the breast a permanent wide appearance, a potentially undesirable outcome that patients should be informed about preoperatively.

Secondary Mastopexy After Expander/Implant Reconstruction

Women with large ptotic breasts may elect not to have a mastopexy with nipple-sparing mastectomy to avoid the periareolar scar and possibly a vertical scar in the lower pole. These patients are informed that the use of large implants 700–800 mL for the reconstruction

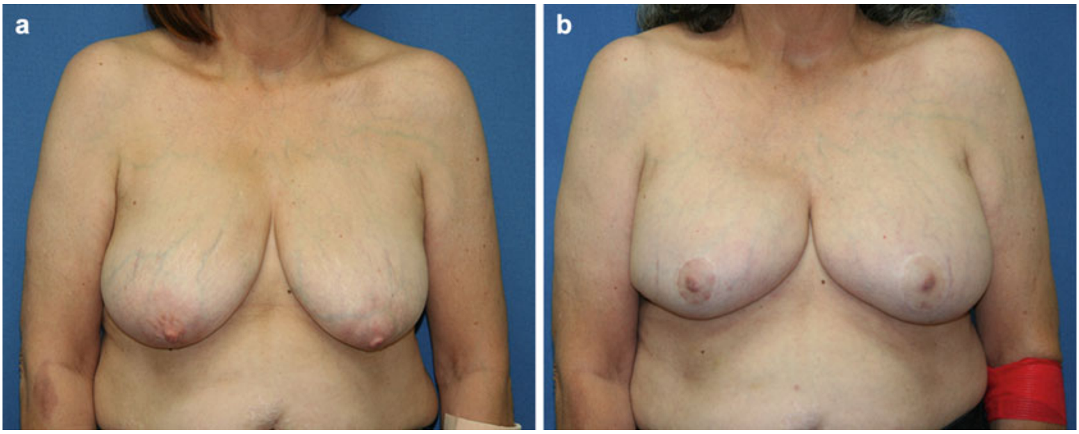

Fig. 7.3 A 62-year-old patient with intraductal carcinoma of the right breast who underwent bilateral buttonhole mastopexy-nipple-sparing mastectomy raising the nipple 8 cm. Preoperative view (**a**). Postoperative view after 2 years (**b**). The patient desired to retain her preoperative breast size

will not correct the ptosis and the upper pole of the breast will remain flat or concave because of the low position of the implant. Raising the position of the implant with acellular dermal matrix will not be helpful because the excess skin will not drape properly over the implant, leaving the nipple-areola at the lower border of the breast mound. In this setting, patients are told that a secondary lift to correct the ptosis after the two-stage expander/implant reconstruction is feasible, though limited to 4–6 cm.

Patients with ptotic breasts who elect to have the breasts reconstructed with large implants may decide at a later date to have their breast size reduced because of increasing discomfort and upper chest pain caused by implant traction on the skin. Others may request a delayed breast lift to improve breast shape and symmetry or correct grade III–IV capsular contracture (Fig. 7.4). A limited mastopexy may be performed in these patients to raise the nipple 4–6 cm depending on the patient's BMI. With higher BMIs and increasing flap thickness the nipple may be raised up to 6 cm.

To perform a secondary mastopexy, the keyhole pattern is used with the limbs of the keyhole measuring 5–7 cm. The keyhole pattern is first deepithelialized in continuity with a 4–6 cm wide inferior pedicle flap and a narrower 2–3 cm superior flap to outline a bipedicle dermal-fat flap. Vertical skin incisions are then made along the margins of the deepithelialized skin and deepened to reach the capsule. The medial and lateral breast flaps are then undermined for several centimeters with the implant in place and the flaps mobilized for the closure. The implant is removed through a vertical incision along the lateral border of the inferior pedicle flap and capsulotomies performed if needed. The flaps are then temporarily approximated with skin staples over the exchanged implant and the patient placed in a semi-sitting position to determine the extent of deepithelialization of the lower medial and lateral skin segments. These segments are marked and deepithelialized, closing the wound with a single layer of dermal absorbable sutures. A drain is used if a capsulotomy is performed.

At least 6 months should be allowed for improved circulation to the nipple-areola before performing a secondary mastopexy. The safety of the operation, which is not much different than a conventional mastopexy-augmentation, depends on the size of the implant and the tension under which the flaps are closed. Fortunately, most patients undergoing a secondary mastopexy after the two-stage reconstruction desire to have the implants exchanged for smaller ones.

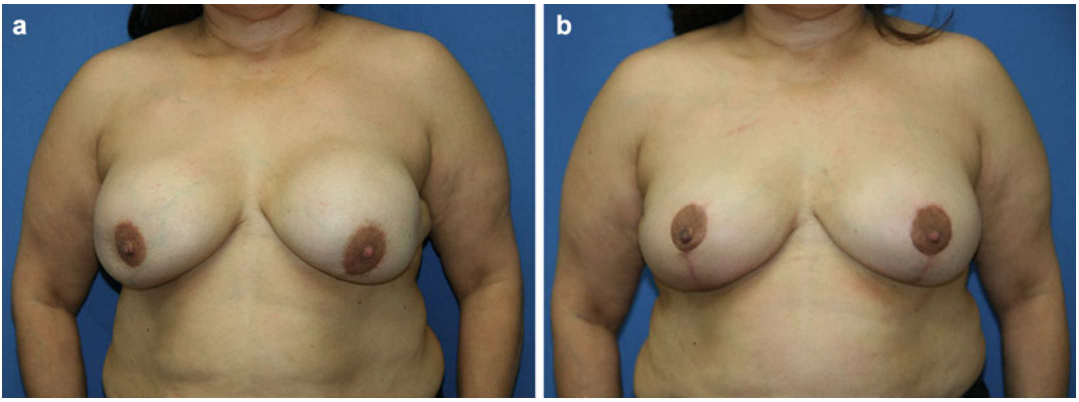

Fig. 7.4 Secondary mastopexy after nipple-sparing mastectomy reconstruction. Fifty-year-old patient with intraductal carcinoma of left breast who underwent bilateral nipple-sparing mastectomy and staged subcutaneous expander/implant reconstruction with 650 mL implants. Preoperative view 3 years after reconstruction showing bilateral grade IV capsular contracture (**a**). The patient desired to have the breast size reduced. Secondary mastopexy result after 1 year (**b**). The nipple was raised 6 cm and the implant exchanged for a 475 mL implant

Conclusion

Patients with large breasts, or patients who desire a major breast lift at the time of nipple-sparing mastectomy, should be given the choice of having a primary mastopexy. The buttonhole mastopexy technique is a safe procedure that may be performed in conjunction with nipple-sparing mastectomy, provided (1) the mastectomy flaps are thick, and (2) a thin layer of tumor-free subareolar breast tissue is retained during the initial nipple-sparing mastectomy and subsequently removed when the implant is exchanged in the second stage.

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8 Nipple-Sparing Mastectomy in the Community Setting

Donald S. Mowlds, Jay K. Harness, Arthur H. Salibian, and Richard S. McNally

The majority of the surgical literature describing institutional experience with nipple-sparing mastectomy (NSM) has come from academic institutions. Little has been published by community-based surgeons who are responsible for more than 80 % of breast cancer surgical treatment in the United States. Chapter 1 provides an overview of the evolution of NSM to where we are today. Nearly all of the 69 references in Chap. 1 are from academic institutions.

In 2009, Spear et al. published an article in which they performed a 15-year review of the scientific literature on the prophylactic as well as therapeutic NSM [1]. The thrust of the article was a consensus statement regarding proper patient selection. The Georgetown approach for therapeutic NSM suggested that patients with peripherally located (greater than 2 cm from the nipple) tumors less than 3 cm in size (without skin involvement) and with clinically negative axillary nodes were suitable candidates for NSM. These early guidelines have given way to more flexible ones outlined in Chap. 1 and other chapters in this book.

In 2015, Peled et al., published a series of 139 patients with stage IIb ($n=25$) or III ($n=114$) disease who all underwent NSM over an 8-year period. During a mean follow-up period of 41 months, 5 % of patients experienced locoregional recurrence, none of which involved the nipple-areolar complex (NAC) skin [2]. Similar to our experience in the community setting, this study challenged the notion that the NSM was reserved for patients with low-risk disease or as a risk-reduction measure. Furthermore, it highlighted the fact that systemic therapies and tumor biology were major drivers of patient outcomes. Nipple-sparing mastectomy afforded patients the opportunity to undergo an extirpative procedure with more aesthetic appeal.

The outcomes and experience at the community level are sparsely reported, at best. As NSM becomes more of an accepted option for breast cancer patients, examining the clinical results at the community level is important. This chapter summarizes the experience of one surgeon (JKH) performing NSMs in the community setting over the past 11 years. We believe that our outcomes parallel that of the broader community hospital setting as well as the outcomes already reported in the surgical literature.

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Our Community Hospital Setting

St. Joseph Hospital is located in Orange, California. Orange, CA is in central Orange County California which is the next county south of LA County and north of San Diego County. The county is part of the metroplex extending from Los Angeles to the Mexican border.

The hospital is a part of St. Joseph Health, an integrated Catholic health care delivery system sponsored by the St. Joseph Health Ministry. It has 16 acute care hospitals and community clinics that serve California, West Texas, and Eastern New Mexico. The Breast Program at St. Joseph Hospital, Orange, was founded because the standard of care for breast cancer patients requires a multidisciplinary approach that is both comprehensive and individualized. Since its inception over a decade ago, the program has grown to the point of treating over 400 new breast cancers each year. The breast team includes five breast surgeons, two plastic surgeons, nine medical oncologists, three radiation oncologists, two breast radiologists, and two breast pathologists who are primarily academic trained and bring with them the commitment to excellence established in the academic setting. Additional team members include genetic counselors, physical therapists, lymphedema specialists, and a social worker. A weekly interdisciplinary treatment management conference is held in order to optimize surgical and medical outcomes through collaboration between all of the needed specialists.

Fundamental to our process is the level of communication between surgeons and other Breast Program members. The breast and plastic surgeons decide preoperatively on the best operative approach to NSM (e.g., inframammary, radial, etc.) depending on factors including: tumor location, breast size, degree of ptosis, etc. Often, the patient is marked by the plastic surgeon the day prior to surgery. Intraoperatively, the breast surgeon and the plastic surgeon discuss the radiographic findings and if needed map the tumor location using ultrasound. The plastic surgeon assists the oncologic surgeon with the NSM. A detailed description of the team approach is described in Chap. 22. Postoperatively, both surgeons see the patients individually, discuss final pathology reports, needed adjuvant therapies, and deal with unexpected issues (e.g., seroma fluid around tissues expanders, tissue loss, etc.). The depth of collaboration is ongoing throughout all phases of care of the NSM patient.

Technique

In essence, a NSM is a skin-sparing mastectomy with preservation of the nipple-areolar complex (NAC). The technique used by the senior authors has been previously described [3]. The mastectomy is performed utilizing two incisions, one in the axilla and the other in the inframammary fold (Fig. 8.1). A team approach is thus taken with one surgeon starting in the axilla while the other begins at the inframammary fold (Fig. 8.2)

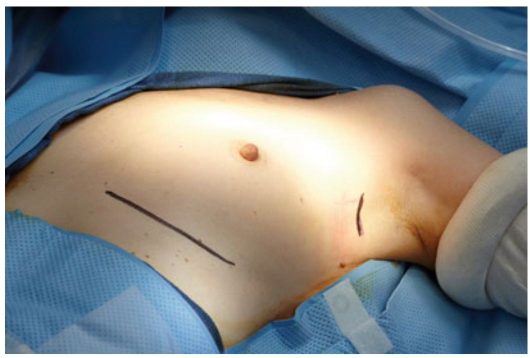

Fig. 8.1 Demonstrating the inframammary and axillary incisions for a left NSM

Fig 8.2 The breast is dissected off the pectoralis major fascia from both the inframammary and axillary incisions

(also see Chap. 22). The axillary incision is used for two aspects of the procedure. The first is the sentinel lymph node biopsy and/or axillary lymph node dissection and the second is the dissection of the axillary tail and upper pole of the breast from the pectoralis major fascia and the overlying subcutaneous fat (Fig. 8.3a, b).

A 12–14 cm incision at the inframammary fold is used to perform the NSM. The initial maneuver is performed by the plastic surgeon who frees the breast off of the pectoralis fascia through the inframammary incision. This dissection ultimately joins the release of the tail of the breast performed concurrently by the oncologic surgeon through the axilla (Fig. 8.4). Following this, the plastic surgeon assists in performing the mastectomy. The anterior mammary fascia is identified and the dissection is carried along this plane, dividing the individual Cooper's ligaments with scissors beneath the dermis (Fig. 8.5a, b). This dissection preserves most of the subcutaneous fat layer with its subdermal plexus blood supply. No hydrodissection is used.

For tumors close to the skin, high-resolution ultrasound is used intraoperatively to determine the extent of subcutaneous flap thinning (Fig. 8.6a, b). The subcutaneous fat is thinned in this location to the level of the superficial fascia. If the superficial fascia is involved, a subdermal dissection is pursued. If there is extension of the cancer into the overlying skin, the skin is excised.

The subcutaneous fat layer of the breast is absent beneath the NAC. Breast tissue adherent to the underside of the areola it is dissected free and the base of the nipple is divided sharply such that no breast tissue is left under the areola and nipple (Fig 8.7a, b). In all cases, a deep biopsy of the nipple base is taken and evaluated with permanent histology, not frozen section. The tissue expander is placed in either a pre- or retropectoral pocket and fixed in place and partially expanded. The mastectomy flaps are then closed over a single fluted drain externalized laterally through a separate incision adjacent to the inframammary fold (Fig 8.8a, b) Antibiotics given

Fig. 8.4 Demonstrating the complete dissection of the breast off the pectoralis muscle

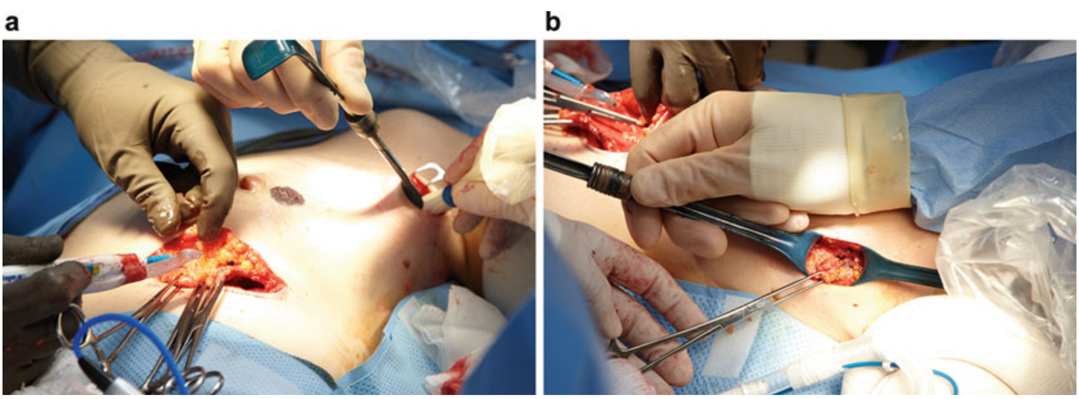

Fig. 8.3 (**a**, **b**) Using a wireless gamma probe to locate a sentinel lymph node which is sent for frozen section analysis

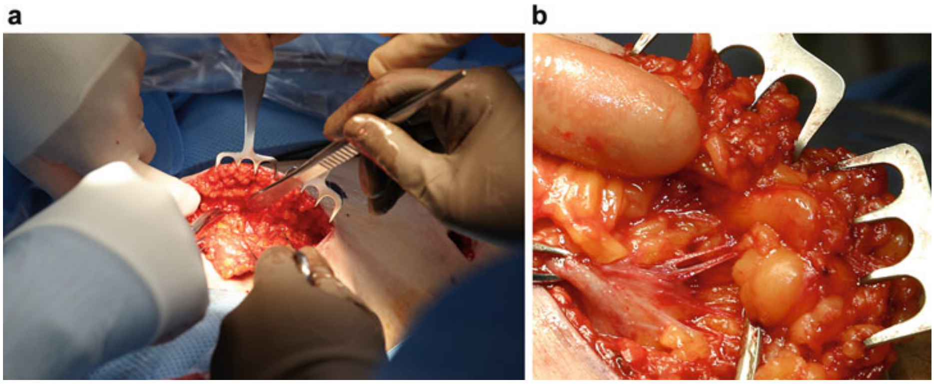

Fig. 8.5 (**a**) Preserving the subcutaneous fat layer by dissecting along the anterior mammary fascia. (**b**) Close-up picture of a Cooper's Ligament arising from the anterior mammary fascia. The ligament is then divided under the dermis

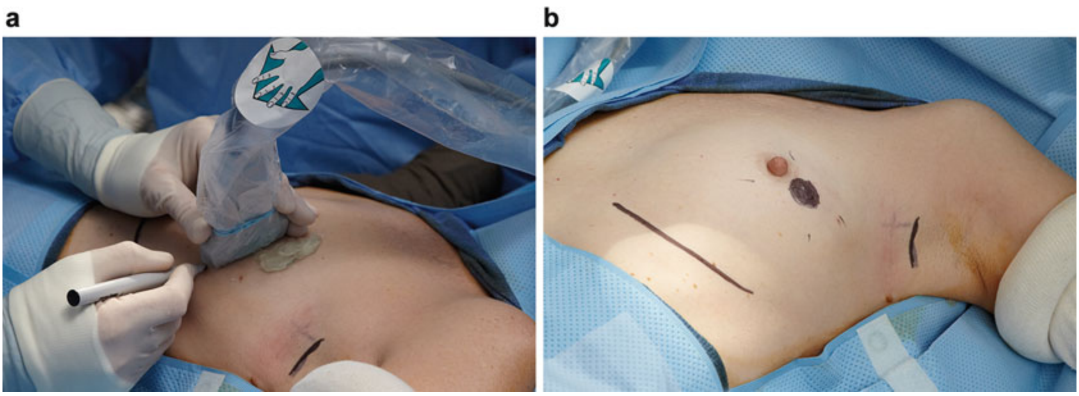

Fig. 8.6 (**a**, **b**) Ultrasounding and marking the location of an infiltrating ductal cancer

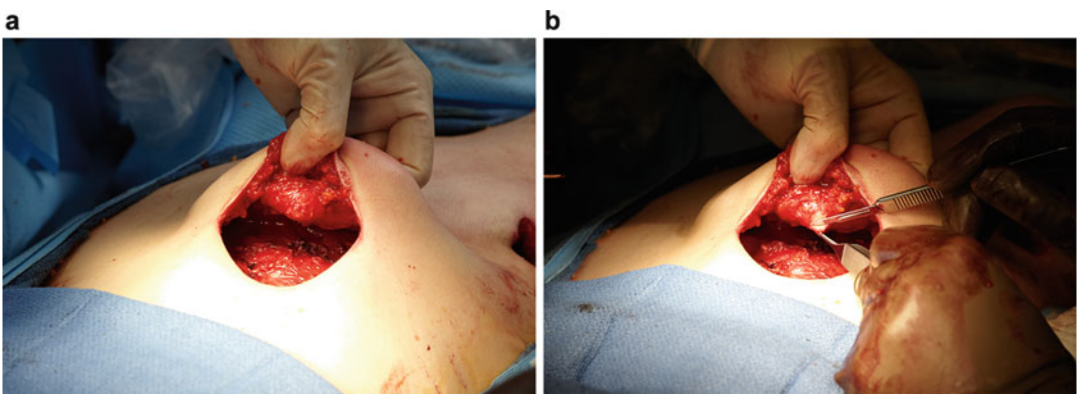

Fig 8.7 (**a**, **b**) View of the dissected underside of the nipple-areolar complex. (**b**) Taking a biopsy of the base of the nipple

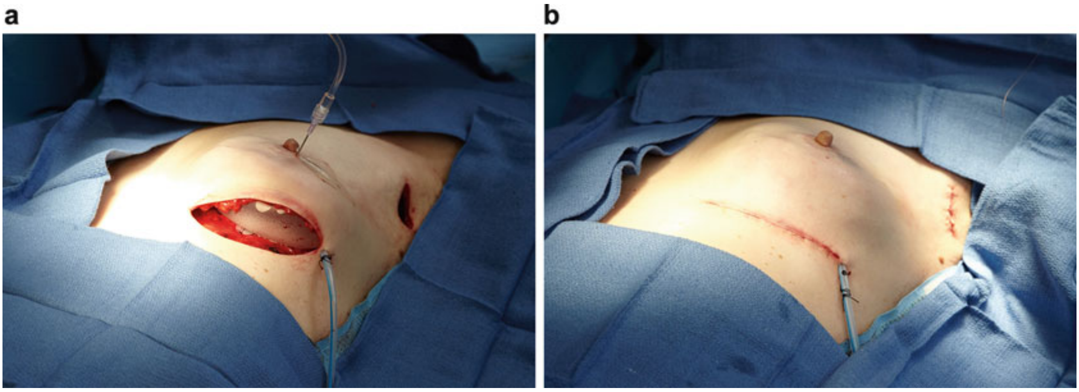

Fig 8.8 (**a**) Partially inflating a suprapectoral tissue expander with single drain in place. (**b**) Closure of both incisions

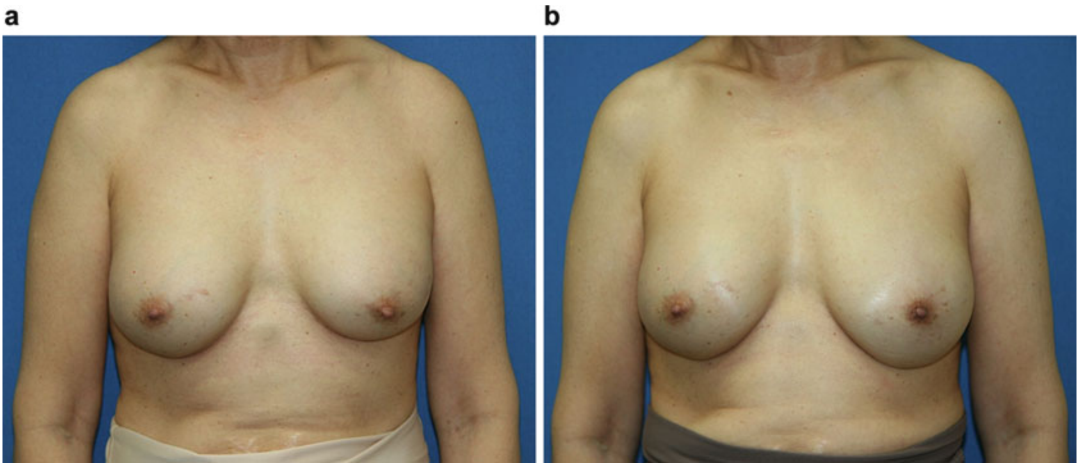

Fig 8.9 Pre-op (**a**) and post-op (**b**) views of a previously augmented 59-year-old female who underwent a left NSM

peri-operatively are continued orally upon discharge from the hospital until the patient's drain(s) are removed.

Figure 8.9a, b demonstrates the outcome of a 59-year-old female who underwent left nipple-sparing mastectomy for moderately differentiated invasive ductal carcinoma. Her history includes previous bilateral augmentation mammoplasty. A preoperative photograph is depicted on the left. She initially underwent prepectoral placement of a 275 cc tissue expander filled to a total volume of 120 cc. Five months later a 400 cc silicone gel implant was placed. The picture on the right is her final result nearly 2 years following final implant placement.

Our Experience

Over the past 11 years, the senior author (JKH) has performed 374 areolar sparing (AS) ($n = 19$) or nipple-sparing ($n = 355$) mastectomies (Fig. 8.10). A retrospective chart review was conducted on 237 patients (236 women and 1 male) who underwent either AS or NSMs during the time period November, 2004 through September, 2015. Pertinent patient data included patient age, sex, comorbid conditions, family breast cancer history, cancer type and stage, operative approach, complications, and neoadjuvant/adjuvant therapies. All 237 patients underwent disease characterization using digital

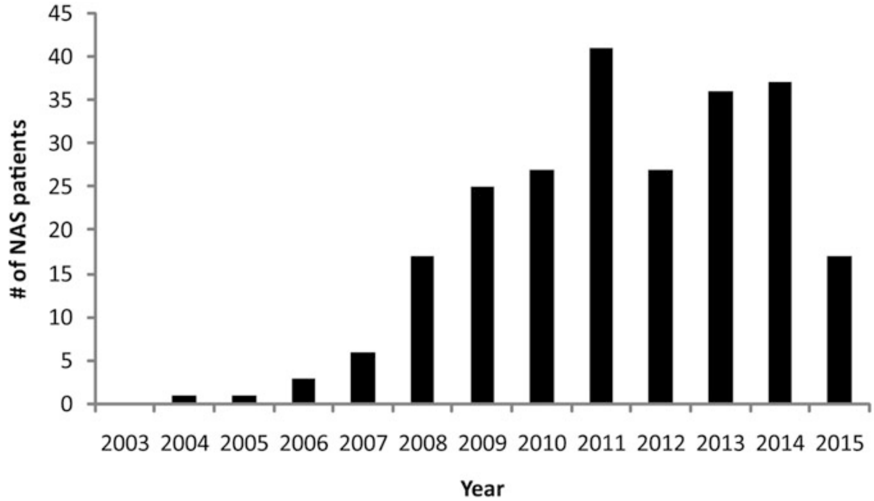

Fig. 8.10 Frequency of NSMs per year by the senior surgeon. Starting in 2012, NSMs were being performed more frequently at St. Joseph Hospital by other surgeons which impacted the senior surgeon's experience

mammography, high-resolution breast ultrasound, and breast magnetic resonance imaging (MRI). Additionally, each patient's case was subjected to review at the weekly multidisciplinary breast conference. Nipple-areolar complex involvement, bloody nipple discharge, or inflammatory breast cancer precluded patients from undergoing AS or NSM. However, lymph node involvement, often necessitating neoadjuvant chemotherapy and/or postoperative radiation therapy were not considered exclusion criteria. The decision to proceed with mastectomy for cancer treatment was multifactorial and included patient choice, extent of breast involvement, and the presence of multicentric disease. One surgeon (JKH) performed all of the mastectomies included in this study and one plastic surgeon (AHS) performed the majority of the post-mastectomy reconstructions.

Two-hundred and thirty-eight (63.6 %) NSMs were performed in 227 patients for cancer intervention and 136 (36.4 %) were prophylactic. The average patient age was 51 years (range, 28–77 years). One-hundred one patients (42.6 %) had a family history of breast cancer, which included 31 patients (13.1 %) who were *BRCA1/2* gene positive. It is important to note that not all patients underwent genetic testing. Past medical histories were significant for heart disease ($n=9$), hypertension ($n=52$), diabetes mellitus ($n=12$), stroke event ($n=4$) and smoking ($n=31$). The histological composition of the cancers included invasive ductal ($n=165$), ductal carcinoma in situ ($n=69$), invasive lobular ($n=22$) and malignant phyllodes ($n=1$). There were two patients (0.54 %) with a positive biopsy of the nipple base, resulting in excision of the nipple-areolar complex during a subsequent operation. Of the patients who were *BRCA1/2* gene positive, two patients who had not developed cancer underwent bilateral prophylactic NAS mastectomies. Twenty-two of the 29 remaining patients had risk-reducing contralateral prophylactic AS or NAS mastectomies.

Tumor markers are measured on all breast cancer cases. We routinely check for estrogen receptor (ER) and progesterone receptor (PR) positivity and Her2/neu in all invasive cancers. One-hundred eighty-eight patients were ER and/or PR positive, 51 were Her-2/neu positive, and 25 were triple negative. Sixty-eight patients underwent neoadjuvent chemotherapy, 67 underwent adjuvant chemotherapy, 131 received adjuvant anti-estrogen therapy and 54 received postoperative radiation therapy to their mastectomy sites, axillae, and supraclavicular regions.

Three-hundred and thirty-six AS or NSM's (90 %) were performed using an inframammary incision. Fifteen radial incisions and 23 nonradial, including 21 Wise pattern incisions, were used for the remaining 38 mastectomies. In these 26 patients, deviation from the inframammary incision was due to a previous partial mastectomy or breast biopsy and in some instances was necessary to achieve breast symmetry.

Four patients (1.7 %) in our study experienced postoperative bleeding requiring operative intervention. Thirty-three (13.9 %) received antibiotics for presumed early infection, of which 28 (7.5 % of all mastectomies) required removal of their tissue expanders.

Full-thickness loss of the NAC or surrounding skin occurred with 13 mastectomies (3.5 %) in a total of 13 patients, which is comparable to what is reported in the peer-reviewed literature [4]. One of these, 13 patients experienced full nipple-areolar loss, which is thought to have resulted from a 6×3 cm area of adjacent subdermal fat thinning that was necessary to obtain adequate tumor-free margins. Following removal of the nipple-areolar eschar and tissue expander, the patient underwent delayed breast reconstruction. Analysis of the remaining 12 patients who experienced full-thickness loss, revealed the following factors to be common among those who developed this complication: past or current tobacco use, concurrent mastopexy, postoperative radiation, adjuvant chemotherapy, and systemic steroids or antimetabolites for chronic disease management.

The mean patient follow-up for the described cases was 47.32 months (range 3–133 months, standard deviation 24.08 months). Nine patients experienced recurrence of their cancer (3.8 %) None of these cases involved the nipple. One patient (0.4 %) developed Paget's disease of the areola 34 months after an AS mastectomy, which was promptly treated with resection of the areola. Histological examination of the nipple demonstrated that ductal carcinoma in situ was not present in the nipple at the time of the AS mastectomy. Nearly 9 years later, she is disease-free and doing well. No consensus has been reached in the current literature regarding the exact incidence of Paget's disease as a local recurrence following nipple-sparing mastectomy. However, following breast conserving therapy, the incidence of Paget's disease appears to be between 2.2 % and 13.3 % of local recurrences [3, 5–8]. In 2012, Lohsiriwat et al., retrospectively analyzed 861 nipple-sparing mastectomies performed at the European Institute of Oncology from 2002 to 2008 with the specific goal of identifying Paget's disease local recurrence. Among these patient's, the local recurrence rate was 4.18 % (n = 36). Among these recurrences, 7 (0.8 %) were Paget's disease with an average latency of 32 months. All seven patients experiencing a Paget's disease local recurrence exhibited primary tumors that were estrogen receptor (ER) and progesterone receptor (PR) negative and six of the seven had overexpression of HER2/neu, a marker of aggressive disease potential [9]. In our single Paget's disease local recurrence, the initial retroareolar biopsy as well as the final nipple histology did not reveal any retroareolar disease. The molecular profile was typical of Paget's disease recurrence in that the primary tumor was ER/PR negative with HER2/neu overexpression. Perhaps the overall primary tumor biology is more closely associated with the potential for Paget's disease local recurrence than previously thought.

The remaining eight recurrences were typical of patients who have undergone skin-sparing mastectomies and experienced locoregional recurrence of their cancer in that they had poor tumor differentiation, large tumor size, node-positive disease, and advanced tumor stage as defined by the American Joint Committee on Cancer (AJCC) at the time of mastectomy [10, 11]. In our study, the average latency between mastectomy and disease recurrence was 39 months. Two patients received neoadjuvant chemotherapy, three received adjuvant chemotherapy, and four underwent radiation therapy. Four of the eight patients presented with poorly differentiated invasive ductal carcinoma, one with poorly differentiated invasive lobular carcinoma and three with high-grade ductal carcinoma in-situ. Five patients were ER/PR positive, while one was triple negative. Three patients were Her2/neu receptor positive. The average tumor size was 4.6 cm. All patients with invasive disease were at least stage IIa (range IIa-IIIa) at the time of initial treatment.

In a comprehensive review of the peer-reviewed literature, Mallon et al. identified 23 studies that performed therapeutic NSM for primary breast cancer. The mean follow-up time was 38.4 months. The overall incidence of NAC recurrence was 0.9 %. The incidence of skin flap recurrence was 4.2 %. Eleven of the studies included in this analysis excluded patients based on tumor-to-nipple distance, five for tumor size, four for lymph node status and four for the use of neoadjuvant chemotherapy [12]. These parameters were not used to exclude patients in our series. Since that article's publication in 2012, several other studies have substantiated these recurrence rates. In 2014, a study by Wang et al. from the University of California, San Francisco reviewed 981 cases in 633 patients over an 8-year period. The overall 5-year cumulative incidence of locoregional recurrence was 3.0 %. There were no observed recurrences in the nipple-areolar skin. As described in their article, patients were eligible for NSM even if the tumor was only 1 cm from the nipple as long as a preoperative MRI, which was not ordered in every case, did not demonstrate direct tumor involvement of the NAC. Patients with clinical stage II and III disease underwent neoadjuvant chemotherapy and were restaged prior to their NSM [13]. In order to meaningfully compare complication and recurrence rates across the literature, attention must be paid to the characteristics of the patient population within each study. As such, the broadened indications used by Wang et al. most closely approximate those used to select patients for inclusion in our series. Their partial or complete full-thickness nipple necrosis rate was 3.8 %, which was comparable to our experience at 3.5 %, but higher than the average of 2.9 % reported in the literature. Our overall incidence of tissue expander infection requiring explantation was 7.5 %. This is comparable to the article by Wang et al. who experienced infection-related implant loss in 8.2 % of their patients [13].

There were five observed deaths in our patient population under study. One patient stands out in particular as she presented with stage IV invasive ductal carcinoma of the left breast. Her young age and optimism warranted bilateral NSM, the right being prophylactic. Despite tolerating the procedure well, liver metastasis rapidly developed and the patient died before completing her final post-mastectomy reconstruction. Of the remaining four patient deaths, one patient was BRCA positive with bilateral disease at the time of initial presentation and another progressed to stage IIIC despite the administration of neoadjuvant chemotherapy. The remaining two had poorly differentiated ductal carcinomas, one of which was triple negative. Due to the progression of their disease and the development of metastasis, all four patients subsequently passed away.

Throughout our 11-year history of performing NSMs in the community setting we have maintained a locoregional recurrence rate comparable to that which has been reported in the peer-reviewed literature as non-inferior to the skin-sparing modified radical mastectomy. There is a dearth of literature to which our experience can be directly compared as most of the published series are based out of major academic centers or cancer institutes. Our inclusion criteria may be considered more assertive when compared with many of the publications available for review. Our complication profile has also been quite satisfactory. The central pillar to our strategy has been the close communication between members of the breast program team. We believe that excellent surgical outcomes are owed to the level of collegiality between the oncologic and reconstructive surgeons as well as all team members. Operative planning must be pursued jointly on a case-by-case basis such that the ultimate reconstructive outcome is optimized. Although not feasible in every setting, we have found that intraoperative assistance by the plastic surgeon during the extirpative portion of the case helps in achieving this goal.

Nipple-sparing mastectomy has been vetted as an oncologically sound procedure in properly selected patients. Nipple-sparing mastectomy is not just a procedure reserved for those patients receiving treatment in a large academic institution, but should be offered in all settings, including the community-based hospital.

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9 Reducing Complications and Margin Issues with Nipple-Sparing Mastectomy

Alice P. Chung and Armando E. Giuliano

Introduction

With advancements in reconstructive techniques, breast imaging and genetic testing, there is a rising rate of mastectomy with an increase in demand for improved cosmesis and better quality of life. Nipple-sparing mastectomy (NSM) with immediate reconstruction has become the preferred surgical approach for the treatment of breast cancer or prophylaxis in appropriately selected patients. To master this technique, one must minimize postoperative complications, reduce the need for secondary operations, and provide optimal local control. This chapter addresses complications and margin issues that are associated with NSM, and provides evidence-based recommendations on how to prevent and manage these potential problems.

Postoperative Complications

Postoperative complications associated with any operation include bleeding, infection, and poor wound healing, but in patients undergoing NSM these complications can ultimately lead to increased cost, patient dissatisfaction, and loss of reconstruction. It is important to recognize these complications early and identify patients who may be at increased risk in advance. As is the case in all operations, careful patient selection is the key to minimizing complications.

There are complications associated with patient factors and those related to surgical technique. Known patient risk factors for postoperative complications include advanced age, positive smoking history, and presence of medical comorbidities, including cardiovascular disease, diabetes, and obesity [1–3]. These factors increase the likelihood of anesthetic or medically related complications as well as wound complications. In NSM wound complications can be further categorized into hematoma, seroma, cellulitis, abscess, necrosis of the nipple–areolar complex (NAC) (partial or complete), skin flap necrosis (requiring or not requiring operative debridement), implant loss, and capsular contracture. The most common complication after NSM with reconstruction has been reported to be wound complications with skin flap and nipple necrosis comprising the majority of wound complications.

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Table 9.1 Reported incidences of postoperative complications following mastectomy with or without reconstruction

Complication	Reported incidence (range), %
Pulmonary embolus [4–6]	0–0.2
Cardiac event [6]	<0.1
Deep venous thrombosis [4–7]	0.3–0.7
Pneumonia [6]	0.2
Bleeding [4, 5, 7]	0.4–11.6
Infection (cellulitis) [4, 6, 8]	1.6–2.8
Infection (abscess) [4, 6]	0.1–1.8
Nipple necrosis (partial) [9–12]	0–38
Nipple necrosis (complete) [9, 11–13]	2–17
Skin flap necrosis (minor) [9, 12, 14, 15]	5.2–8
Skin flap necrosis (requiring operative debridement) [9, 14, 16]	0.6–5
Loss of reconstructed breast [1, 2, 9, 10, 16]	0.8–2.8

The reported incidences of the most common complications are listed in Table 9.1.

Skin Flap and Nipple Necrosis

Ischemia of the skin and nipple can lead to skin flap or nipple necrosis. These events place the patient at increased risk for infection, operative intervention, and implant loss and are likely to result in a significant level of patient dissatisfaction [17–19]. Nipple loss due to ischemia is a complication that is unique to NSM, but the factors that increase risk for skin flap necrosis are similar to factors that increase the risk for nipple necrosis. Patient characteristics (i.e., age, ethnicity [20], smoking history [9, 21, 22], history of diabetes [13, 14], BMI [9, 10, 13, 14], breast cup size, prior irradiation, prior breast surgery [9, 11, 14, 23], indication for mastectomy (malignancy versus prophylaxis), location of the NAC [13, 24]), surgical technique (type of mastectomy incision, mastectomy technique [14, 15, 25–28], type of reconstruction [1, 4, 11, 13, 22, 23, 29], volume of expander fill [13, 25, 27], unilateral versus bilateral mastectomy [1, 30], use of prosthetic material [13, 23, 31], concurrent axillary surgery [13]), tumor characteristics (more advanced cancer stage [32], aggressive tumor characteristics [9, 33], use of neoadjuvant chemotherapy [34]), surgeon experience [13] and post-mastectomy radiation have all been implicated as factors that may increase risk of ischemia to the nipple.

There are conflicting results among retrospective studies that have assessed patient age as a potential risk factor for complications following NSM and skin sparing mastectomy. Some studies have found that older age is associated with higher rates of necrotic complications [2], while others have determined that young age is a predictor of complications, and still others have found no association between patient age and complication rates [9, 20, 21, 35]. It is unclear from the current literature whether age alone is a significant risk factor for necrotic complications following NSM.

Ethnicity has been shown to be associated with incidence of wound complications. De Blacam and colleagues assessed over 10,000 patients who underwent mastectomy and found that Asian and Pacific Islanders had lower rates of wound infection compared to other races [20]. Akinyemiju et al. studied over 71,000 women treated for breast cancer and found African-American race to be associated with a higher rate of postsurgical complications [36]. The study included wound complications, infections, urinary, pulmonary, gastrointestinal, or cardiovascular complications. Butler et al. compared postoperative morbidity of 138 African-American women to 654 Caucasian women treated with mastectomy and free-flap autologous reconstruction and found no difference in either major or minor postsurgical complications [37]. Studies on how ethnicity impacts complications specifically in NSM are limited.

Multiple studies on risk factors in NSM have found smoking to be a significant risk factor for nipple necrosis [3, 10, 13, 14, 20–22]. Gould et al. evaluated nipple necrosis in 233 cases of NSM and found that smokers had a nipple necrosis rate of 44 % compared to 15 % in non-smokers. Fischer and colleagues identified over 9300 patients treated with mastectomy and immediate tissue expander reconstruction and identified active smoking as a highly significant risk factor for implant or expander loss [1, 2]. In Colwell et al.'s evaluation of complications after NSM, smoking was found not only to be a risk factor for nipple necrosis but was also associated with having multiple postoperative complications, including infection, hematoma, and implant loss. Smoking compromises the arterial supply to tissues, and the nipple and mastectomy flaps are particularly vulnerable because of the diminished blood supply caused by removal of the breast, as well as the large dead space underlying the wound. Patients who smoke should be counseled that they are at increased risk for postoperative complications and smoking cessation prior to surgery should be encouraged.

There are a number of physiologic factors that contribute to deficient wound healing in patients with diabetes, including impaired growth factor production, angiogenic response, macrophage function, collagen accumulation, and fibroblast migration and proliferation [38]. Because of these factors, diabetes has been postulated to be a risk factor for nipple necrosis. De Blacam et al. conducted a prospective study of over 10,000 patients undergoing mastectomy and found that diabetes was a significant independent risk factor for wound complications, namely infection [20]. Matsen and colleagues evaluated risk factors for skin flap necrosis in over 600 patients undergoing mastectomy with immediate reconstruction and found that diabetes was not a significant risk factor for mild necrosis [14]. On univariate analysis, diabetes was associated with moderate and severe necrosis, but this finding did not persist on multivariate analysis. Gould et al. compared the rates of nipple necrosis in patients with comorbidities versus those who did not have comorbidities and found that patients with diabetes or hypertension had a much higher rate of nipple necrosis than those who did not have either medical condition (58 % vs. 16 %, p –0.09) [13]. Diabetes may more likely be a significant risk for nipple necrosis when combined with other risk factors.

Obesity is another patient characteristic that has been associated with necrotic complications after NSM. De Blacam prospectively studied over 26,000 patients treated with breast cancer surgery and found BMI > 25 kg/m^2 to be the strongest predictor of wound complications when compared to multiple other comorbidities (i.e., smoking, diabetes, hypertension, heart failure, steroid use, chemotherapy, or radiation therapy) [20]. Fischer et al. studied over 15,000 cases of breast reconstruction and found an incidence of obesity of 27 %. The authors found that progressively higher BMIs were associated with higher rates of complications, including wound complications and loss of reconstruction [39]. Among studies of NSM, high BMI was strongly associated with skin and nipple necrosis [10, 13, 14].

Breast cup size is an important factor because it is associated with the length of the mastectomy flaps. The larger the breast cup size, the longer the flap and the higher the risk of ischemia to the skin flaps and NAC [9, 13, 14, 23, 40]. Gould and colleagues found that patients with a C cup breast size or larger had a 34 % risk of nipple necrosis, whereas those with A–B cup sizes only had 6 % risk of nipple necrosis [13]. The authors attribute this finding to longer distance between the nipple and surrounding blood supply from the chest wall, potential for decreased vascular perfusion to the skin envelope during dissection, and increased manipulation of the skin envelope. Wang et al. compared rates of necrosis in patients who had NSM with tissue expander reconstruction with breast size greater than 352 g (n = 115) to those with breast size less than 352 g (n = 109) [40]. They found that the larger sized group had an 8.1 % higher rate of superficial nipple necrosis, but found no difference between the groups with respect to necrosis requiring operative intervention. Based on these studies, larger breast size alone should not be a contraindication to NSM. However, when combined with additional risk factors, counseling regarding increased risk may be warranted in patients with larger breast size.

Women with significant ptosis are considered poor candidates for NSM due to excessive skin flap length and risk of ischemia [24]. In addition, there is the perception that the NAC cannot be reliably repositioned on a breast mound after mastectomy. Therefore, they are considered better candidates for skin-sparing mastectomy with subsequent nipple reconstruction. Gould et al.

evaluated risk factors among 113 patients undergoing NSM and did not find an association between ptosis and risk of nipple necrosis [13]. However, the authors did not report the number of patients with ptosis in the study. Chidester and colleagues report successful free nipple grafting as a technique for sparing the NAC in a small series of five patients with significant ptosis undergoing mastectomy. They reported no nipple losses and only one patient who had partial nipple loss [24]. Doren et al. performed free nipple grafting on a slightly larger series of patients undergoing mastectomy ($n = 36$) and reported no complete nipple losses with an average graft take of 94 %, which are similar rates seen with reduction mammoplasties [41]. DellaCroce et al. published a series of 116 NSM cases performed in patients with grade 2–3 ptosis who had immediate autologous tissue flap reconstruction followed by delayed mastopexy [42]. The autologous flap provides vascular ingrowth to support perfusion to the NAC despite the complete incisional interruption during mastopexy. The authors reported a 7.7 % rate of wound dehiscence, 3.4 % rate of skin flap necrosis with no cases of NAC necrosis, demonstrating that mastopexy after NSM in patients with severe ptosis is possible.

Prior irradiation is considered a significant risk factor for ischemia following mastectomy. Multiple studies evaluating NSM in patients who have received prior radiation therapy or post-mastectomy radiation therapy demonstrate that irradiated patients have a higher risk of postoperative complications [43–47]. One of the largest recent series was published by Sbitany and colleagues who compared outcomes of NSM in 727 non-irradiated breasts, 63 previously irradiated breasts, and 113 breasts that were irradiated after NSM [45]. Any radiation was associated with a 21 % increased rate of infection requiring antibiotics, and a 19 % increased rate of expander loss. Radiation prior to NSM was associated with a higher rate of wound breakdown. All groups had a similar rate of nipple or areolar necrosis. Tang and colleagues studied a similar number of patients that were divided into three cohorts (816 with no radiation, 67 with prior radiation, and 97 who had post-mastectomy radiation) [47]. They also found that radiation before or after NSM increased overall complications (10, 22, and 18 % for the respective cohorts), but they found a higher rate of nipple loss in the radiated breasts, though infrequent (1, 4, 4 %, respectively). Other complications reported included malposition of the NAC (17–28 %), capsular contracture (12–17 %) and reconstruction failure (3–8 %). Despite the higher rate of complications, the rate of nipple retention and reconstruction retention remained high in patients treated with radiation.

History of prior breast surgery may increase the risk of wound complications in NSM due to existing scars that may compromise the blood supply to the NAC. In Matsen's prospective study of skin flap necrosis in 606 mastectomies with reconstruction, the authors found history of prior breast reduction to be strongly associated with increased rates of necrosis [14]. Dent and colleagues reviewed their series of 398 NSM cases where 41 patients had prior cosmetic breast surgery, including reduction mammoplasty, augmentation, and mastopexy [48]. The authors performed NSM with implant-based reconstruction using the inframammary fold incision with an average time interval of 8 years between the time of the cosmetic surgery and NSM. Patients with prior breast surgery had higher rates of mastectomy flap ischemia and hematoma compared to those who had never had prior cosmetic surgery, and among those who had prior breast surgery, single stage reconstruction was associated with higher rates of full-thickness ischemia. The authors concluded that patients with history of prior cosmetic breast surgery should be cautiously considered for NSM with implant-based reconstruction, especially in the setting of single stage reconstruction.

The indications for mastectomy have been evaluated as potential risk factors for complications following NSM. Those who receive NSM for the treatment of malignancy have *not* been found to have a higher rate of complications when compared to patients having NSM for risk reduction [12, 49] Among patients treated with NSM or skin-sparing mastectomy for risk reduction, Gould et al. found a significantly higher rate of overall complications in patients who had

NSM compared to those having skin-sparing mastectomy [13], but the addition of axillary surgery did not affect the rates of complications in either group. In Lee's study of 130 patients undergoing NSM with reconstruction, among those who had tissue expander reconstruction, higher degree of axillary intervention was correlated with higher rates of wound complications, specifically skin flap necrosis [29].

A number of studies have identified incision type as a predictor of skin flap or nipple necrosis [9, 10, 21, 22, 49, 50]. The most common types of incisions in NSM include radial, periareolar, inframammary, mastopexy, and transareolar. Endara et al. conducted a review of 48 studies on NSM with 11 of the studies reporting complication rates according to incision type [11]. The combined nipple necrosis rate in procedures where a radial incision was used was 8.8 %. This rate was similar to 9 % with the inframammary incision and increased to 17 % with the peri-areolar incision. The mastopexy incision was associated with the lowest rate of nipple necrosis (5 %). Transareolar incision resulted in an unacceptably high rate of nipple necrosis (82 % in 11 procedures), and is not recommended. Among patients treated with post-mastectomy radiation, Peled and colleagues found a higher rate of incision breakdown with the inframammary incision compared to other incision types (21 % versus 10 %) [50]. In addition, the authors found that when inframammary incision breakdown occurred, a higher rate of implant loss was observed. This suggests that the inframammary incision should be used with more caution in patients planning to receive post mastectomy radiation.

Technique of mastectomy has been investigated as a factor for increased rates of skin flap necrosis. There are conflicting reports regarding the association of the tumescent mastectomy technique with skin flap or nipple necrosis. Among several series of risk factor analyses for NSM, Mlodinow et al. and Chun et al. found tumescent technique to be associated with skin flap necrosis, while Khavanin et al. and Matsen et al. did not find a correlation between tumescent technique and necrosis [14, 15, 25, 27]. Seth and colleagues compared outcomes in 333 patients who had mastectomy with tumescent technique to 565 patients who had mastectomy without tumescence. The authors found that the total complication rate was significantly higher in the tumescence group (23 %) compared to the non-tumescence group (18 %), with higher rates of operative complications, non-operative complications, and major skin flap necrosis in the tumescence group [26]. Abbott and colleagues compared complication rates in 70 mastectomy cases performed with tumescent technique to 64 cases performed with electrocautery [28]. and the authors did not observe a significant difference in complication rates between the two groups. The tumescent technique can be safely utilized in NSM, but perhaps caution should be used with this technique in patients with multiple risk factors for complications.

The use of reconstruction adds complexity to the mastectomy and one would expect an increase in the incidence of postoperative complications. Fischer and colleagues compared complication rates in 30,440 women treated with mastectomy without reconstruction to 12,383 women who had mastectomy with tissue expander reconstruction and found that reconstruction did not confer increased risk in medical, wound, or overall 30-day morbidity [4]. Kim et al. compared complication rates in 70 patients who had NSM with autologous reconstruction to 60 patients treated with NSM and tissue expander reconstruction and found that the autologous reconstruction group had a significantly lower rate of complications (10 % versus 23 %) after adjusting for factors such as age, body mass index, breast size, and tumor factors [29]. The authors hypothesize that higher rates of necrotic complications in tissue expander reconstruction may be due to the dead space beneath the mastectomy flap which is more reliably obliterated in autologous reconstruction. The fluid in the dead space can interfere with revascularization of the skin flaps, thereby increasing the risk of necrosis. In a systematic review of 48 studies of NSM performed by Endara et al., 45 % of cases were two stage tissue expander reconstruction with nipple necrosis rate of 4.5 %, 41 % of cases were single stage direct implant reconstruction with a 4 % nipple necrosis rate, and 14 % were autologous tissue reconstruction cases which had a nipple necrosis rate of 17 % [11]. The authors did not attempt to explain the difference in nipple necrosis rates observed; however, there were only two studies of autologous reconstruction included in the pooled analysis, one study had a 23 % rate of nipple necrosis and the other study only had 2 % with nipple necrosis. In a risk analysis of necrotic complications following 170 NSM in which 37 % of NSM cases had autologous reconstruction, Garwood et al., identified autologous reconstruction as an independent risk factor for necrosis [22]. The data appears to be somewhat conflicting with regards to whether type of reconstruction increases rates of necrotic complications and is limited by small numbers of patients and presence of multiple confounders.

Volume of tissue expander fill can affect the blood supply to skin flaps. Therefore, higher fill volumes should be associated with higher rates of skin flap and nipple necrosis. Mlodinow and colleagues reviewed over 1560 mastectomies with tissue expander reconstruction cases and found that 8.6 % experienced skin flap necrosis [15]. Regression analysis identified high intraoperative tissue expander fill volume (>67 % of total expander volume) to be strongly correlated with skin flap necrosis. Lee et al. assessed complication rates in 130 patients who had NSM, 60 of whom had tissue expander reconstruction, and did not find expander fill volume to impact rate of complications [29]. The mean percentage of volume fill was only 34 %, which is much lower than observed in Mlodinow's study.

The use of prosthetic or biological material, such as acellular dermal matrix, for coverage of tissue expanders or implants has increased over the last decade. Several investigators have evaluated the impact of its use on postoperative complications. Peled et al. conducted a prospective study of 450 cases in 288 patients who had NSM with or without placement of acellular dermal matrix [31]. They found that acellular dermal matrix reduced the incidence of major complications, including infection, unplanned reoperation, and implant loss. In a risk analysis performed by Gould et al., use of biomaterials was not associated with a significant difference in rate of nipple necrosis [13]. Dent et al. reviewed risk factors for NAC ischemia in 318 NSM cases and found use of acellular dermal matrix to be significantly associated with ischemia of the NAC [23]. While the impact of biomaterials on the rate of nipple necrosis is unclear, proponents feel there may be a reduction in the rate of more significant complications that warrant its use in breast reconstruction.

Use of methylene blue dye has been associated with skin necrosis in surgical patients. Lee et al. reported six cases of skin necrosis associated with use of methylene blue dye in patients undergoing mastectomy and sentinel node biopsy followed by immediate implant-based breast reconstruction [51]. Reyes and colleagues reported two cases of severe necrotic complications of methylene blue use in breast surgery that required multiple surgical debridements and negatively impacted the cosmetic outcome in both cases [52]. In patients undergoing sentinel node biopsy at the time of NSM, lymphatic mapping with either Isosulfan Blue or radioisotope should be strongly considered. Methylene blue should always be diluted to avoid necrosis.

The incidence of contralateral prophylactic mastectomy (CPM) has increased dramatically in the last decade, with reported rates increasing by 150 % in the last decade [53]. The addition of CPM has increased the potential for more surgical complications. Osman and colleagues compared complication rates in 3722 patients who had unilateral mastectomy to 497 patients treated with bilateral mastectomy for breast cancer treatment [30]. The authors found a significantly higher rate of postoperative complications in the bilateral mastectomy group (5.8 %) compared to the unilateral group (2.9 %) at 30 days. Wound complications were the most common complication in both groups. Type of reconstruction was not reported in this study. Silva et al. identified over 20,000 patients from the National Surgery Quality Improvement database who had either unilateral mastectomy ($n = 13{,}268$) or bilateral mastectomy ($n = 7233$) with reconstruction [54]. The authors found that bilateral mastectomy was associated with longer hospital stays, higher rates of transfusion, reoperation, and wound disruptions. There was no difference between the unilateral and bilateral mastectomy groups in terms of medical complications. Sharpe and colleagues reviewed the National Cancer Database, which included 315,278 patients who had unilateral mastectomy, 75,437 patients who had bilateral mastectomy, and 97, 301 had reconstruction [55]. They reported no difference in 30-day mortality or readmission rates between unilateral and bilateral mastectomy groups but found significant delays to surgical and adjuvant therapy with bilateral mastectomy, regardless of whether reconstruction was performed. There has not been any such comparison specifically in NSM reported in the literature.

NSM was initially introduced for selective use in early breast cancer due to concerns regarding oncologic safety. The majority of early studies did not identify an association between tumor characteristics and overall complication rates [22, 35, 56]. Lohsiriwat et al. evaluated the effect of tumor features on the rate of nipple necrosis in 934 NSM performed for breast cancer with the only exclusion criteria being NAC involvement by imaging or a positive retroareolar margin identified by intraoperative frozen section [33]. They found no association of clinicopathologic features, including tumor size, nodal status, histology, tumor grade, presence of extensive in situ component, lymphovascular invasion, tumor receptor status, and Ki67, with nipple necrosis. Burdge et al. performed skin sparing mastectomy or NSM on 60 patients with locally advanced disease who had post-mastectomy radiation [57]. They report a wound and necrosis complication rate of 16.7% and implant loss in 5% which is comparable to reports in patients with earlier stage disease. Santoro and colleagues performed 186 NSM in patients with breast cancer; 51 had neoadjuvant chemotherapy [58]. The authors found no correlation between use of neoadjuvant chemotherapy and overall complication rate or nipple necrosis rate. It appears that NSM can be performed in patients with larger, more aggressive tumors with complication rates comparable to those with earlier stage disease even after chemotherapy.

In summary, there are multiple factors that contribute to skin and nipple necrosis, and higher risks are associated with cases where multiple risk factors are present. Despite the relatively moderate incidence of wound complications associated with NSM, skin or nipple necrosis rarely leads to loss of reconstruction. Careful selection of patients is warranted for successful execution of NSM and caution must be exercised in high risk cases.

Techniques for Prevention of Nipple Necrosis

A number of techniques have been proposed to prevent nipple necrosis in high risk patients. Jensen and colleagues reported successful NSM in 20 high risk patients who were treated with a surgical delay procedure in an effort to maximize viability of the NAC [59]. The authors propose that creation of a surgical wound stimulates the body to improve blood supply to the wounded tissue. They selected patients who had breast ptosis, prior breast scars, or active smoking history who desired NSM. The patients were initially taken to the operating room for elevation of skin flaps directly beneath the NAC and surrounding breast tissue. Approximately 4–5 cm of surrounding breast tissue was undermined, and a biopsy of the nipple ducts was performed at this time. The incision was closed without removal of any breast tissue other than the sub-areolar biopsy. Definitive NSM with immediate reconstruction was then performed 7–21 days later. In two patients, the sub-areolar biopsy was positive for malignancy requiring subsequent removal of the NAC at the time of mastectomy. Of the remaining patients, all had survival of the NAC following NSM. This technique may increase surgical options for patients at high risk for nipple necrosis following NSM. Figure 9.1 shows an example of a patient who was at increased risk for nipple necrosis due to history of prior periareolar incision. The surgical delay procedure was performed and she was able to retain her native nipple–areolar complex despite experiencing an initial period of ischemic change in the

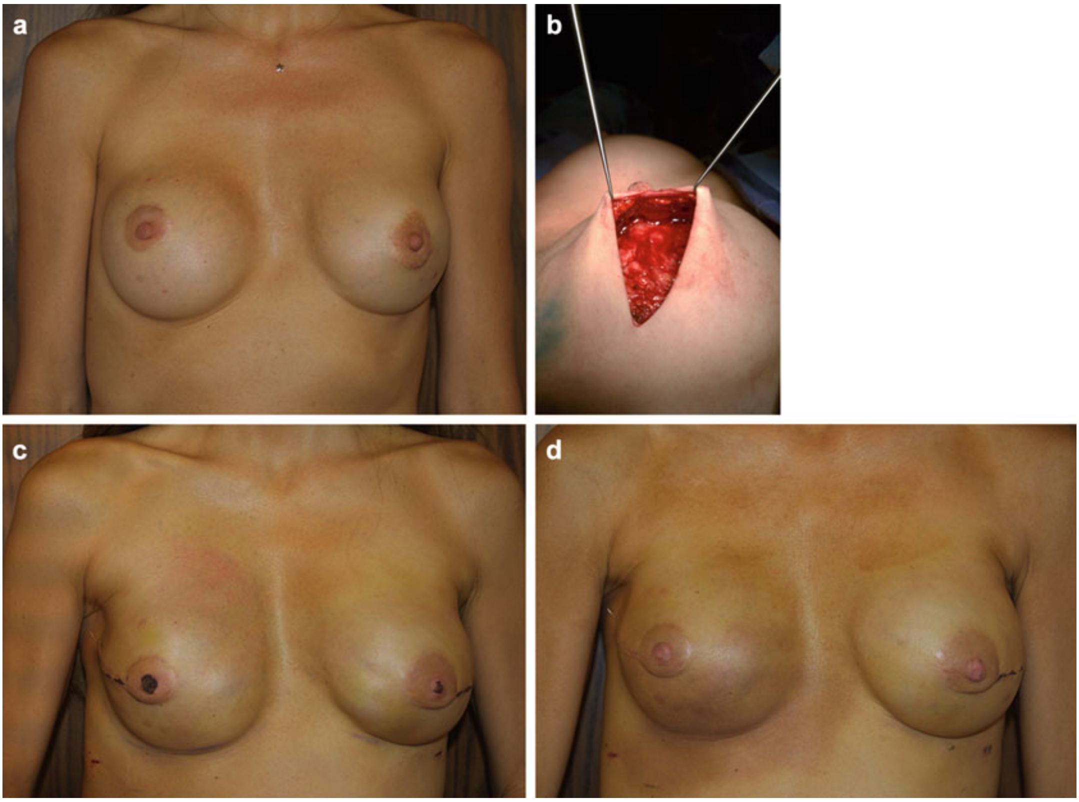

Fig. 9.1 (**a**) Patients with pre-existing periareolar scars are at high risk for nipple necrosis after nipple-sparing mastectomy because once the breast is removed, the entire blood supply to the remaining nipple–areolar complex must come from surrounding skin. Skin perfusion is known to be limited by surgical scars. (**b**) A surgical delay procedure works by stimulating blood supply to increase in tissues which will remain attached during and after the planned mastectomy. This delay procedure preserves all blood supply which might come from the surrounding skin (maintaining 360° skin perfusion) and separates the nipple–areolar complex from the underlying breast. Over the next 7–14 days, blood supply to the nipple from the surrounding skin improves. (**c**) Following mastectomy, the patient is seen to have sustained partial thickness injury to the nipples bilaterally but not full thickness nipple loss. (**d**) Two weeks following mastectomy and placement of breast implants, bilateral survival of the nipple–areolar complexes is evident

nipple. Figure 9.2 demonstrates the use of the surgical delay in a patient with severe ptosis who initially had nipple ischemia but ultimately was able to preserve her nipple–areolar complex.

Swistel and colleagues describe the use of preoperative Doppler ultrasound of the internal mammary artery perforators as a procedure to improve viability of the NAC in NSM with implant-based reconstruction [60]. Prior to NSM, location of the internal mammary artery perforators was identified by Doppler ultrasound and marked on the patient. During the NSM, the perforators corresponding to the Doppler mapping were then identified and spared. The authors compared outcomes of 97 NSM in which the internal mammary artery perforators were mapped to 97 NSM that did not have the vessels mapped by Doppler. The application of the Doppler mapping added an average of 4 min to the NSM procedure. There was no significant difference in wound complications between the two groups. The authors concluded that Doppler ultrasound may be a useful, inexpensive adjunct to improve NAC viability in NSM, but that their study was underpowered to draw any correlative conclusions about the various factors that may contribute to rates of skin or nipple necrosis.

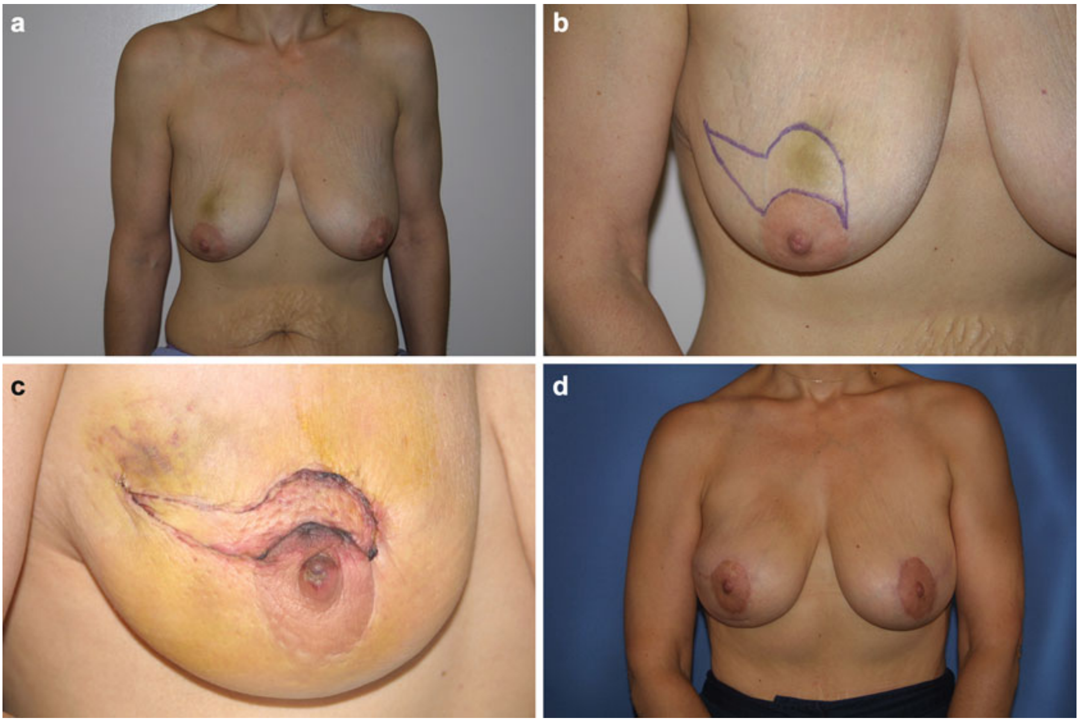

Fig. 9.2 (**a**) Patients with breast ptosis who are active smokers are generally considered to be poor candidates for nipple-sparing mastectomy. The distance from the suprasternal notch to the nipples in this patient was 27 cm. (**b**) A "hemi-batwing" incision is used to elevate the nipple–areolar complex off from the underlying breast. Undermining of the breast skin is done for 4 or 5 cm around the skin island so as to "delay" the nipple–areolar complex and the surrounding skin. (**c**) Undermining of the nipple–areolar complex and surrounding skin has resulted in signs of injury to the tissue but not in loss of the tissue. Improvement in blood supply which occurs as this tissue heals demonstrates the "delay phenomenon." (**d**) The patient is seen following a right mastectomy and free flap breast reconstruction with complete survival of the nipple–areolar complex. The left nipple–areolar complex was elevated using a "hemi-batwing" breast reduction. Thus, patients with breast ptosis who are active cigarette smokers can benefit from nipple-sparing mastectomy using the technique of the surgical delay

Intraoperative perfusion mapping using laser-assisted indocyanine green imaging has been reported as an effective method of defining vascular perfusion of the mastectomy skin to predict necrosis in breast reconstruction cases [61]. This technology has been successfully used intraoperatively to identify areas of poor vascular perfusion in time to make intraoperative decisions that may minimize complications in the postoperative period [62, 63]. It has not been shown to be cost-effective for use in all cases of mastectomy with reconstruction but perhaps may be reserved for cases where patients may be at increased risk of skin flap necrosis [64].

Once ischemia of the skin flap or nipple is identified postoperatively, there are techniques that may inhibit progression of ischemia and enhance survival of the skin or nipple. Nitroglycerin ointment is a topical vasodilator that increases local blood flow to the skin by relaxing the smooth muscle walls of the subcutaneous arteries and veins. Gdalevitch et al. conducted a randomized controlled trial evaluating the impact of topical nitroglycerin on skin flap necrosis in patients treated with mastectomy and reconstruction [65]. The target accrual was 400 patients, but the trial was stopped early due to proof of efficacy following the initial interim analysis. One hundred and sixty-five patients were randomized to receive either a single dose of 45 mg of topical Nitroglycerin or placebo at the time of placing the surgical dressing. With minimum follow-up of 27 days, there was a significant absolute difference in mastectomy flap necrosis rate of 18.5 %, with a rate of 15 % in the group that received Nitroglycerin compared to 34 % in the group that received the placebo. The application of a single postoperative dose of Nitroglycerin decreased the incidence of flap necrosis by 50 % and is a simple, cost-effective, efficacious method of reducing skin flap necrosis in patients undergoing mastectomy with immediate reconstruction.

Hyperbaric oxygen therapy has been shown to successfully salvage mastectomy skin flap necrosis in several case reports [66–68]. By using a closed chamber with increased atmospheric pressure and oxygen concentration, the partial pressure of oxygen in tissues can be increased. Patients may require multiple treatments to mitigate the consequences of ischemia of the skin or NAC, but the treatments are minimally invasive and well tolerated. Further research is needed to determine the role of hyperbaric oxygen in the treatment of skin flap ischemia, but it is currently an option that may have benefit in cases where skin or NAC viability is threatened.

The literature to support use of these more novel techniques remains limited at this time. As the use of NSM continues to increase, more data on methods of minimizing or preventing nipple and skin flap necrosis are likely to be obtained. We currently must rely on preoperative risk assessment and judicious patient selection to minimize wound complications of NSM.

Margin Issues in Nipple-Sparing Mastectomy

Positive margins following mastectomy have been reported to range from 5 to 12 %, and close or positive margin status after mastectomy has been associated with increased risk of local recurrence even in early node-negative breast cancer [69–71]. Margin involvement following mastectomy is an indication for either reoperation or radiation therapy, both of which can lead to significant patient dissatisfaction. Retroareolar margin involvement typically warrants removal of the NAC. When there is a positive margin in a location other than the retroareolar tissue after mastectomy, identifying the exact location on the skin flap where the margin is involved can be challenging. If re-excision is not possible, radiation therapy may be necessary. In the remaining section of this chapter, techniques of minimizing positive margins as well as management of positive margins will be discussed.

Prediction of nipple involvement would allow selection of patients for NSM with lower risk of positive retroareolar margins that may require subsequent NAC removal. Brachtel and colleagues studied occult nipple involvement in 316 mastectomy specimens, and found 21 % with occult nipple involvement [72]. Tumor factors that were strongly associated with occult nipple involvement on multivariable analysis included Her2 amplification, larger tumor size, and shorter tumor–nipple distance. Zhang et al. pooled data from 27 studies of NSM that investigated the risk factors for occult nipple involvement [73]. Significant predictors of nipple involvement included tumor–nipple distance ≤2.5 cm, nodal involvement, stage 3 or 4 disease, tumor size >5 cm, ER-negative status, PR-negative status, Her2-positive status, and DCIS as compared to invasive primary tumor. Several studies have suggested using preoperative breast imaging to predict nipple involvement [74–76]. Karamchandani et al. found that suspicious enhancement on MRI or suspicious findings on mammography within 20 mm of the nipple was predictive of nipple involvement in 85 % of cases. Ponzone and colleagues correlated imaging findings with pathologic findings in 112 NSM cases and found that the combination of intraoperative assessment of the retroareolar margin plus tumor to nipple distance on MRI yielded specificity and accuracy rates of predicting nipple involvement of 96.2 and 84.1 %, respectively.

Intraoperative frozen section analysis of the retroareolar tissue at the time of NSM is a reliable means of determining whether the NAC can be preserved. A positive intraoperative report allows immediate removal of the NAC, sparing the patient from a second operation to remove the NAC. In Brachtel's evaluation of occult nipple involvement in 316 mastectomy specimens, the authors found that a positive retroareolar margin correlated with occult involvement of the nipple papillae and distal nipple structures with a sensitivity of 0.8 and a negative-predictive value of 0.96 [72]. Duarte et al. compared accuracy, sensitivity, and specificity rates of frozen section, imprint cytology, and permanent histology in the evaluation of sub-nipple tissue for 68 NSM cases [77]. The authors found that the accuracy rates of frozen section and permanent histology were very similar and were better at predicting occult nipple involvement than imprint cytology (Table 9.2). False-negative rates in retroareolar biopsies have been attributed to incomplete excision of tissue beneath the nipple base as well as to underestimation by frozen section analysis of the retroareolar tissue fragments. The tissue frequently becomes distorted during frozen section causing difficulty in accurately assessing the margins. Piato and colleagues proposed a technique of frozen section analysis of retroareolar tissue that was reported to have an increased accuracy rate for prediction of occult nipple involvement [78]. The authors suggest using sharp dissection and cold bistoury for tissue dissection to avoid artifacts that can be caused by cautery. They excised 1.5 cm diameter of tissue below the nipple base, and had 4 μm histologic sections cut at 200 μm intervals. The false-negative rate of the frozen section analysis was only 1.3 % (Table 9.3).

Table 9.2 Comparison of frozen section, cytology, and permanent histology of sub-nipple tissue in predicting occult nipple involvement

	Frozen section (%)	Imprint cytology (%)	Permanent histology (%)
Accuracy	87	77	87
Sensitivity	50	38	63
Specificity	92	82	90
Negative predictive value	44	21	46
Positive predictive value	93	91	95

From Duarte GM, Tomazini MV, Oliveira A et al. Accuracy of frozen section, imprint cytology, and permanent histology of sub-nipple tissue for predicting occult nipple involvement in patients with breast carcinoma. Breast Cancer Res Treat 2015; 153: 557–563 with permission

Local recurrences following NSM have been reported to range from 0.6 to 6 % with follow-up ranging from 13 months to 5 years [22, 79, 82, 85, 86]. Kneubil and colleagues evaluated risk factors of locoregional recurrence in patients who had false-negative frozen section or close margins of retroareolar specimens [82]. The 5-year cumulative rates of locoregional recurrence and NAC recurrence were 11.2 and 2.4 %. Locoregional recurrence rates were highest in patients whose retroareolar biopsies contained atypia. In situ carcinoma as the primary tumor was a significant predictor of NAC recurrence. Lohsiriwat and colleagues analyzed 861 cases of NSM treated with electron beam intraoperative radiotherapy [87]. With mean follow-up of 50 months, 36 patients (4.2 %) presented with local recurrences, among which seven (0.8 %) presented with Paget's disease of the nipple. Treatment of the Paget's recurrences consisted of excision of the NAC, and one patient with significant invasive disease received external beam radiation following NAC removal. After 47.4 months of additional follow-up, none of those with Paget's recurrences developed local or distant recurrence and all were alive at date of last contact. Significant predictors of Paget's recurrences included DCIS as primary tumor, invasive tumor with extensive intraductal component, negative hormone receptors, overexpression of Her2, and high tumor grade.

Management of positive margins after NSM includes re-excision, radiation, or no further treatment. Amara and colleagues performed 1176

Table 9.3 Comparison of false-negative rates of frozen section analysis of retroareolar biopsy

Reference	No. of patients	False-negative	%
Crowe et al. [79]	37	6	16.2
Benediktsson et al. [80]	205	3	1.5
Luo et al. [81]	52	8	15.4
Kneubil et al. [82]	948	88	9.3
Alperovitch et al. [83]	219	9	4.1
Eisenberg et al. [84]	325	9	2.8
Piato et al. [78]	158	2	1.3

NSM in 751 patients and identified nipple involvement in 2.7 % of cases [88]. Eleven (34 %) were treated with removal of the NAC, five (6 %) had radiation without removal of NAC, and eight (25 %) had no further treatment. With mean follow-up of 31.3 months, there were no recurrences in the preserved NAC. Camp et al. found 22 out of 438 (5 %) patients who had NSM with positive retro-areolar biopsies [89]. Management included excision of the nipple in eight patients and removal of the NAC in nine patients. Only 4/17 excised nipples had residual malignancy. The authors suggest that removal of the nipple or NAC may not be necessary in all cases of retroareolar involvement. Becker and Billington report a case of a patient who had NSM with a positive retroareolar margin who strongly desired preservation of the nipple skin [90]. The authors performed re-excision of the glandular tissue with preservation of the overlying nipple skin via direct vertical incision of the NAC to minimize disruption of the blood supply to the nipple. The base of the NAC was excised leaving only skin, and a drain and platelet-rich plasma were left in the subcutaneous pocket prior to wound closure. The authors reported successful nipple preservation with no necrosis.

Post-mastectomy radiation is another means of managing positive margins after mastectomy. Agarwal and Agarwal evaluated the Surveillance, Epidemiology, and End Results database from 2006 to 2010 and found that patients who had NSM ($n = 470$) were more likely to receive post-mastectomy radiation therapy compared to those who had mastectomy without preservation of the NAC ($n = 112, 347$) [91]. The authors did not have data regarding margin status; therefore, it is unclear if NSM cases had radiation for treatment of positive margins or merely for concern for leaving ductal tissue behind. Gomez and colleagues conducted a literature review of 30 studies of NSM with nipple involvement and found a paucity of data regarding the role of radiation therapy following NSM [92]. The authors reported rates of nipple recurrence in patients who did not receive post-NSM radiation to range from 0 to 12 %, compared to rates of 0 to 2 % for those who did receive post-NSM radiation, with a pooled review estimating a rate of nipple recurrence of 0.9 % in 2314 patients. Petit et al. evaluated over 1000 patients who had NSM with perioperative radiation therapy [86]. The authors report relapse rate of 1.4 %, although the low recurrence rate may be due to selection of low risk patients. Seventy-nine patients were found to have retroareolar involvement but there were no nipple recurrences, suggesting that radiation played a role in control of microscopic disease.

In summary, close or positive retro-areolar margins in NSM may be avoided by careful selection of patients. Close or positive margins are associated with increased risk of local recurrence and may be managed with re-operation or post-mastectomy radiation, although the benefit of radiation therapy in NSM remains unclear. More research is needed to identify whether there may be subgroups of patients with close or positive margins who can be managed expectantly.

Conclusion

NSM is associated with low rates of morbidity and mortality. Nipple and flap necrosis is a feared complication that rarely leads to harmful consequences if identified early and managed appropriately. Positive retro-areolar margins after NSM can be avoided by appropriate patient selection and use of intraoperative frozen section analysis. Local recurrence rates following NSM are low.

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Techniques to Avoid Nipple and Flap Necrosis

10

Alan Stolier

Introduction

Breast cancer survival is improving, and the surgery for breast cancer is substantially less radical than prior decades. One would therefore conclude that surgery has had little impact on this improved survival. However, what is true today, which was not true in the past is that the breast surgeon is now an integral part of the reconstructive team. Today's breast surgeon is now responsible not only for good oncologic outcomes, but cosmetic outcomes as well. It is not hyperbole to state that without a well-done mastectomy an excellent cosmetic outcome is unlikely. This chapter focuses on a personal approach to mastectomy, which is based on anatomy and grounded in accepted surgical principles.

Vascular Supply of the Anterior Chest Wall

Reducing the risk of nipple and skin necrosis is dependent on maintaining blood supply to the skin of the anterior chest wall. Intimate knowledge of the vascular anatomy is therefore crucial in reducing the risk of necrosis. By most accounts, blood supply to the nipple-areola complex (NAC) comes from the perforating branches of the internal thoracic artery (internal mammary) and the lateral thoracic artery [1–4]. Though variations are not uncommon, Fig. 10.1 schematically and radiographically demonstrates the usual course of these vessels on the anterior chest wall. The vessels do not follow the duct system nor do they run just under the dermis, but run in the subcutaneous fat layer between the skin and the breast parenchyma (Fig. 10.2) [3].

Palmer and Taylor studied the blood supply to the anterior chest wall using dye injection and radiographs [4]. They agreed that the vascular supply indeed originated from the internal and lateral thoracic arteries. They found that peri-areola vascularization universally originated from either the internal or lateral thoracic artery. They noted that the internal thoracic dominated in 68 % while the lateral thoracic dominated in 20 %. They found the lateral and internal thoracic providing equal contribution in 12 % of cases. They agreed with other authors that there was usually a dominant perforator originating from the internal thoracic artery and noted that the second intercostal perforator was dominant in 60 % of cases.

Van Deventer noted that the internal thoracic perforating arteries 1–4 contributed blood supply to the NAC. Using latex injections in 27 breasts he noted

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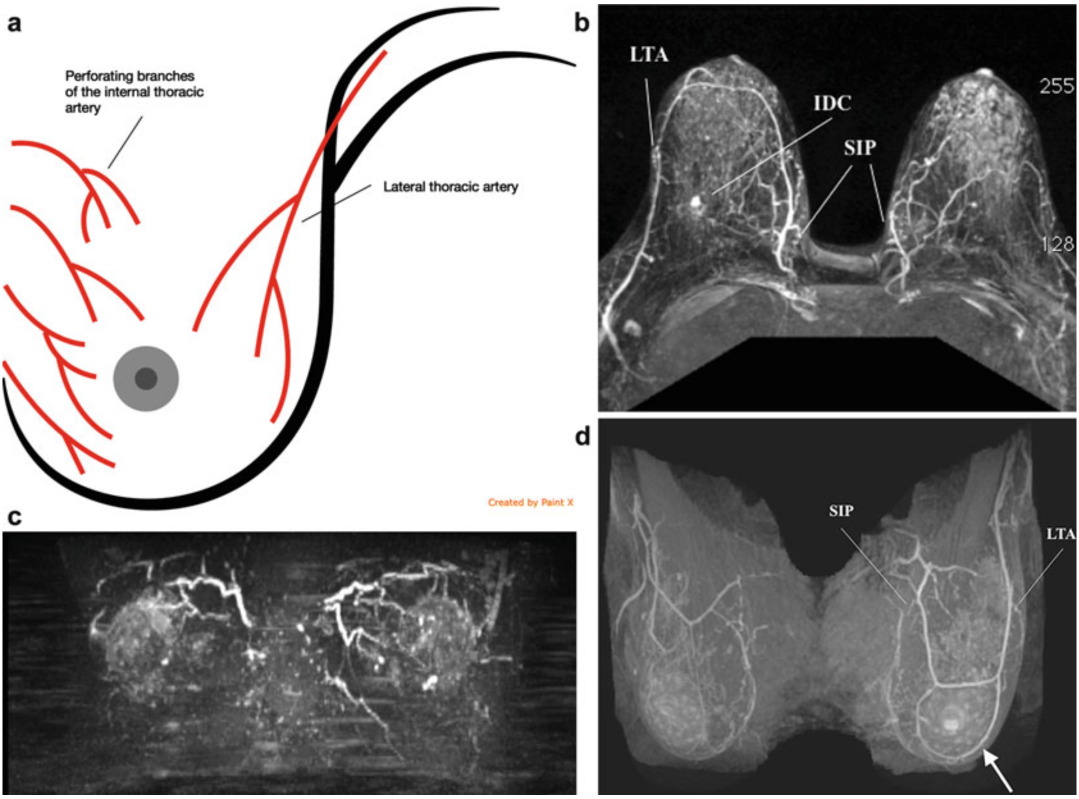

Fig. 10.1 Vascular supply anterior chest wall (**a**) Perforating vessels off of the internal thoracic artery and usual course of the lateral thoracic artery. (**b**) MRI showing lateral thoracic artery (LTA) and second intercostal perforator (SIP), invasive ductal carcinoma (IDC). (**c**) MRI showing internal thoracic artery (ITA), LTA, and nipple-areola complex (NAC). (**d**) MRI showing periareola anastomosis of the LTA and SIP (*arrow*)

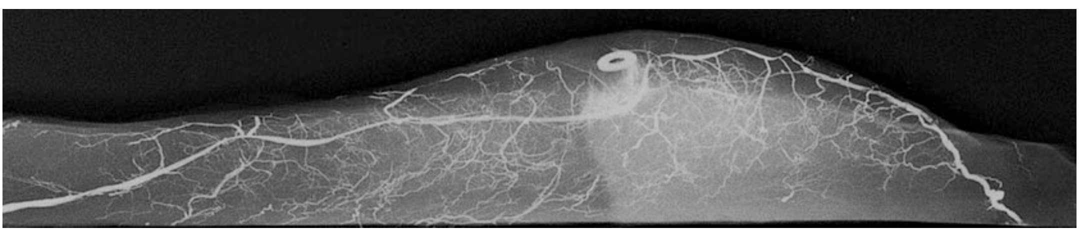

Fig. 10.2 MRI: internal thoracic perforator running through subcutaneous fat

that the third perforator was dominant in 47.5 % of cases compared to 25 % for the second perforator [3]. Furthermore his findings suggested that the blood supply to the NAC came primarily from the internal thoracic artery and to a lesser extent by the anterior intercostal (24.4 %) and the lateral thoracic artery (23.2 %). Importantly, he noted more inconsistency in the blood supply from the lateral thoracic compared to the internal thoracic.

Our own experience would suggest that the second perforator is dominant in a majority of cases (Fig. 10.3). There are, however, a great deal of inconsistencies in which vessels are dominant and are thereby likely to be most important in supplying the NAC. In Fig. 10.4, there are two dominant perforators, one from the fourth intercostal space, 1 from the second. In this instance the perforator from the fourth space

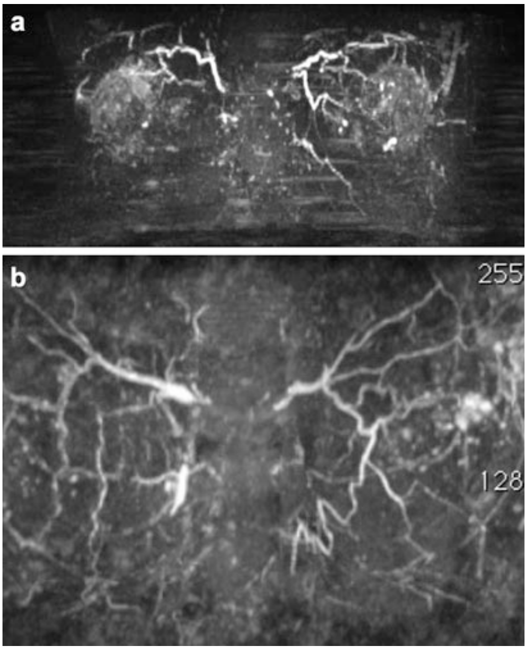

Fig. 10.3 Both (**a**) and (**b**) show dominant second intercostal perforators which are commonly the dominate vessels on the anterior chest wall

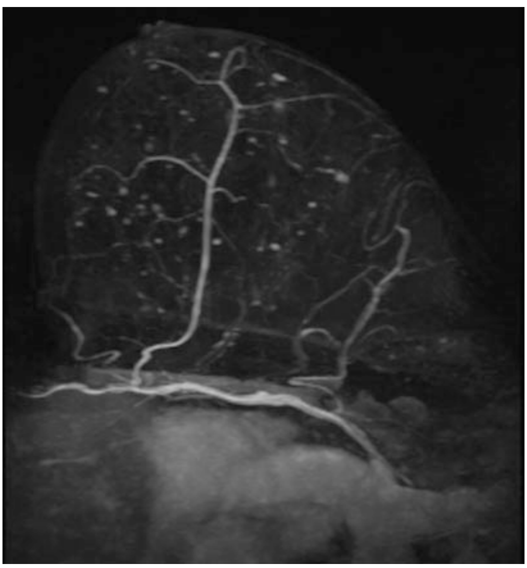

Fig. 10.4 Two dominate perforators, second and fourth. Fourth appears to be supplying the NAC

appears to be supplying much of the flow to the NAC. We have also noted that the dominant perforator could in some instances differ from side to side in the same patient. In Fig. 10.5, the dominant perforator on the right side originates from the second intercostal space whereas on the left, from the fourth intercostal space.

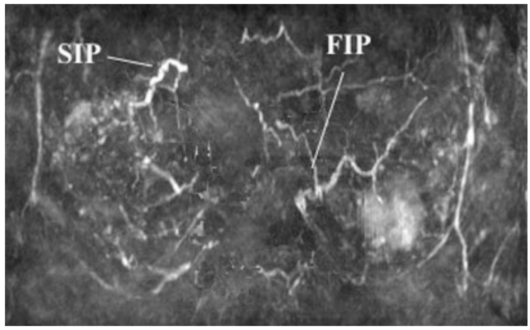

Fig. 10.5 Second intercostal perforator is dominant on right, fourth intercostal perforator dominate on *left*

Incisions

Incisions for nipple sparing mastectomy should meet several criteria. Most importantly, when performed for cancer, the incision should address any cancer-related issues. Commonly, superficial cancers in many instances require removal of overlying skin. Skin excision can frequently be included in the mastectomy incision. In Fig. 10.6a, the cancer is superficial and requires skin excision. Here it is incorporated into a radial incision at the 2:00 position. In Fig. 10.6b, the tumor is at the 6:00 position and can similarly be incorporated into a 6:00 radial incision.

Not all cancers are located in positions that can easily be incorporated into standard mastectomy incisions. In Fig. 10.7, the tumor is located in the central upper breast. In this instance if overlying skin excision is required it is suggested that the skin over the tumor be excised through a separate incision and then perform the mastectomy through an incision appropriate for this particular breast type. In this instance a 6:00 radial incision is used to perform the mastectomy.

There are other options for dealing with superficial tumors. A small suture can be left in the skin overlying the tumor (Fig. 10.8). The suture is left in place until the final pathology report is

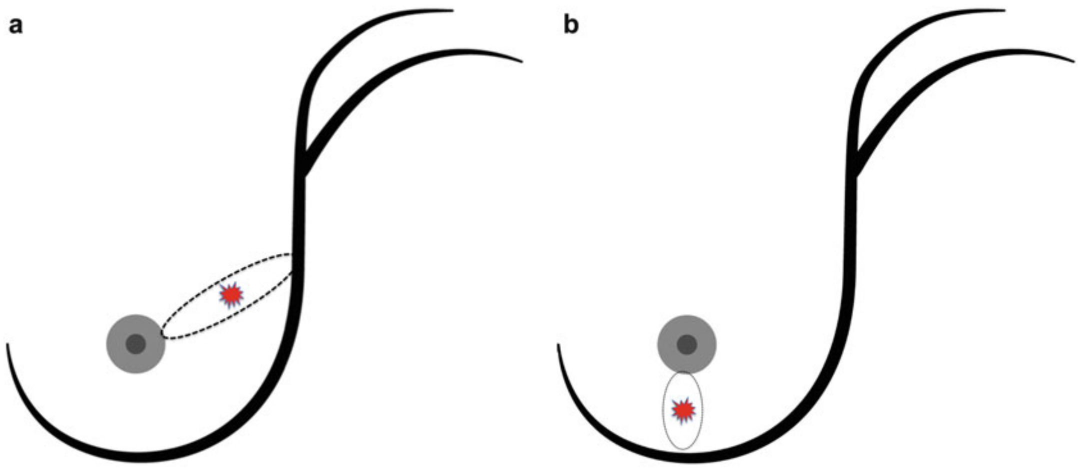

Fig. 10.6 (**a**) Skin excision incorporated into a lateral mastectomy incision. (**b**) Skin excision incorporated into a 6:00 vertical incision

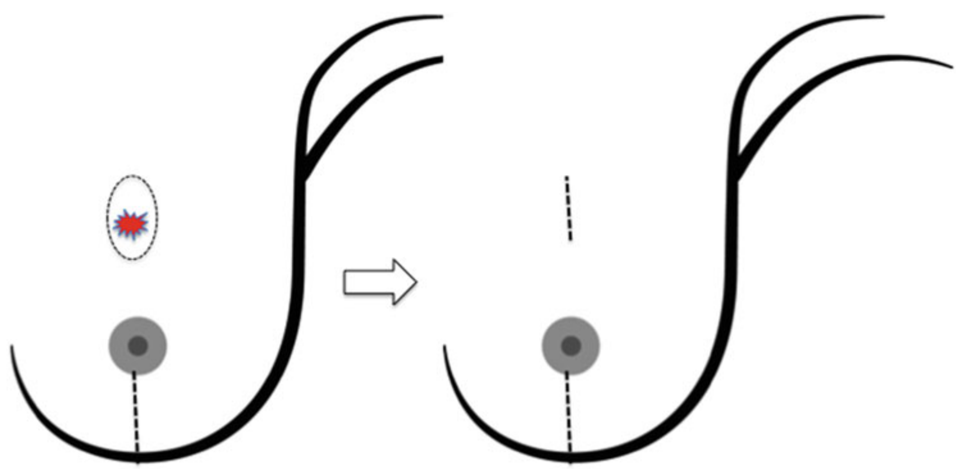

Fig. 10.7 Tumor location that cannot easily be incorporated into a standard mastectomy incision can be approached by excising skin over the lesion and use a separate incision for the mastectomy

available. This allows the breast surgeon to excise the skin or a new margin should the pathology report indicate a close or involved margin. Additionally, one can remove the subcutaneous fibro-fatty layer down to the dermis overlying the tumor, either leaving it attached to the breast specimen or removing it as a separate specimen following mastectomy. Even in these instances one should consider leaving a suture in the overlying skin.

In patients with cancers lying deeper in the breast parenchyma or in patients undergoing risk reduction mastectomy, considerations change. One cannot overemphasize the need for cooperation with the reconstructive surgeon when planning an incision. Both adequate exposure and a good cosmetic outcome are the hallmarks of a good incision. Equally important, the incision needs to be made in such a way as to preserve blood supply to the skin flap. As noted in a prior section much of the vascular supply to the anterior chest wall comes from medial and lateral as opposed to superior and inferior. There is also abundant experience now to suggest that some incisions carry a higher risk of

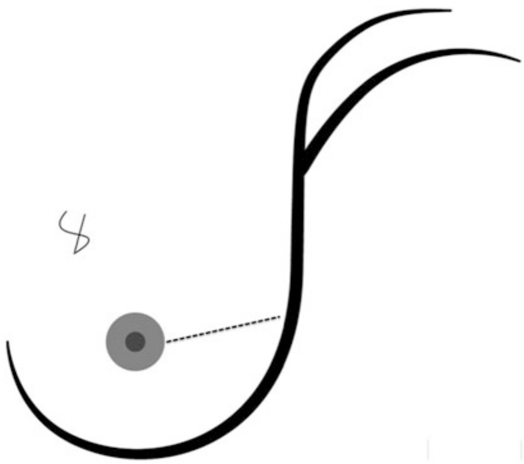

Fig. 10.8 When tumor location is easily determined, a suture is left over the tumor until final pathology report is available. This will allow easy access in case of a positive margin

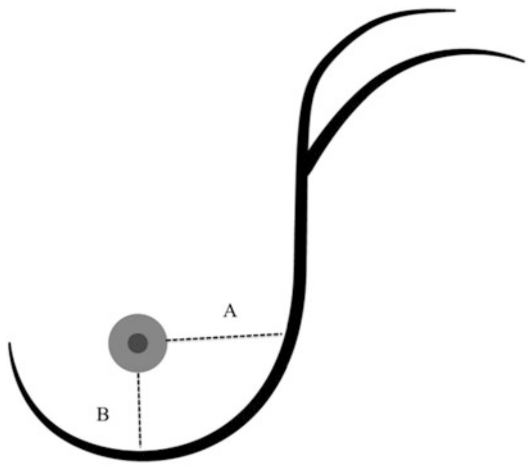

Fig. 10.10 Radial incisions: (**a**) lateral incision (**b**) 6:00 vertical incision

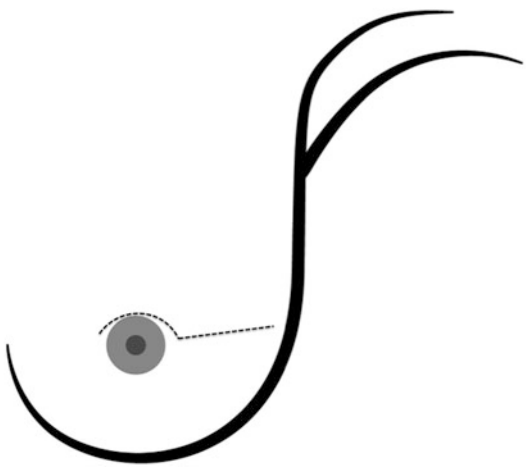

Fig. 10.9 One hundred and eighty degree periareola incisions traversing over 25 % of the areola margin may increase the risk of NAC necrosis

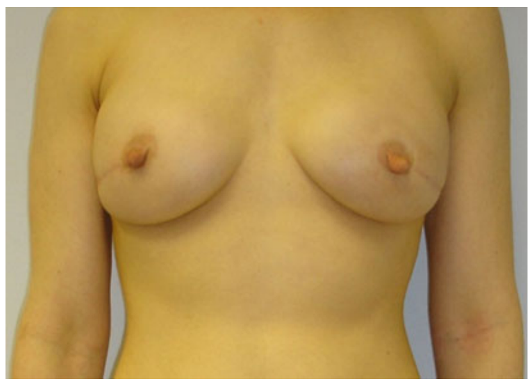

Fig. 10.11 Lateral incision with gluteal artery perforator (GAP) flap reconstruction.

nipple necrosis than others. Whereas incisions that traverse over a quarter of the diameter of the areola give the surgeon wonderful exposure, they are likely to significantly increase the risk of necrosis [5] (Fig. 10.9).

In a great majority of cases, we use one of two incisions; both are radial in orientation [6]. The first is a lateral incision (Fig. 10.10a). We have found that the lateral incision has the lowest incidence of skin edge necrosis and can be applied to a majority of patients. We use lateral incisions in patients who have little or no ptosis and will not require subsequent mastopexy (Fig. 10.10b). For those just beginning to perform nipple-sparing mastectomy, the lateral incision also provides more familiar exposure. Lateral incisions can also be longer than vertical since they can be extended to the anterior axillary line with little diminution in cosmetic outcome (Fig. 10.11). If needed, lateral incisions can also be extended around the areola but again, not more than 25 % of the circumference.

The second most commonly employed incision in our series is a 6:00 vertical incision (Figs. 10.10b and 10.12). In our own series of

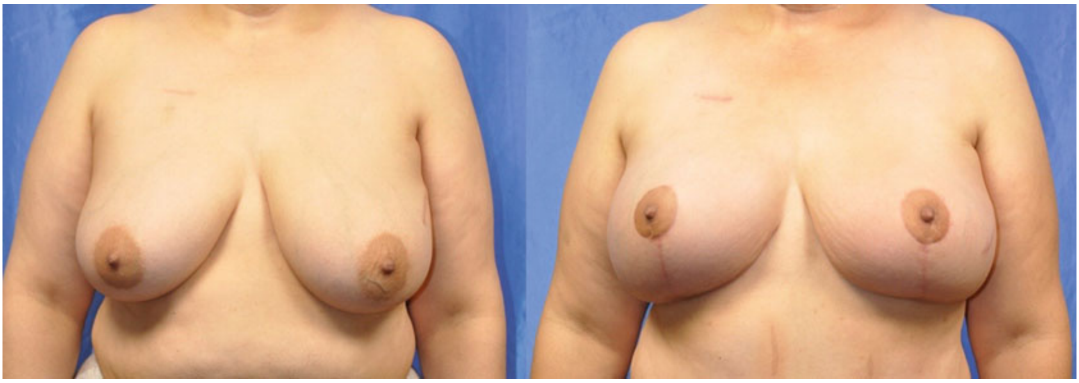

Fig. 10.12 6:00 vertical incision with DIEP flap reconstruction

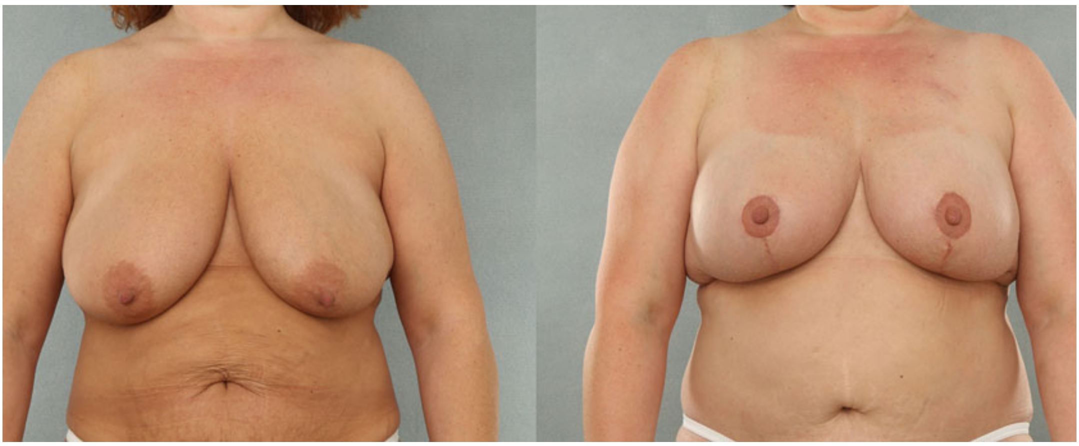

Fig. 10.13 Patient with grade III ptosis with DIEP reconstruction. Postsurgical mastopexy with improved breast shape and nipple position (From Stolier AJ, Levine EA. Reducing the risk of nipple necrosis: technical observations in 340 nipple-sparing mastectomies. Breast J. 2013 Mar-Apr;19(2):173–9 with permission)

over 900 nipple-sparing mastectomies, vertical incisions were used in approximately 60 % of cases. We use these incisions in most patients with ptotic breasts as they can easily be incorporated into mastopexy incisions at a later date (Fig. 10.13) [7]. Exposure through this incision is variable and is highly dependent on the distance between the nipple-areola complex and the inframammary fold with longer incisions offering better exposure. In those patients with a very short nipple to inframammary fold distance, exposure can be quite difficult and may require slight variations in the incision. There are several alternatives that can be used to increase exposure. The incision can be extended into the areola ending at the base of the nipple. It may seem counterintuitive, but the cosmetic results can be quite good with this approach (Fig. 10.14). Another option is to utilize a "lazy S" incision (Fig. 10.15). One to two centimeters can offer significant improvements in exposure, particularly when the additional length is near the NAC. Finally in those women with ptosis, a triangular incision at the 6:00 position has the advantage of providing a significant increase in exposure even in patients with a short vertical distance; and also provides some ptosis correction and an excellent cosmetic result (Fig. 10.16).

The third most commonly used incision in our series is an inframammary fold incision [6]. This

Fig. 10.14 Incision carried through the areola with excellent cosmetic results

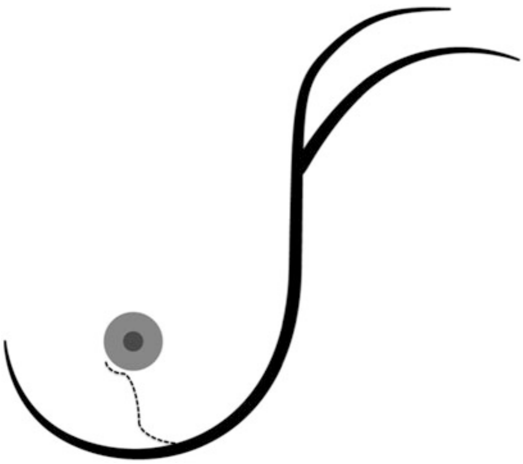

Fig. 10.15 Lazy S modification of a 6:00 vertical incision

is clearly the most difficult incision to work through given the longer distance between the upper flap and the inframammary fold. In general, smaller breasts with little ptosis are the most ideal candidates. Also women with wide-based breasts are more suitable than those with narrower teardrop-shaped breasts (Fig. 10.17). With most of the vascular supply to the anterior chest wall coming from medial and lateral, the length of the inframammary fold incision is not critical. It should certainly not extend so medial as to be visible adjacent to the sternum and not so lateral as to interrupt the laterally based blood flow. A well-placed incision can be quite long and provide very good exposure. Despite little interruption in the medial and lateral blood flow to the anterior chest wall, this incision does not offer immunity to skin and nipple necrosis. Using laser Doppler and fluorescein dye Perbeck and Proano evaluated blood flow to mastectomy flaps in 69 patients having either lateral or inframammary fold incisions [8]. They consistently found an area of vascular compromise in an area 2 cm below the NAC in those having an incision in the inframammary fold. This mirrors our own experience with areas of ischemia less likely to develop in the NAC than in the skin just below it.

A variation of the inframammary fold incision is the lateral inframammary fold incision or what has been termed by some, an "envelop incision" (Fig. 10.18) [9, 10]. This incision gives excellent exposure and visualization of the upper breast is quite good. It is however best suited to patients having implant reconstruction as access to the internal thoracic (mammary) vessels is limited making exposure for microsurgical anastomosis more difficult.

In summary, incisions should be planned to deal with an underlying malignancy as well as to maximize blood supply to the anterior chest wall. Planning the incision in conjunction with your reconstructive surgeon goes a long way in maximizing the cosmetic outcome.

Elevating Skin Flaps (Finding the Plane)

When performing a mastectomy, there is little to be gained by the removal of subcutaneous fat. There is ample evidence to suggest that no matter what type of mastectomy is performed, it is unlikely that all breast tissue is removed [11, 12]. The exception to not removing subcutaneous fat of course occurs when a cancer either lies at the breast–fat interface or when it extends into the subcutaneous fat layer. *A defined preset skin flap thickness should not be used.* Flap thickness can vary greatly dependent entirely on the thickness of the subcutaneous fat layer. It should be noted that this layer is not dependent upon breast size or body mass index [13]. It is not unusual to find

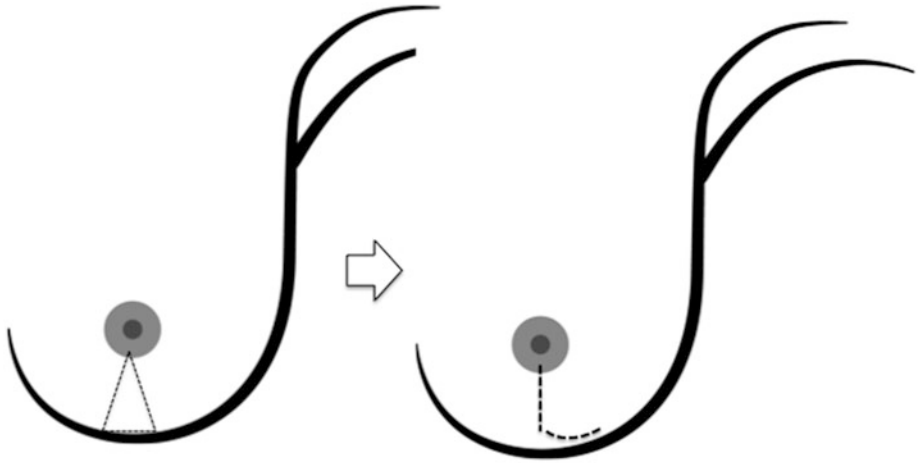

Fig. 10.16 Triangular modification of a 6:00 vertical incision closes in an L-shape

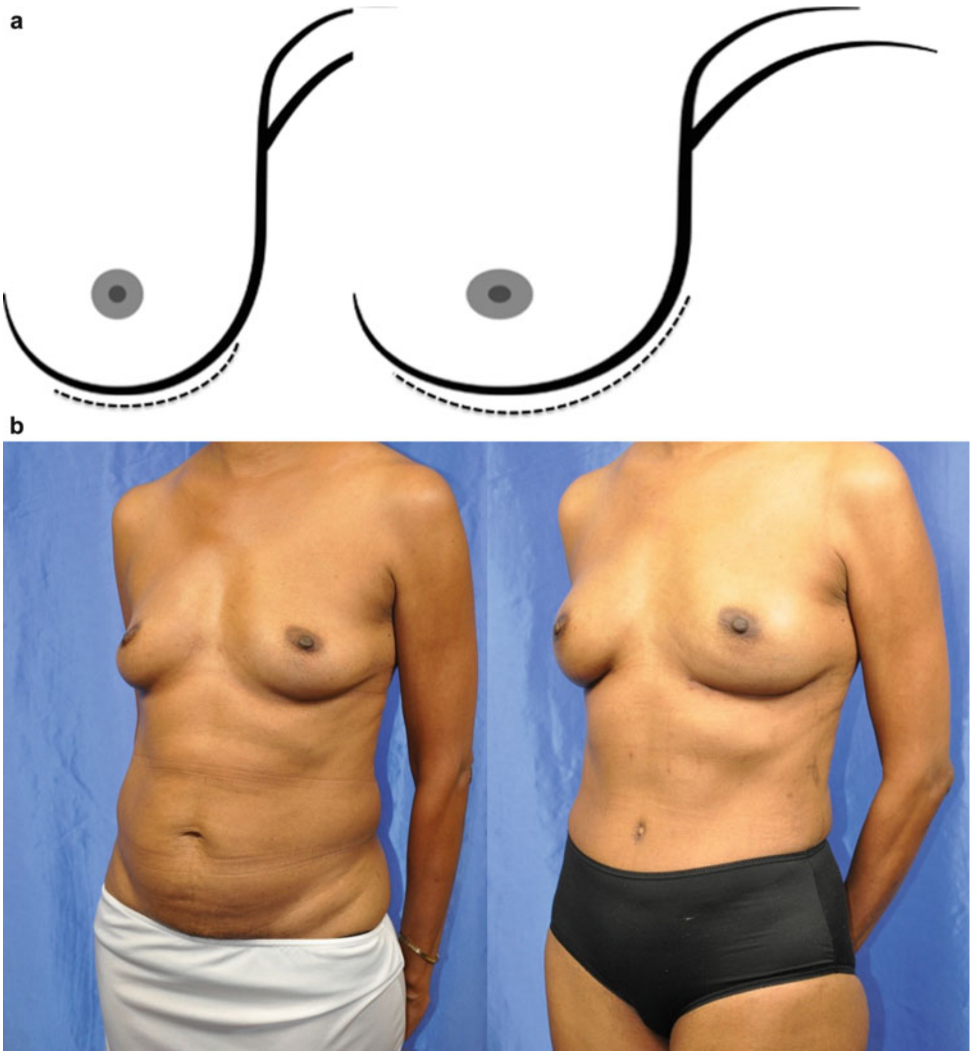

Fig. 10.17 (**a**) Inframammary fold incision allows more exposure through a longer incision in a patient with a wide chest wall (**b**) compared to those with a narrow chest or a teardrop-shaped breast (**a**). (**b**) inframammary fold incision with DIEP flap reconstruction

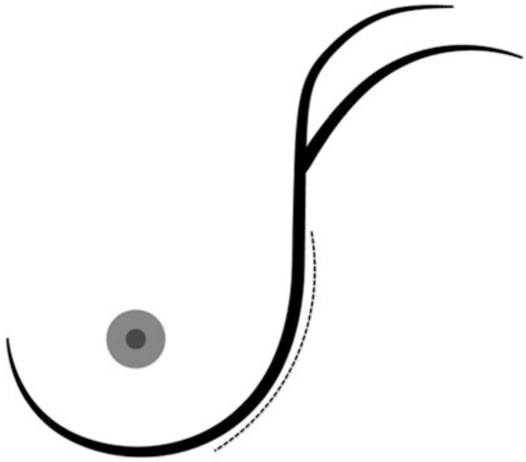

Fig. 10.18 Lateral inframammary fold incision (envelop incision)

a rather thin subcutaneous fat layer on an obese woman with large breasts. Nor is it unusual to have a rather thick area of fat in small-breasted women. The latter can be quite problematic in some patients as the thicker skin flaps and shorter incisions in a small breast can severely limit exposure.

The Surgical Plane

The surgical plane exists! It is not the plane of the superficial fascia that has been described just beneath the dermis [14, 15]. The surgical plane lies between the subcutaneous fat and breast parenchyma. In Fig. 10.19a, MRIs clearly show the fat–breast parenchyma interface. The interface can also be seen clearly on mammography and ultrasound. (Fig. 10.19b, c). Except under the NAC, the plane runs deep to a variable thickness of subcutaneous fat. Under the NAC, the plane consistently runs just beneath the dermis (Fig. 10.20). With the exception of superficial tumors, it is in this plane that the skin flaps are elevated. The plane is best seen in patients with extremely dense breasts (Fig. 10.21a). Unfortunately this is not the norm. Figure 10.21b shows a breast that more clearly represents the norm, a mixture of fat and breast parenchyma. Yet the plane exists in all patients, even in those with fatty replaced breasts. Figure 10.21c clearly demonstrates the surgical plane even in this fat-replaced breast.

In Fig. 10.22 you will note that the line of incision along the surgical plane is not straight but is filled with undulations following the breast tissue with its extensions along Cooper's ligaments as well as those irregularities created by traction and counter-traction along a curved surface. This is not to say that the surgical plane is always easily discernable. At times locating the correct plane can be quite difficult. However, when losing the plane, the pace of the procedure should slow and every attempt made to find the surgical plane again. The plane is generally more consistently defined in the lower breast and high in the upper outer quadrant approaching the axillary tail. The area just superior to the NAC and the far lateral breast tend to show more variation.

Flap Thickness is Not Uniform

When following the surgical plane, do not expect the breast flap thickness to be uniform throughout. As a general rule the flaps will thicken, sometimes imperceptibly as one dissects away from the NAC. This gradual flap thickening can easily be seen in both MRIs and in mammograms (Fig. 10.23). Attempting to retain uniform flap thickness for the sake of uniformity will needlessly remove normal fatty tissue, potentially injure blood supply, and ultimately affect the peripheral breast contour.

The Areola Edge: A Critical Transition

As the breast parenchyma reaches the edge of the areola the subcutaneous fat layer disappears. This can easily be seen on breast MRI (Fig. 10.24). Without a fatty layer, the surgical plane now shifts to the subdermal area. The plane remains in the subdermal area throughout the entirety of the NAC. At the edge of the areola, the surgical plane suddenly shifts to a deeper level as a layer of subcutaneous fat returns. This transition from the subdermal plane to a deeper plane beneath the

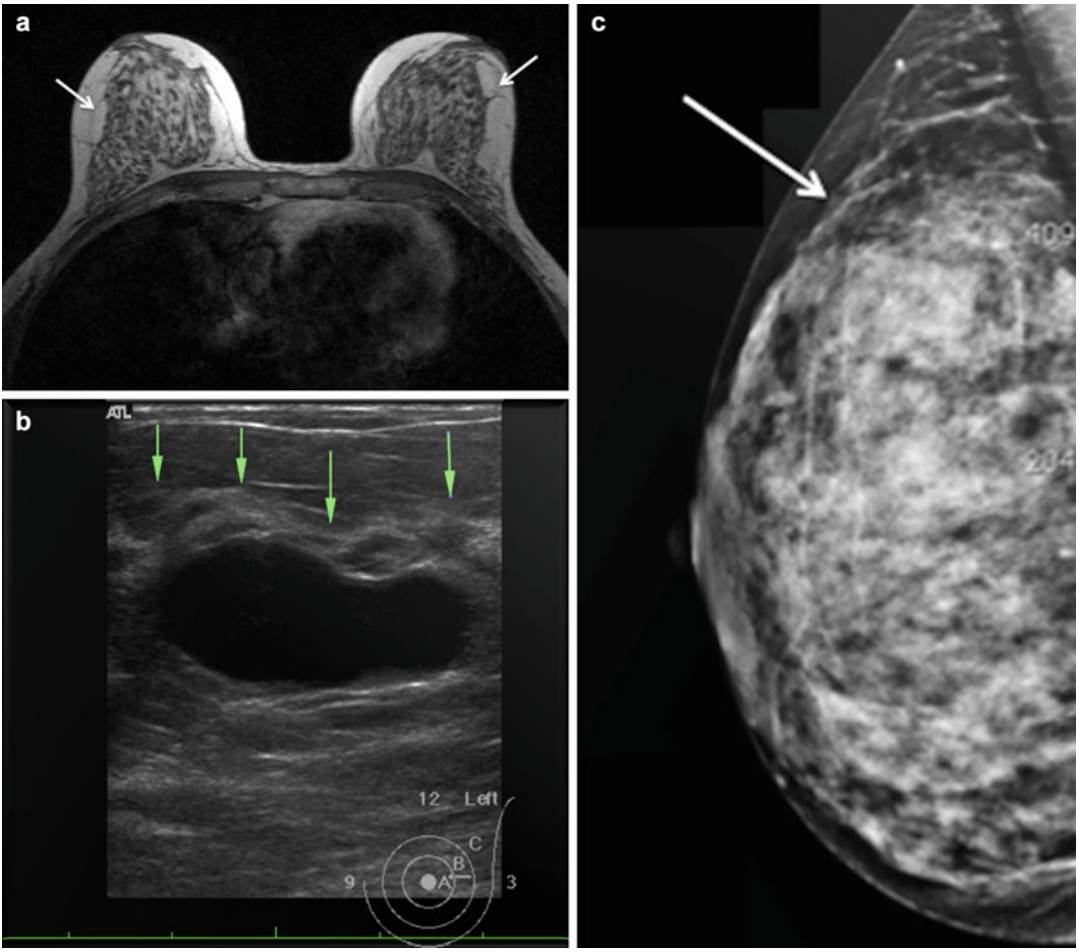

Fig. 10.19 Fat–breast parenchyma interface can easily be seen on (**a**) MRI, (**b**) ultrasound, (**c**) mammography

Fig. 10.20 The breast parenchyma tightly adherent to the undersurface of the NAC

subcutaneous fat is important to recognize. Failure to recognize this transition will result in a very thin flap in the periareola region, which may increase the risk of devascularizing the NAC. It is recommended that surgeons take great care as dissection approaches the edge of the areola so as to recognize this crucial transition.

The Lateral Dissection

It can be quite difficult to determine where to terminate the lateral mastectomy flap. Where the breast is extremely dense and dissection proceeds

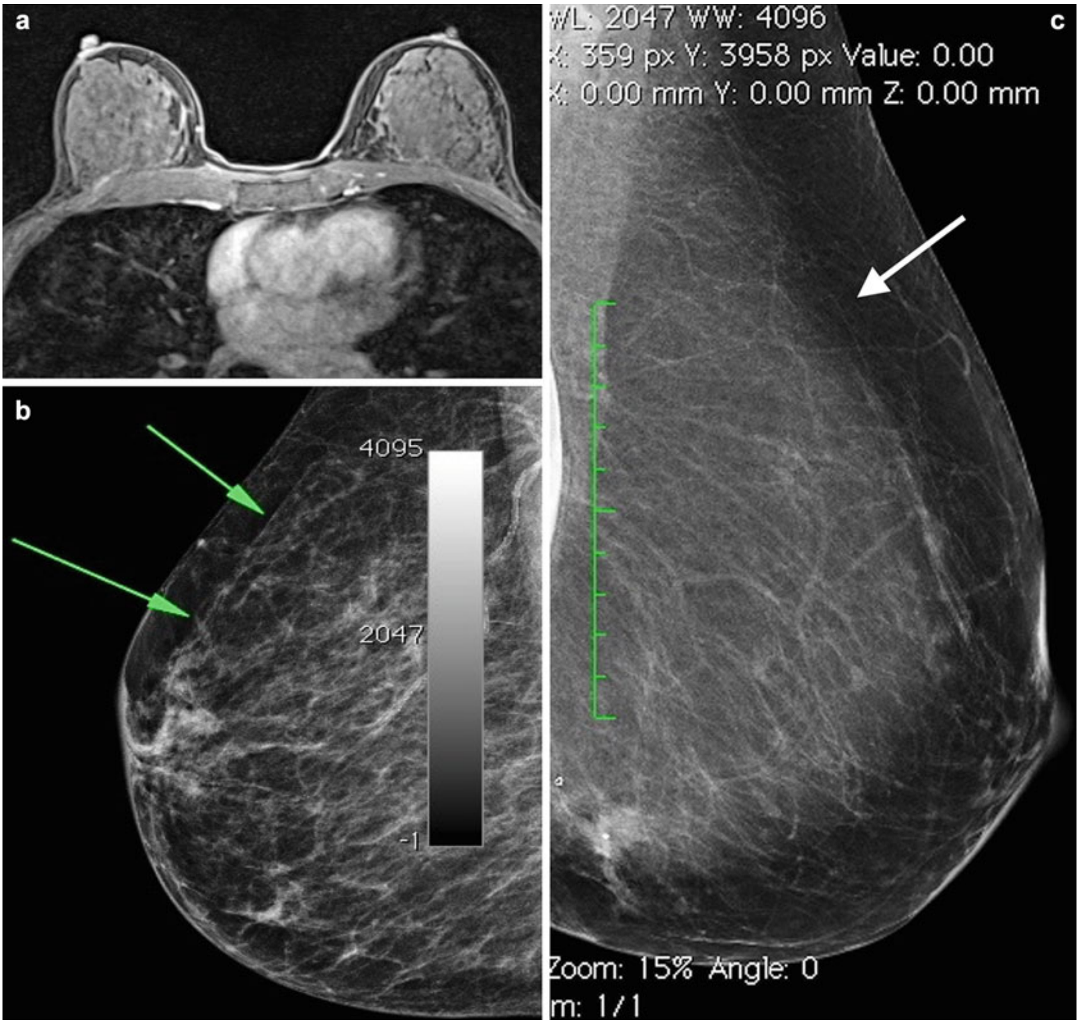

Fig. 10.21 The interface of parenchyma with subcutaneous fat can be identified in women with (**a**) extremely dense breast (**b**) mixed consistency (**c**) fat replaced

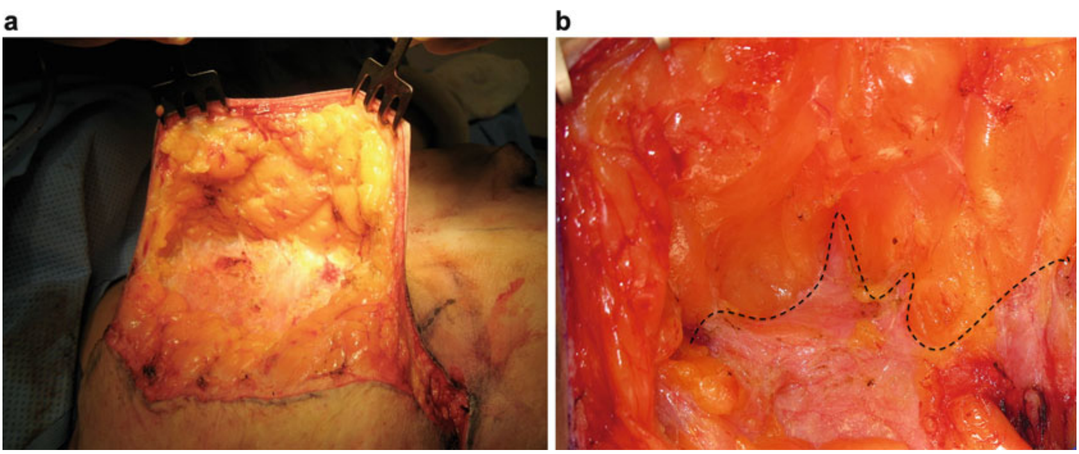

Fig. 10.22 (**a**) subcutaneous fat–breast parenchyma interface (**b**) Dissection follows the undulations created by straight retraction on a curved surface and islands of breast following Cooper's ligaments towards the skin

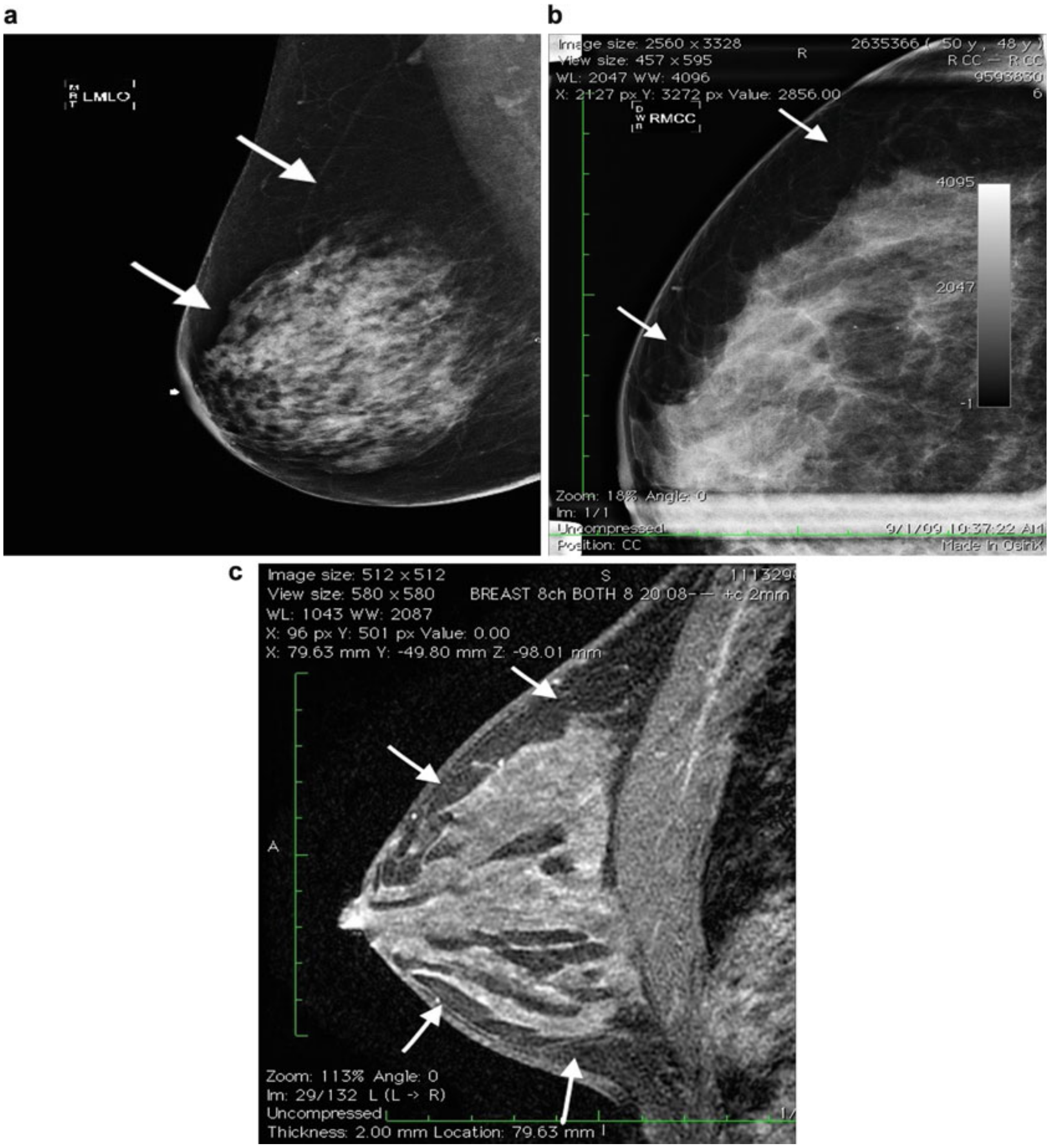

Fig. 10.23 Flap thickness increases as dissection proceeds away from the NAC. This can be seen on mammography (**a**, **b**) and on MRI (**c**)

along the subcutaneous fat–parenchyma interface the lateral edge of the breast can be easily discerned. In the more fat-replaced breast it can be more problematic. One should remember that the branches of the lateral thoracic vessels run along this lateral flap (Fig. 10.25). As previously noted, the lateral thoracic vessels are the dominant blood supply to the NAC in at least 20 % of cases [3, 4]. Branches of the intercostal vessels also arch onto the lateral flaps. Continuing dissection beyond the lateral edge of the breast and certainly beyond the anterior edge of the latissimus dorsi magnifies the opportunity for inadvertent damage to these vessels.

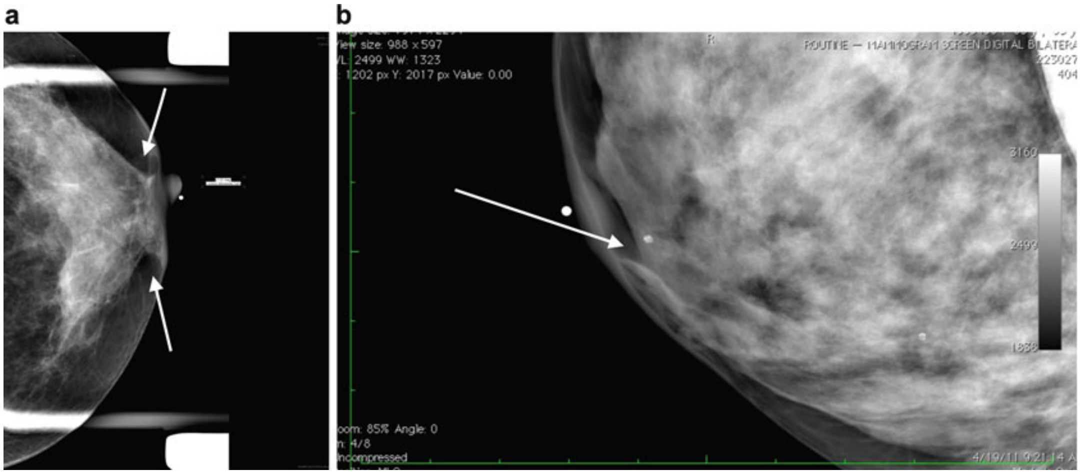

Fig. 10.24 (**a**, **b**) Crucial transition to a deeper surgical plane can be easily seen (*arrow*)

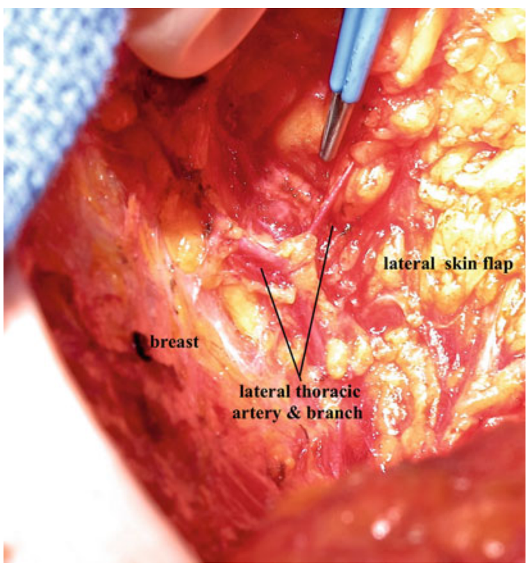

Fig. 10.25 Lateral thoracic artery and a branch supply the lateral mastectomy flap

Instruments and Lighting

Instruments

There are many instruments available to elevate mastectomy skin flaps. With proper use all are likely to yield equivalent results. There are two general options. One approach uses scissors or scalpel with scant use of electro-surgery. The other uses some form of electrosurgical device. In most instances those using scissors or scalpel dissection also use tumescence to minimize blood loss. Scissors dissection with tumescence accounts for only a small proportion of the cases that I have performed. Furthermore there is some suggestion that tumescence may increase the risk of skin flap necrosis [16–18]. Despite the niceties of working in an almost bloodless field I have personally maintained the use of electrosurgical instruments to elevate mastectomy skin flaps; and because of this I will limit my discussion to the use of these devices.

The cautery can be a dangerous weapon! Because cautery is so commonly used to perform mastectomies, a word about the pitfalls of cautery use is in order. When using monopolar cautery, the "coag mode" emphasizes voltage whereas the "cutting mode" emphasizes amperage or current. There is resistance (measured in Ohms) to electrical flow determined not by the surgeon but by the tissue [19]. For instance, fat offers more resistance than muscle. As resistance increases, heat is generated. When using the "coag mode", as the voltage increases, there is an increased possibility of driving stray energy and heat outside of the immediate target area [19]. "Cutting mode" uses lower voltage than coag, and therefore limits the danger of unintended damage.

When elevating a mastectomy flap, the longer the cautery is held in place and the higher the coag setting, the more likely there will be unwanted heat damage. Because the branches of the internal thoracic and lateral thoracic vessels branch and arborize in the subcutaneous fat layer, heat damage and the consequent coagulation necrosis can have a real world impact. It is recommended that one elevate skin flaps using either pure cut or blended current. This is particularly true when skin flaps are relatively thin. The NAC is in most instances the thinnest part of the mastectomy skin flap. The cautery can be used under the NAC but with great caution. Pure coagulation current should be reserved for a brief touch of small bleeding points. Surgical clips can also be used for vessels too large to coagulate. Even with cutting or mixed current, brief strokes should be used to minimize the generation of heat. It is less the case in the upper pole of the breast where flaps naturally thicken. However, particular attention is required as one approaches the medial aspect of the flap and the origin of the intercostal perforators (Fig. 10.26). Even in patients with very thick flaps, it is strongly recommended that pure or blending current be used in this crucial area of dissection, so as not to inadvertently damage these vessels.

The other electrosurgical option is the PEAK® PlasmaBlade (Medtronic, Minneapolis, MN). The Peak instrument uses pulsed plasma radiofrequency energy delivered by their proprietary generator. There is data to suggest that the PlasmaBlade delivers reduced thermal injury depth [20]. In theory this should reduce the risk of coagulation necrosis of the skin and, most importantly reduce the risk of inadvertent injury to the arching vascular supply to the anterior chest wall and NAC. To date there is no randomized data to support a reduction in flap necrosis.

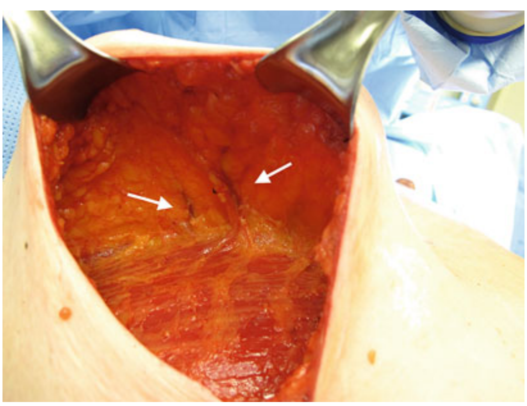

Fig. 10.26 Internal thoracic perforators exiting from the third and fourth intercostal spaces

In summary, good surgical outcomes can be achieved with all of the techniques noted. Whether using tumescence with scissors or scalpel, or one of the electrosurgical devices, staying in the proper surgical plane and minimizing damage to the subcutaneous vascular supply are mandatory for a viable NAC.

Lighting

Good lighting is crucial when trying to elevate long skin flaps through a small incision. Lighting options are numerous. Standard overhead surgical lights are adequate until the depth of the incision requires constant light movement with the focal distance of the light, in many instances not matching the depth of the incision.

There are at least three good alternatives and additions to overhead lighting. The first is lighted retractors with a built-in light source. Older models tended to have a fiberoptic light exiting the tip of the retractor. This works well in many instances but when "towing in" the retractor the light falls on the upper flap and not at the breast–skin flap interface where it is needed. Newer lighted retractors place the light on the proximal blade at the angle of the blade and handle (Eikon™, Invuity, Inc., San Francisco, CA). This floods the operative field giving excellent visibility no matter what the retractor angle. The downside is that the entire system including the retractor and disposable light is expensive compared to alternatives.

Another alternative is similar to the Invuity retractors, but in this instance the light is disposable and taped to the retractor of your choice (LightMat®, Lumitex MD, Strongsville, OH). The benefits of a taped-on light source are the ability to use your own retractor as well as lower cost per use. The downside is the tendency, if not installed perfectly, for these flexible light tapes to become loose requiring replacement during the procedure.

The final option for good lighting is a headlight. Headlights have the advantage of directing light into the operative field, moving as the field moves. However, many surgeons reject headlights due to the pressure that they can exert on the scalp. Newer lightweight, ergonomically balanced lights have mostly eliminated this concern. Moreover, newer LED lights provide much better than average illumination directly onto the operative field. In summary, no matter what your choice or personal preference, good lighting is crucial to a good surgical outcome.

Summary

The breast surgeon controls two factors that enhance the likelihood of a viable nipple-areola complex. The first is maintaining blood supply. An incision that takes into consideration the cancer if present as well as cosmetics and blood supply is the beginning. Elevating mastectomy skin flaps in the proper plane also maintains blood supply to the NAC limiting damage to the arching vessels traveling in the subcutaneous fat and is also important. Secondly, appropriate use of operating instruments, particularly the cautery is crucial to a good outcome. Incorrect use of the cautery can damage blood supply to the NAC resulting in necrosis and undoing the good of making an appropriate incision and remaining in the correct surgical plane. *In short, good outcomes are dependent on attention to detail!*

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11 Using the Breast Reconstruction Risk Assessment (BRA) Score: An Individualized Risk Calculator to Assist Expectation Management and Reconstructive Decision Making in the Mastectomy Patient

Alexei S. Mlodinow, Steven T. Lanier, Robert D. Galiano, and John Y.S. Kim

Introduction: The Utility of Risk Calculators

Over 100,000 breast reconstructions are now performed annually in the United States alone [1]. The reconstructive surgeon has a variety of modalities to choose from, and there is a large body of literature addressing the risks and benefits of each [2–15]. These papers can present a daunting and sometimes conflicting array of risk factors for numerous complications, each meant to assist in incremental risk stratification. Risk calculators simplify this process by providing concrete estimates based on the *combined* characteristics of the *individual* who is undergoing surgery.

While many superb papers have set benchmarks and informed clinical practice, the majority provide population-based estimates of risk, drawn from the average of the population studied. However, there are two pitfalls in attempting to apply these. First, risk of any given complication is often broadly distributed and skewed. Thus, the average may provide an overestimate for many, and a crucial underestimate for others. Second, the averages are often hard to reconcile into a reliable gestalt when there are multiple comorbidities or conflicting characteristics. As a result of these issues, surgery is, like many fields, moving away from high-level, population-based averages and the resultant uncertainty in their application, and towards data-driven, granular tactics to personalize the conversation [16–21].

The final benefit of risk calculators is their interactive nature. Whether online or on a mobile device, an increasing premium is put on the ability to engage patients in discussions about their health and grant them a degree of efficacy [22, 23]. This, in turn, supports expectation management, as the engaged patient is able to see in real time what her risks are given various situations or modalities. This multitude of benefits has led the Center for Medicare and Medicaid Services (CMS) to consider incentivizing patient-specific discussion of risk before every elective operation [24].

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What Is the BRA Score?

The Breast Reconstruction Risk Assessment (BRA) Score is an easy-to-use and open-access risk calculator for reconstructive surgeons and their patients [25–29]. It is available online at www.BRAScore.org. More recently, it has been made available as a mobile phone app, for Android operating systems. The online and mobile platforms function similarly, accepting preoperative and treatment characteristics of a given patient, and returning predicted probabilities of each of five surgical complications, as well as reoperation and medical complications. These predicted probabilities differ by method of reconstruction, and are laid out as such.

Details of the methodology utilized to construct the BRA Score have been well described in the literature [25–29]. The calculator is based on data from high-quality, large-scale registries including the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP), the American Society of Plastic Surgeons' Tracking Operations and Outcomes for Plastic Surgeons (ASPS TOPS), and the Mastectomy Reconstruction Outcomes Consortium (MROC). Logistic regression was used to assess for independent risk factors for each outcome of interest. The results of these regressions, specifically the constants and beta values, are transformed into predicted probabilities using a logit function [30, 31]. In order to make this analysis intuitive and clinically useful, the user interface simply takes characteristics of an individual and presents final results of this statistical prediction model. This process is depicted in Fig. 11.1.

A striking example of the utility of individualized risk calculators is seen in the broad and skewed distribution in predicted risk among the cohort used to develop the BRA Score. Figure 11.2 depicts the broad and skewed distribution of risk of surgical complications overall within the TOPS cohort. Figure 11.3 demonstrates that this holds across all complications, as the minimum and maximum predicted probabilities among this cohort widely differ for each complication.

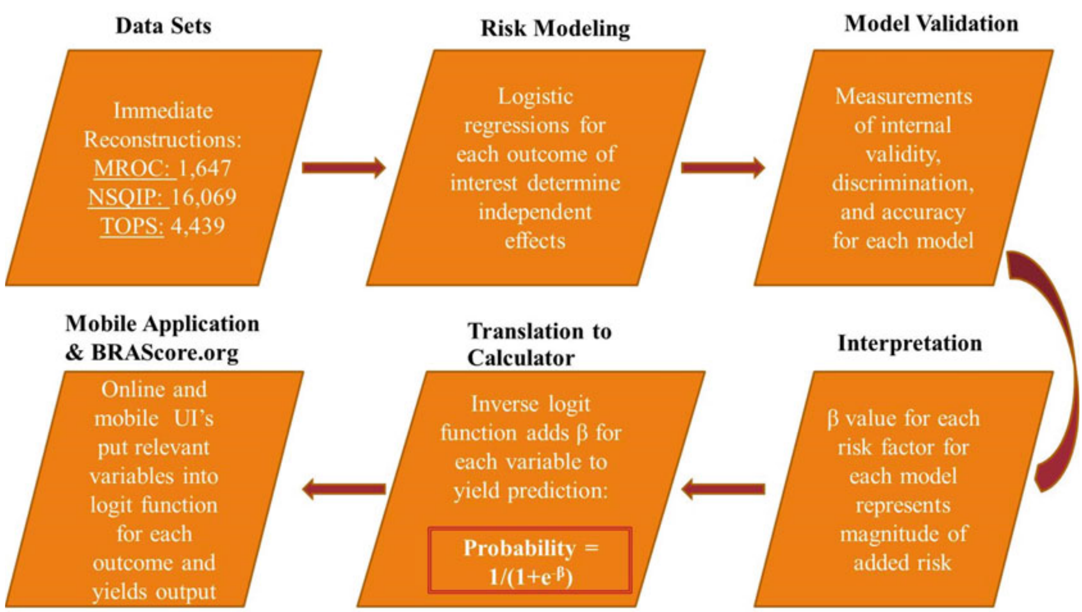


Fig. 11.1 BRA Score development methodology

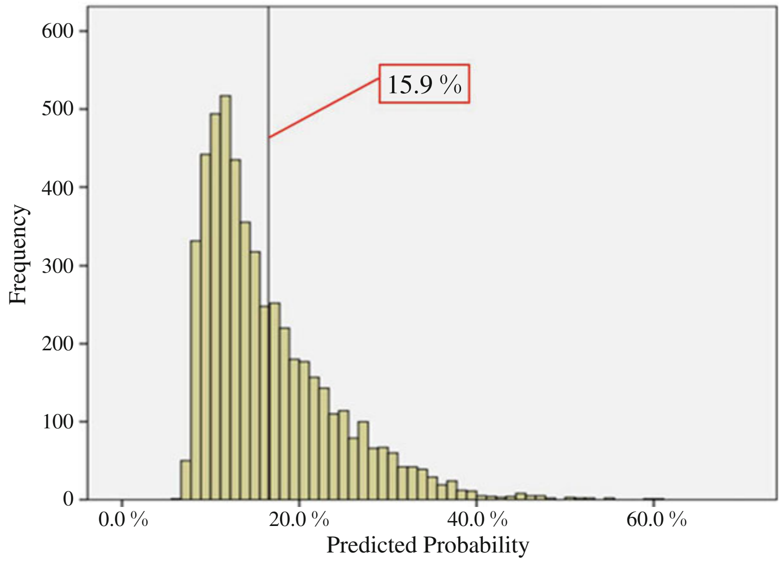


Fig. 11.2 Histogram depicting distribution of predicted probabilities of surgical complications across the TOPS reconstruction cohort

Fig. 11.3 Average incidence, minimum predicted probability, and maximum predicted probability of each complication examined within the TOPS cohort

Complication	Overall Incidence	Minimum Probability	Maximum Probability
Seroma	3.37%	1.21%	22.24%
SSI	3.96%	0.87%	29.89%
Dehiscence	6.13%	2.22%	50.19%
Flap Failure	7.00%	1.24%	50.57%
Explantation	3.70%	1.14%	52.08%
Reoperation	6.42%	1.79%	23.01%
Overall	15.92%	6.84%	62.50%

How Should the BRA Score Be Used?

The BRA Score was developed for use by reconstructive surgeons and their patients. It has potential utility in both surgical planning and informed consent. Seeing quantifiable risk estimates for different complications across various modalities can help the surgeon weigh them against the advantages of each modality. Similarly, walking a patient through this information can increase her involvement in and understanding of the surgical planning process. However, the BRA Score should *not* be used to determine surgical *candidacy* for any patient. It yields only one side of a two-sided equation and cannot replace the clinical judgment of the reconstructive surgeon. Similarly, it cannot be the sole basis of the informed consent process, but helps facilitate it with accessible and consolidated risk information. It is important to note the limitations of data from which the BRA Score is derived, as well as the absence to date of a study examining the tool's external validity.

Case-Based Examples of BRA Score Utilization

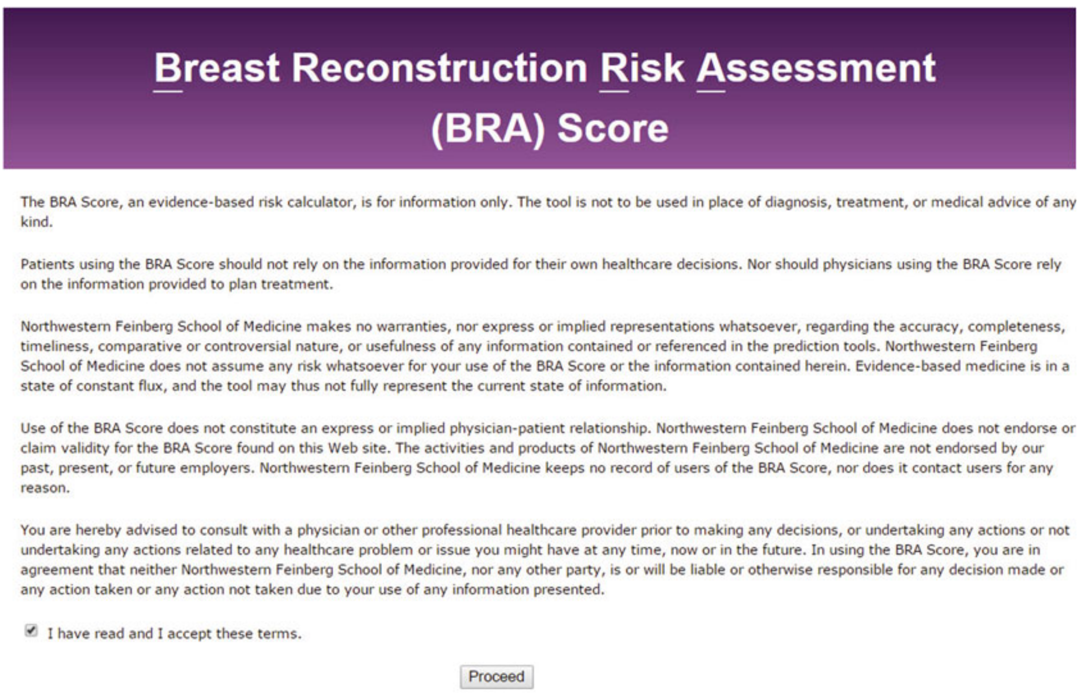
It is easiest to discuss the use and utility of the BRA Score with actual case-based examples. The examples that follow are two hypothetical patients undergoing mastectomy with immediate breast reconstruction. Let's look at these patients and use the BRA Score to quantify the difference in risk for these two women. For demonstration purposes, one case example will be assessed using the BRA Score website, while the second will be assessed using the BRA Score App.

Patient A is a 30-year-old woman who has chosen to undergo a prophylactic risk-reducing double mastectomy for her recently diagnosed BRCA carrier status. She is 5′6″ tall and weighs 120 lbs. She does not smoke and has no comorbidities. This is the type of patient that is seen more and more often in clinical practice as we witness continuing improvements and the publicity in both genetic testing for and prophylactic treatment of high-risk mutations [32] www.BRAScore.org.

We start at the landing page in Fig. 11.4, which outlines some of the uses and limitations discussed above. We acknowledge understanding and click "Proceed."

The homepage in Fig. 11.5 presents us with the characteristics that are taken into account in the BRA Score statistical models. There are demographics, comorbidities, and treatment details to fill in. Once these are complete with the details for "Patient A," we can click the "Calculate Risk" button that appears, as in Fig. 11.6.

We see a risk profile that pops up for Patient A, shown in Fig. 11.7. In interpreting this, there are a few things to note, independent of the actual results. One is the superscript on various categories. These tell us which cohort the data is derived from. For example, the latest work with the Mastectomy Reconstruction Outcomes Consortium (MROC) [29] yielded sufficient statistical power only for an analysis of "overall" complications, but had more single stage cases than prior studies, allowing for inclusion of those patients. Thus, the single-stage modality, the newest addition to the BRA Score, has a result for only "overall" complications. Similarly, the studies from which each data point is



Breast Reconstruction Risk Assessment (BRA) Score

The BRA Score, an evidence-based risk calculator, is for information only. The tool is not to be used in place of diagnosis, treatment, or medical advice of any kind.

Patients using the BRA Score should not rely on the information provided for their own healthcare decisions. Nor should physicians using the BRA Score rely on the information provided to plan treatment.

Northwestern Feinberg School of Medicine makes no warranties, nor express or implied representations whatsoever, regarding the accuracy, completeness, timeliness, comparative or controversial nature, or usefulness of any information contained or referenced in the prediction tools. Northwestern Feinberg School of Medicine does not assume any risk whatsoever for your use of the BRA Score or the information contained herein. Evidence-based medicine is in a state of constant flux, and the tool may thus not fully represent the current state of information.

Use of the BRA Score does not constitute an express or implied physician-patient relationship. Northwestern Feinberg School of Medicine does not endorse or claim validity for the BRA Score found on this Web site. The activities and products of Northwestern Feinberg School of Medicine are not endorsed by our past, present, or future employers. Northwestern Feinberg School of Medicine keeps no record of users of the BRA Score, nor does it contact users for any reason.

You are hereby advised to consult with a physician or other professional healthcare provider prior to making any decisions, or undertaking any actions or not undertaking any actions related to any healthcare problem or issue you might have at any time, now or in the future. In using the BRA Score, you are in agreement that neither Northwestern Feinberg School of Medicine, nor any other party, is or will be liable or otherwise responsible for any decision made or any action taken or any action not taken due to your use of any information presented.

☑ I have read and I accept these terms.

Proceed

Fig. 11.4 Landing page screenshot

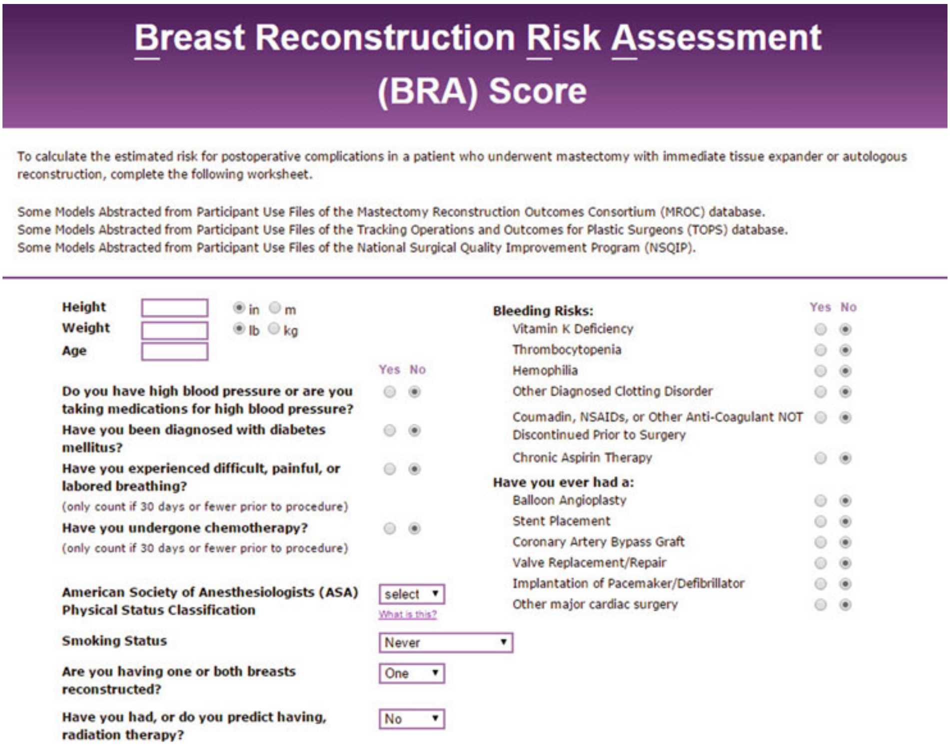


Fig. 11.5 Blank homepage

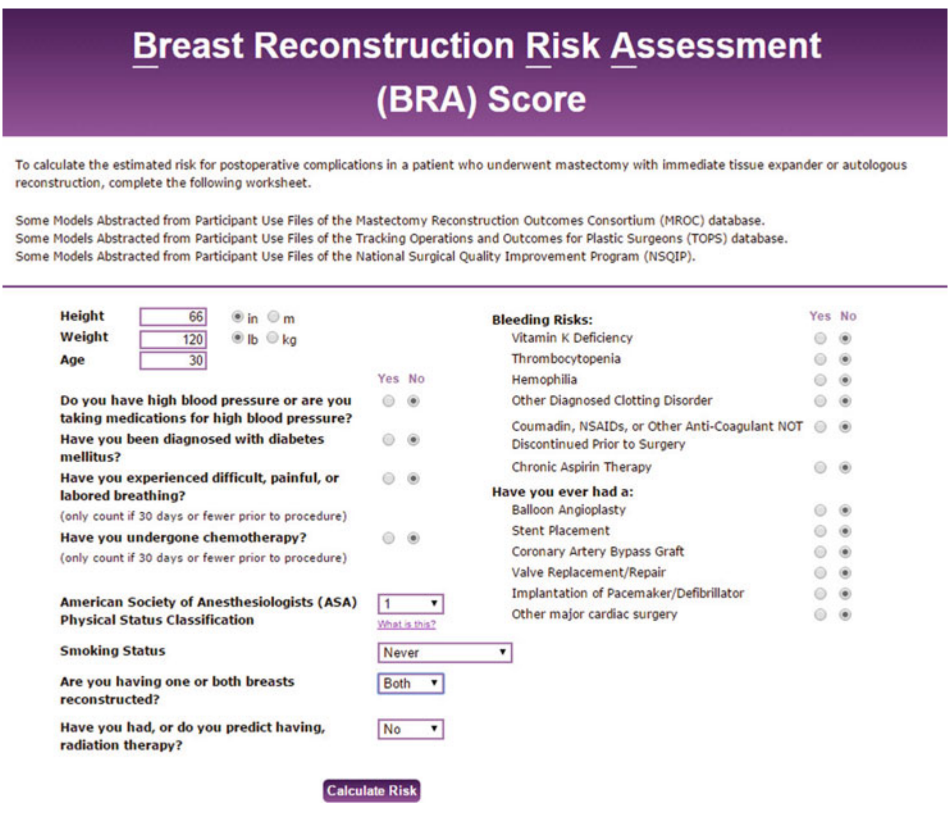


Fig. 11.6 Completed questions for "Patient A"

Estimated Risk of Complication:

Outcome	Reconstructive Modality				
	Tissue Expander	Pedicled Abdominal (TRAM) Flap	Latissimus Flap	Microvascular Reconstruction	Single-Stage Implant
Overall Complications	7.61%[1] - 7.63%[2]	17.78%[1] - 22.55%[2]	12.17%[1] - 28.37%[2]	12.93%[1] - 22.78%[2]	16.52%[2]
Overall Medical Complications[3]	1.08%	3.98%	1.49%	8.15%	
Overall Surgical Complications[1]	7.61%	17.78%	12.17%	12.93%	
Surgical Site Infection[3]	1.54%	2.50%	1.14%	2.59%	
Seroma[1]	1.10%	1.93%	3.55%	1.66%	
Dehiscence[1]	2.63%	9.77%	3.61%	4.46%	
Flap Loss (Partial or Total)[1]	n/a	4.42%	1.20%	4.27%	
Explantation[1]	1.42%	n/a	n/a	n/a	
30-Day Reoperation[1]	2.70%	4.39%	1.98%	4.84%	

[1] Abstracted from TOPS data
[2] Abstracted from MROC data
[3] Abstracted from NSQIP data

Fig. 11.7 Complication predictions for "Patient A" stratified by reconstructive technique

estimated vary in the exact definitions of the input and their weighting in the regressions. For example, those with granular familiarity with the ACS-NSQIP database know that it lacks thorough radiotherapy information [33]. Thus, the information that we input regarding radiotherapy is not factored into estimates based on NSQIP data, but is used for those derived from MROC data.

We can see from the probabilistic estimates in Fig. 11.7 that Patient A is a fairly low-risk patient across the board, as expected. Though we can intuit that she has a "low" risk of complications relative to published means, it is beneficial to have numerical estimates, particularly in this increasingly common patient with little outcomes data available because of the rarity of her situation prior to the era of testing and prophylactic double mastectomy.

Patient B is a 65 year-old woman undergoing unilateral mastectomy for a newly-diagnosed invasive ductal carcinoma and wants to minimize added procedures including those to the contralateral breast. She is 5′6″ tall and weighs 170 lbs. She smokes, but has agreed to quit 30 days prior to the procedure. She also has diabetes and hypertension. She has been deemed American Society of Anesthesiologists (ASA) class II due to the burden of her comorbidities.

The app is freely available in the Google Play and Apple Apps store for Android, respectively. We download and open the app to arrive at the screen depicted in Fig. 11.8. Information within

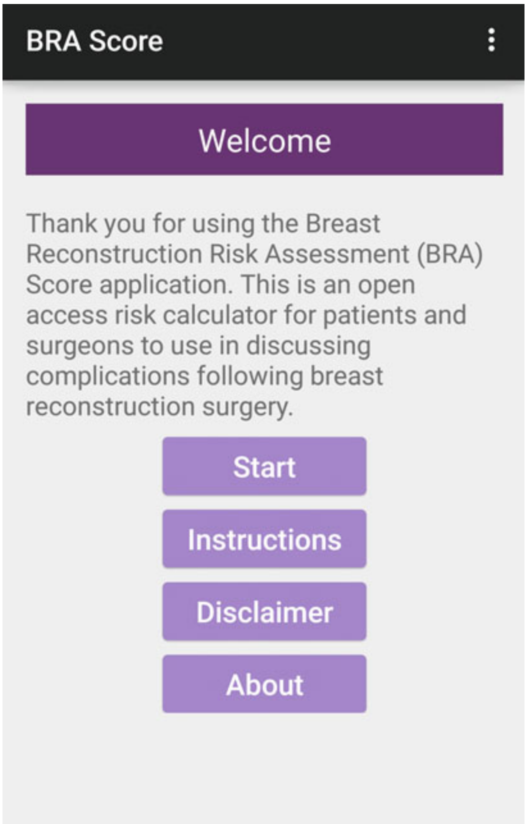


Fig. 11.8 Home screen of BRA Score mobile application

the "Instructions," "About Us," and "Disclaimer" options are largely covered above, so we will proceed to press "Start."

The app walks us through several questions, capturing the same information that is captured by the online interface in Fig. 11.9. After answering the last question and pressing "Next," a review screen is offered to ensure that all questions were answered correctly and giving us the opportunity to change answers as appropriate, as shown in Fig. 11.10. When all characteristics are correctly entered, pressing "Results" takes us to the output.

The BRA Score app output for Patient B is depicted in Fig. 11.11. As expected, we see significantly higher risks across all categories than we did for Patient A. The default modality displayed on the results screen in the app is staged expander-implant reconstruction. However, we can also view predicted risks for autologous reconstructions. When selecting "Latissimus Flap," for example, the results array changes to reflect the predicted probabilities for the relevant surgical technique, as shown in Fig. 11.12. Again, more specific numerical estimates of risk in this context allow for better cross-technique

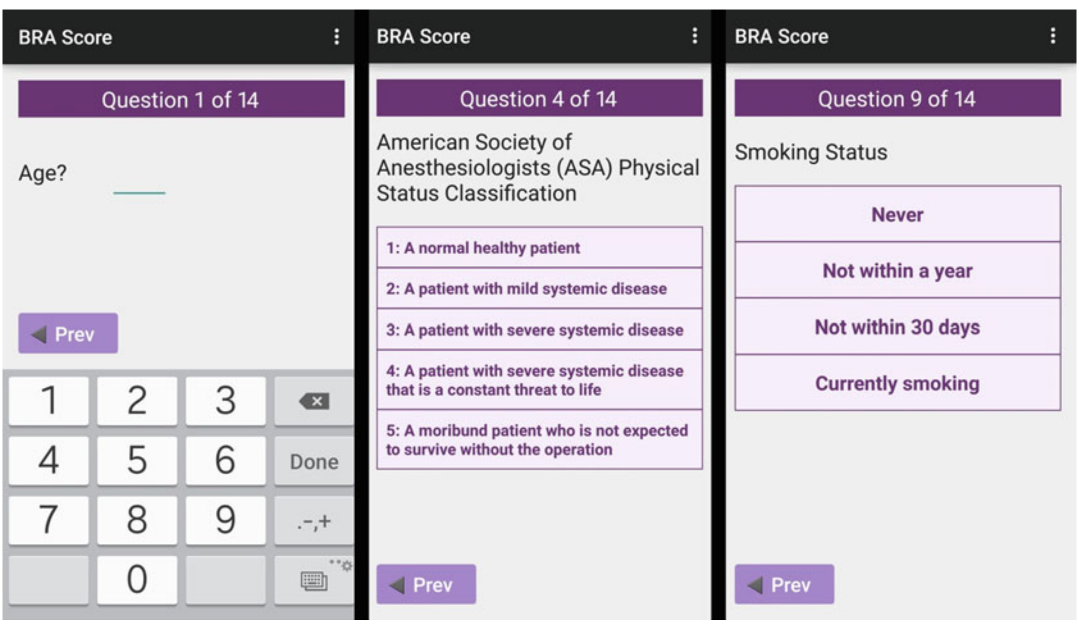


Fig. 11.9 Sample question screens in mobile application

Fig. 11.10 Information review screen

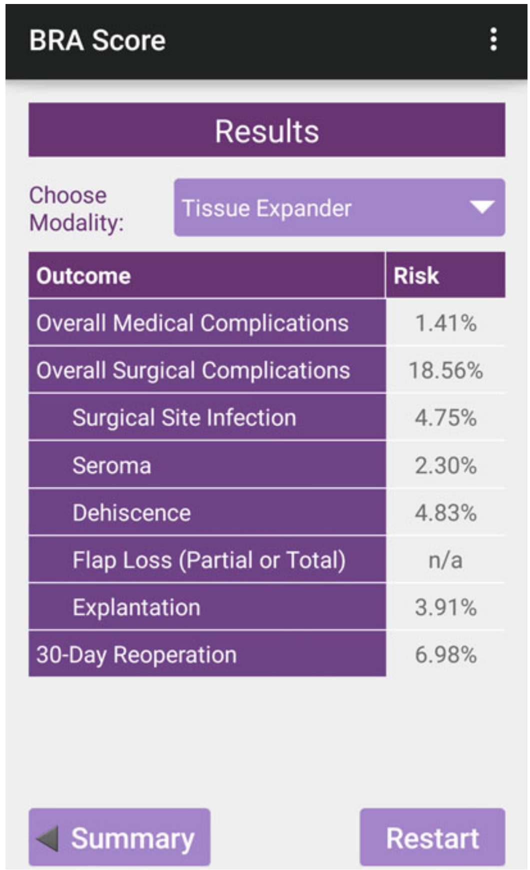


Fig. 11.11 Complication predictions for "Patient B" using tissue expander reconstruction

comparisons and expectation management. One notable limitation to the former use in this context is the fact that the data from which the risk models were derived code using Current Procedural Terminology (CPT) codes, which preclude differentiation between microvascular techniques.

Summary

The Breast Reconstruction Risk Assessment (BRA) Score is an evidence-based tool that provides individualized estimates of postoperative complication risk in immediate breast reconstruction. It is available as both online (www.BRAScore.org) and mobile (Android) platforms for free and easy access to reconstructive surgeons and their patients. Taken with appropriate clinical judgment, patient selection, and informed consent procedures, the BRA Score can be a useful part of surgical decision-making and expectation management. Limitations to both formulation and use of the BRA Score should be kept in mind when using it. A follow-up prospective study of both predictive accuracy and patient satisfaction is warranted.

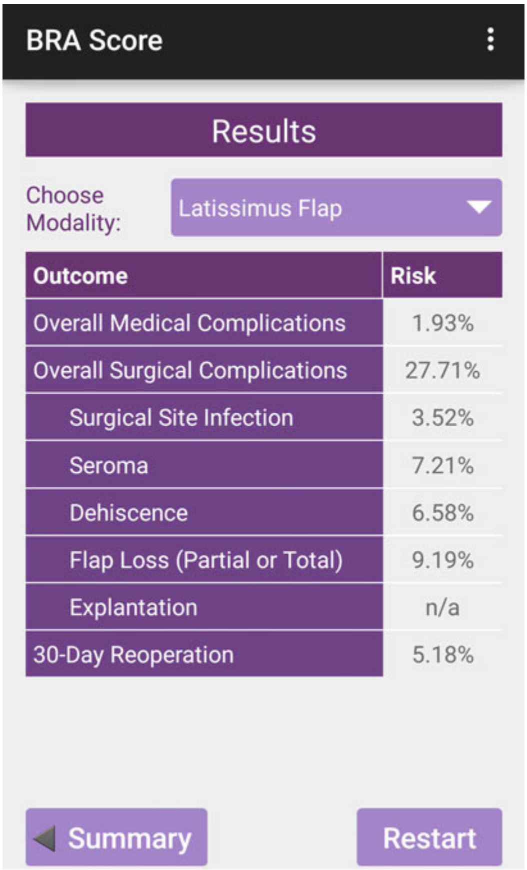


Fig. 11.12 Complication predictions for "Patient B" using latissimus flap reconstruction

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12 Plastic Surgery Considerations in Reconstruction After Nipple-Sparing Mastectomy

Steven J. Kronowitz

It's hard to argue against the aesthetic advantages of nipple-sparing mastectomy (NSM), especially with one-stage, direct-to-implant (DTI) breast reconstruction. Typically, at the time of the immediate breast reconstruction, the contralateral breast also undergoes a breast implant augmentation for symmetry and a mastopexy, if required. Although in the authors practice, DTI is only an option with patients undergoing NSM, it offers a one-procedure surgery, including tumor extirpation, reconstruction, and a symmetry procedure at lower cost, and often with a better aesthetic outcome than two-stage implant breast reconstruction. With implant-based reconstruction along with NSM, an inframammary mastectomy incision is preferred because it is hidden and camouflaged within the lower breast crease. With shaped breast implants, ADMs, and fat grafting, most NSM patients, especially those who do not receive irradiation can receive excellent outcomes with implant-based reconstruction.

With a deep inferior epigastric artery perforator (DIEP) flap, access to the internal mammary blood vessels for microsurgical anastomoses usually requires a lower vertical incision, to be placed directly below the nipple areola complex (NAC) extended down to the inframammary fold, which usually allows for adequate access for nipple-sparing mastectomy, microsurgical anastomoses, and insertion of the flap into the breast skin envelope. Although mastectomy incisions placed directly on the breast adjacent to the NAC can compromise the perfusion to the NAC and decreases the overall aesthetic outcome of the reconstruction, the lower vertical incision is an excellent and safe option.

NSM is more convenient for patients while allowing for the mastectomy incisions to be camouflaged with a more-natural ptotic outcome. However, it does require a technical breast surgeon to perform it in order to preserve an adequate blood supply to tolerate the increased demands on the breast skin envelope associated with DTI [1]. An acellular dermal matrix (ADM) sling to support the implant and take the pressure off the overlying breast skin and nipple-areola complex (NAC) makes it safer by relieving pressure off the breast skin and NAC for improved perfusion. The key question is when should a tissue expander be placed as opposed to a permanent implant at the time of NSM?

In 2013, to determine which patients are at risk for NAC necrosis with NSM, the author published the NSM experience at The MD Anderson Cancer Center [2]. The study showed no difference in overall complications in the NSM group (28 %) when compared with the non-NSM (27 %) group. The only factor found that significantly increased

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complications with NSM was C-cup-sized breasts or larger. So, DTI for NSM in C-cup- or larger-breasted patients may not be preferable. Total nipple necrosis was infrequent (2 %), however partial necrosis was more prevalent (19 %). Interestingly, the breast surgeons experience with performing NSM was not predictive of outcome. Surgeons who had performed more NSMs did not have fewer episodes of NAC necrosis. Surgical technique was more important than surgeons experience in performing NSM. We concluded that NSM with immediate implant placement (DTI) may safely be performed in patients with A- or B-cup-sized breasts with a technical breast surgeon, and not necessarily a breast surgeon who has performed many NSMs.

Immediate placement of the permanent implant does have some disadvantages. One such disadvantage is when the breast skin looks compromised postoperatively. Immediate placement of a tissue expander as opposed to the permanent implants allows for perioperative deflation of the expander to relieve pressure on the overlying breast skin and NAC that may enhance the chance for skin survival in skin flaps with borderline viability.

To answer the question of whether immediate placement of a permanent implant adversely affects perfusion to the NAC and breast skin with a subsequent increased incidence of necrosis, the author published a study in 2011 [3] to assess the degree to which intraoperative saline-filling of a tissue expander impacted the rate of complications in 164 patients. Surgical characteristics of the study group included equal ratios of patients receiving sentinel lymph node biopsy versus axillary lymph node dissection. Varying intraoperative saline fill volumes were used. Thirty-two percent of patients had complete intraoperative saline filling of expander at the time of mastectomy. Twenty-nine percent of the reconstructed breasts experienced at least one complication. In those patients, the mean intraoperative saline fill volume was 78 %. Patients without complications had a mean saline fill volume of only 64 %. For every 10 % increase in the intraoperative saline fill volume, the complication risk significantly increased 1.15 times ($p=0.018$). The study suggested that DTI and tissue expanders inflated ≥64 % are at a higher risk of overall complications. Specific complications were not associated with percent tissue expander fill volumes.

Although the eligibility for NSM is expanding with increasing knowledge and experience, not all patients are candidates for NSM because of oncologic reasons. However, more patients with breast ptosis as well as those patients who will receive post-mastectomy radiation therapy (PMRT) are now being offered NSM.

From a reconstructive aspect, patients with breast ptosis who undergo NSM can be categorized based on surgical approach. Patients who are planned for prophylactic or risk reducing mastectomy can have a mastopexy performed several months prior to NSM and implant-based breast reconstruction [4]. Those patients with breast ptosis who have breast cancer tend to have NSM performed through a lower vertical incision with immediate insertion of a tissue expander. Approximately 3–6 months after NSM and tissue expander placement, the affected breast undergoes a de-epithelialized vertical mastopexy with placement of the permanent breast implant along with an ADM sling to support the higher implant position. In cases of unilateral reconstruction, a contralateral vertical mammoplasty is also performed, that results in symmetry of incisions without the stigma of breast cancer surgery. Fat grafting of the affected breast is also performed at this second procedure because the author prefers prepectoral placement of implants with NSM.

In regards to patients who undergo NSM who will receive PMRT, it is currently unclear whether ADMs decrease contracture when a permanent implant is radiated. However, clinical observation shows that when ADMs are used, especially along with fat grafting, outcomes and safety are improved. Studies have shown that ADMs decrease the inflammatory response and the formation of a pseudocapsule around the implant, at least in the near term following PMRT [5]. The reason why contracture is an important issue with NSM and PMRT, is that PMRT can affect the final nipple position and symmetry with the contralateral breast, which can be a problem in some patients.

Another issue to consider is whether a patient who may or will require PMRT should undergo DTI or start with tissue expander (two-stage approach) at NSM. There are two main points to consider with NSM patients who receive PMRT. Firstly, consideration is whether the radiation oncologist is comfortable in delivering radiation with an intact implant on the chest wall. This issue continues to be institutional and radiation oncologist dependent and varies considerably. It is usually a matter of whether or not radiation will be delivered to the internal mammary nodal basins, especially with left-sided breast cancers to avoid excess radiation injury to the lungs and heart. Some radiation oncologists use IMRT, others prefer a partially deflated tissue expander because it flattens the geometric shape of the superomedial aspect of the chest wall, and others are adamant about having no permanent implant on the chest wall due to the obstructing nature. Most importantly, this point emphasizes that the radiation oncologist should be involved preoperatively in the decision making process in these patients who undergo NSM, especially with a plan for DTI who may or will receive PMRT.

The second consideration relates to capsular contracture of radiated implants. DTI does not allow for revision of a radiated capsule around the permanent implant to perform capsular release and fat grafting, which is usually performed at the second stage (exchange of tissue expander for permanent breast implant) of a two-stage implant reconstruction after PMRT. There is no debate that radiation increases the rates of capsular contracture and complications in implant-based breast reconstruction [5]. The opportunity to perform a capsulotomy (surgical release of implant capsule after radiation) followed by fat grafting into the radiated scar contracture released breast skin is significant. However, this advantage needs to be balanced against the risk for wound healing problems that result from performing the second stage of implant reconstruction after PMRT. These patients have a significant risk for implant loss due to mastectomy incision dehiscence and implant infection. These are catastrophic complications in a radiated patient in which the breast skin subsequently becomes unusable for further reconstruction because it shrinks and contracts after implant removal. Unfortunately, after this complication, the ability to place another tissue expander to attempt to recreate a breast skin envelope and place another implant is fraught with even more disastrous complications like rupturing or tearing of the expanding, radiated breast skin. Most of these patients require an autologous tissue flap reconstruction in order to salvage breast reconstruction, the outcome of which is often suboptimal.

DTI without NSM is not preferred because of the benefit that the tissue expander provides in recreating the 3-dimensional shape of the breast skin envelope that is usually lost with resection of the NAC. Except for very small NACs, most NACs comprise a significant portion of the central breast mound, and resection results in a flattened shape without central projection. The tissue expander assists in recruiting additional skin and restoring central projection and the desired teardrop shape back to the breast mound. In addition, resection of the NAC as performed with non-NSM, except for large-breasted patients, can make it difficult to place the desired breast implant size at the time of mastectomy. Of course, placement of the implant at mastectomy, even without NAC preservation, is possible in large-breasted patients, which obviates the need for a second surgical procedure to exchange the tissue expander for the implant. This reduces the risk for surgical infection, which is significant for these high-risk larger-breasted patients.

The potential need for delayed resection of the NAC is something very important for the reconstructive surgeon to keep in mind. An important consideration with NSM is the impact that a positive NAC margin found on permanent section will have on the chosen method of breast reconstruction. Even medical centers that routinely perform intraoperative frozen sections of the NAC tissue may reveal residual disease on permanent sections that can necessitate the need for delayed resection of the NAC. When the permanent implant is placed at the time of NSM, delayed NAC resection requires a significant revision of the breast reconstruction because the breast implant must be exchanged for a tissue expander. As a result of delayed resection of the NAC, the reduced dimensions of the breast skin envelope will not continue to accommodate the breast implant. To the contrary, when a tissue expander is placed at NSM, the need for delayed NAC resection does not require a significant revision. It usually just requires some removal of saline from the expander and linear closure of the breast skin defect that results from delayed NAC resection. Therefore, the breast reconstructive surgeon should consider in patients at risk for positive NAC tumor margins, placement of a tissue expander placement and not a permanent implant at NSM.

A similar circumstance arises in the setting of significant postoperative NAC necrosis with subtotal or total loss of the NAC due to inadequate perfusion. As with delayed NAC resection because of a positive tumor margin, significant nipple loss due to inadequate blood flow, usually will not adequately heal when the permanent implant was placed at NSM. However, in cases that ADM was utilized along with DTI and NSM, secondary healing of a necrotic NAC may occur without the need for implant removal and exchange for a tissue expander. In patients that appear intraoperatively to have compromised perfusion to the NAC after completion of NSM, the reconstructive breast surgeon should consider tissue expander placement, instead of a planned permanent implant. It is prudent for the reconstructive breast surgeon to always order a tissue expander in addition to a permanent implant when performing DTI along with NSM.

Historically, most patients who require axillary lymph node dissection (ALND), as opposed to sentinel lymph node biopsy (SLNB) were not considered candidates for NSM. However, an increasing number of breast cancer patients with more-advanced stages of disease, even those patients who will receive radiation therapy, are being considered for NSM. In these patients, it is important to remember that ALND, but not SLNB, can decrease the blood supply to the NAC and subsequently increase the risk for necrosis [2]. In these patients who undergo NSM along with ALND, immediate placement of a tissue expander and not the permanent implant may be preferable to limit the pressure on the overlying NAC and allow for the ability to deflate the expander postoperatively in the event the NAC appears mottled during the perioperative period.

Another evolving trend in NSM breast reconstruction, especially with DTI and ADM is to not use the pectoralis major muscle as a component of the breast reconstruction. Placement of the permanent implant in the prepectoral position provides many advantages and a few disadvantages (Fig. 12.1). Leaving the pectoralis muscle attached to the chest wall and undisturbed leads to less postoperative pain and a faster recovery. Not including the pectoralis muscle in implant-based breast reconstruction avoids an animation deformity, postoperative contraction of the pectoralis muscle overlying the breast implant, which is troubling to patients and difficult to repair. However, absence of the pectoralis muscle can leave the patient deficient of tissue in the superior pole of the reconstructed breast. Shaped, breast implants with high vertical dimensions (tall implants) can help minimize this deformity, but these patients often still require serial fat grafting to the upper pole of the reconstructed breast. Not having the pectoralis major muscle underlying the mastectomy incision or the NAC can lead to exposure of the breast prosthesis due to postoperative wound dehiscence or NAC necrosis in patients that undergo non-NSM or NSM, respectively.

Despite the many advantages of prepectoral implant placement, the author still prefers to include the pectoralis muscle in non-NSM implant-based breast reconstruction. However, the author uses complete coverage of the expander or implant with a full sheet of ADM for both NSM and non-NSM. In the circumstance of a non-NSM with a standard mastectomy incision, the pectoralis muscle is positioned overlying the ADM in a vest-over-pants fashion, which allows for the pectoralis muscle to be underlying the mastectomy incision. With an inframammary mastectomy incision, which is preferred with NSM, the pectoralis muscle is not needed for the reconstruction. In this scenario, the prepectoral position is used for the direct insertion of a permanent implant at the time

Fig. 12.1 A 42-year-old female with stage 1 right breast cancer who also desired a left prophylactic mastectomy. Preoperative views (**a**, **b**, and **c**) the patient had C-cup-sized breasts without breast ptosis. Postoperative views (**d**, **e**, and **f**) the patient underwent bilateral nipple-sparing mastectomies with prepectoral positioning of a shaped, silicone gel implant (DTI) along with complete implant coverage with ADM. Note, the deficiency of tissue coverage in the upper aspects of the reconstructed breasts. This results from the absence of the pectoralis muscles and is usually treated with autologous fat grafting

of NSM. However with SSM, utilizing the standard mastectomy incision located on the breast mound, it is essential to position the pectoralis muscle underlying the mastectomy incision. Placement of the pectoralis muscle underlying the standard mastectomy incision is imperative for adequate wound healing. ADM only underlying a standard mastectomy incision leaves the mastectomy incision vulnerable to dehiscence and poor wound healing if it becomes exposed during the healing process.

Although immediate placement of the permanent implant can be less expensive and more convenient, it has some disadvantages when compared with a two-stage approach with placement of the tissue expander at NSM, followed by exchange for a permanent implant, typically 3–6 months later. Other patients who may benefit from a two-staged approach to implant-based breast reconstruction include: patients who may or will receive PMRT, patients with ptotic-shaped breasts (breast ptosis, grade 2 or 3), patients with D-cup-sized breasts or larger who will require a large-sized permanent breast implant (greater than 600 cc), patients with the potential for a close or positive postoperative NAC tumor margin, patients at risk for a nontechnical performed NSM, and those patients who will receive ALND.

A two-staged approach to implant reconstruction with NSM allows for some additional advantages including the ability to fat graft the breast envelope at the second stage (exchange of tissue expander for permanent breast implant). By the time of the second stage, the ADM placed at the first has already integrated into the undersurface of the breast skin envelope. Integration of the ADM into the lower pole breast skin allows for a tissue plane for fat deposition which is not readily available at the time of NSM when a DTI, one-stage approach is used for breast reconstruction.

It is important to understand that a ptotic-shaped, natural-appearing reconstructed breast that is symmetric with the contralateral native breast can be achieved with two-stage breast reconstruction as long as intraoperative saline filling of expanders is performed at the time of insertion. A two-staged approach with NSM also allows for second stage conversion of the reconstruction to a flap if PMRT is found to be required after review of the permanent sections, or to perform so-called, "interval fat grafting" overlying the tissue expander after PMRT prior to exchange for permanent implant. The author developed interval fat grafting to decrease the risk for implant loss after exchange of a radiated tissue expander for a permanent breast implant. In addition, a two-staged approach to implant reconstruction with NSM, allows for the breast reconstructive surgeon to "wait and see" the reaction of the breast skin envelope to the radiation, and then determine the best definitive method for breast reconstruction (implant, implant and flap, or flap).

Despite some promising studies showing the ADM may reduce capsular contracture in radiated breast reconstructions [5], it is unclear whether it is preferable to radiate the permanent implant or the tissue expander and then exchange for the permanent implant. The author prefers to not radiate the permanent implant, but rather to place a tissue expander with complete ADM coverage and then to radiate the tissue expander. The author then performs interval fat grafting, 3 months after PMRT, and then exchanges for the permanent implant, 3 months after the interval fat grafting procedure. This approach allows for the ADM to fully incorporate into the breast skin prior to permanent implant placement, which may lesson capsular formation and subsequent long-term contracture. This can be especially important in patients who have NSM and will undergo PMRT. Despite the advantages that have been mentioned with a two-stage approach, the risk for infection with 2 separate prosthetic placements is certainly higher, along with a higher associated cost.

With the increasing use of PMRT in conjunction with NSM, it has become critical to understand if ADMs decrease the adverse effects of radiation on implant-based breast reconstruction, specifically, if ADMs decrease the incidence of capsular contracture and the need for reoperation, especially in the setting of PMRT [4]. Early clinical results indicate that ADMs may decrease capsular contracture by decreasing, slowing, or delaying the inflammatory process and pseudocapsule formation around the breast implant [4]. These findings are especially important for patients who have NSM, of which the majority undergo implant-based reconstruction along with an ADM. As more reconstructive breast surgeons gain more clinical experience, the use of NSM in patients that will receive PMRT is becoming only a relative contraindication.

If the assumption is that ADMs decrease capsular contracture, it becomes important to understand how long it takes for the ADM to revascularize into the breast skin envelope. When a permanent implant is placed at NSM along with ADM in patients who will receive PMRT, it is imperative for the surgeon to know if the benefit of the ADM in reducing the inflammatory response and reducing peri-implant capsular formation will be achieved. The timing of delivery of PMRT in relation to the placement of the ADM can vary depending on whether the patient will receive neoadjuvant or adjuvant chemotherapy. It may be that two-stage implant reconstruction, which allows for the permanent implant to be placed after complete integration of the ADM into the skin envelope, especially in the circumstance of neoadjuvant chemotherapy, may offer the greatest benefit. This may be an important consideration in patients who will receive PMRT in whom the risk for capsular contracture is significant.

An important animal study performed a microcirculatory analysis that revealed early ADM angiogenesis at 4 weeks on the breast skin flap surface only, not the tissue expander surface [6] and, a well formed vasculature on both surfaces at 8 weeks. Both surfaces were highly vascularized by 12 weeks. ADM showed complete remodeling and revascularization by 12 weeks after implantation. Therefore, in patients who undergo neoadjuvant chemotherapy, a two-staged implant reconstruction should be considered because the ADM will not be fully integrated into the breast skin prior to PMRT, and the patient may not receive the anti-inflammatory advantages of ADM. In these patients who receive neoadjuvant chemotherapy and subsequent NSM and DTI along with ADM, who then require PMRT, usually 4–6 weeks after surgery, it is unlikely that the ADM will be protective from the adverse effects of radiation on the breast implant. Adjuvant chemotherapy, often administered over a 4- to 6-month period after the surgery, prior to PMRT, should allow adequate time for complete integration of the ADM into the breast skin prior to PMRT. In these patients, the tissue expander is usually exchanged for the permanent breast implant usually 4 months after the completion of PMRT, thereby allowing the patient to potentially benefit from the protective effects of the fully integrated ADM. However, as mentioned above, the author performs an interval fat grafting procedure overlying the radiated tissue expander, and then waits 3 months for the grafted fat and mesenchymal stem cells to lead to neo-angiogenesis and neo-adipogenesis, before exchanging for the permanent breast implant.

Other animal research studies [7, 8], that have evaluated ADMs and irradiated breast implants have found no differences in ADM thickness when ADM is irradiated or not irradiated. These studies have also shown diminished early cellular invasion into the implant capsule, decreased radiation-related inflammation and diminished pseudoepithelium formation around the breast implant.

A recent study in humans [4] evaluated irradiated and non-irradiated breast implants along with the use of ADM or nonuse of ADM. Biopsies of periprosthetic capsules of six patients were analyzed histologically. There were no differences in cell counts between non-ADM periprosthetic capsules and ADM periprosthetic capsules. However, the architectural makeup showed a five times reduction in macrophages and 2.5 increase in elastin in ADM periprosthetic capsules. Irradiating the ADM did not significantly alter the architecture or cellular components of the ADM capsules. In general, cellular counts in the peri-implant capsules were greatly increased by irradiation. However, cell counts were significantly greater in irradiated, non-ADM capsules than in the irradiated, ADM capsules.

A practical question to answer for the reconstructive breast surgeon, is how often will patients who undergo NSM, especially those who have DTI, subsequently require the NAC to be excised for a positive tumor margin? The published literature is clear that NAC preservation is safe in selected patients, with a long term incidence of direct NAC recurrence of approximately 1 % [9–20]. Most studies have shown that intraoperative frozen section of the NAC is a relatively accurate predictor of NAC involvement. To ensure a low rate of postoperative positive NAC tumor margins and the subsequent need for NAC resection, many medical centers perform an intraoperative assessment of the NAC, including an intraoperative specimen radiograph to assess for retained microcalcifications extending to the NAC and four quadrant frozen sections of the posterior NAC tissue in patients undergoing NSM along with DTI.

In summary, excluding the clinical situations mentioned above in this chapter, the author recommends NSM in patients in which the oncology is conducive because of the significant benefits it provides to patients not only in regards to the improved outcomes but also because of the convenience of a single surgical procedure and the reduced complexity for reconstruction. Preservation of the NAC preserves the 3-dimensional shape of the breast skin envelope which is essential for excellent outcomes in breast reconstruction.

Conflicts of Interest Dr. Kronowitz has no conflicts of interest to report.

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13 Acellular Dermal Matrices: To Use or Not?

Maurice Y. Nahabedian

Introduction

Over the past decade, advancements in the management of breast cancer have fostered our ability to achieve oncologic safety and provide excellent reconstructive outcomes. Achieving excellent outcomes is dependent upon a variety of factors that make this possible. Nipple-sparing mastectomy coupled with the use of prosthetic devices, acellular dermal matrices (ADM), and autologous fat grafting has enabled reconstructive breast surgery to mimic aesthetic breast surgery. The concept of the bioengineered breast has revolutionized the methods by which breast reconstruction is now performed. Prosthetic devices are available in shaped and round forms with filler materials consisting of saline and silicone gel with variable degrees of cohesivity. Autologous fat grafting has gained acceptance as a safe and effective method of incorporating the patient's own body fat into the reconstructed breast to improve contour and skin quality. Finally, the use of acellular dermal matrix (ADM) can provide additional tissue support and reduce the incidence of capsular contracture. All of these elements are important factors that have improved the quality of prosthetic breast reconstruction.

Another equally important advancement is that breast surgeons and plastic surgeons now have an improved understanding and appreciation of one-another's expectations and practices. Breast and plastic surgeons acknowledge that the perfusion, thickness, and quality of the mastectomy skin flap are important factors leading to an optimal aesthetic outcome. During the mastectomy, breast surgeons preserve the internal mammary perforating vessels that will improve the vascularity of the skin flaps, use gentle retraction systems to minimize tissue trauma, and maintain the thickness of the subcutaneous layer to provide a soft tissue cover over the prosthetic device. Adoption of these practices have enabled nipple-sparing mastectomy to become a reality with a low incidence of tissue-related complications.

With the increasing acceptance of nipple-sparing mastectomy, plastic surgeons have a broad armamentarium of reconstructive options. Prosthetic breast reconstruction can be performed as a direct-to-implant (DTI) or in two stages using a combination of tissue expanders and implants. Prosthetic reconstruction can also be performed using total muscle coverage, partial muscle coverage, or prepectoral techniques. Partial muscle coverage and prepectoral techniques are facilitated by the use of ADM (Figs. 13.1 and 13.2). Total muscle coverage techniques do not require the use of

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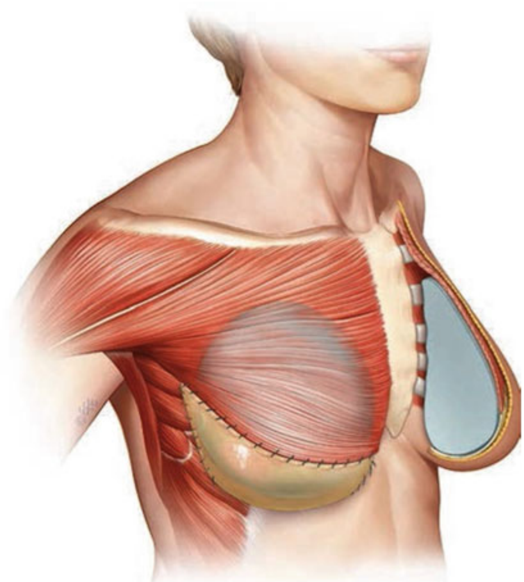

Fig. 13.1 The partial subpectoral approach depicted and is facilitated using ADM. The ADM is sutured to the inferior edge of the pectoralis major muscle and to the inframammary fold (Image courtesy of Acelity—A LifeCell company)

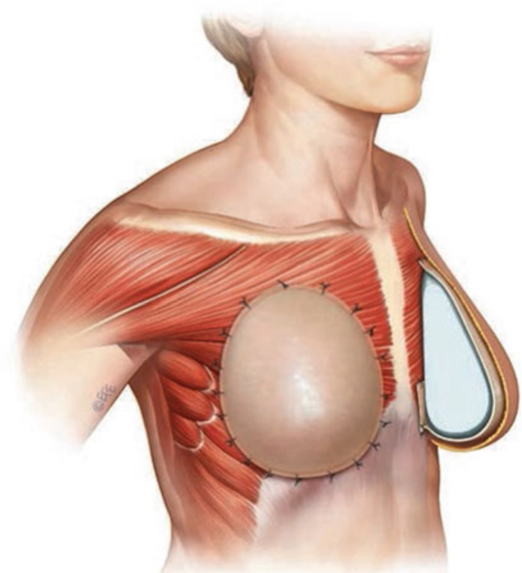

Fig. 13.2 The prepectoral approach is depicted using ADM. The ADM is sutured circumferentially around the prosthetic device (Image courtesy of Acelity—A LifeCell company)

ADM. Advocates for ADM argue that aesthetic outcomes are improved and that long-term complications are reduced [1–3]. Opposing views are that excellent aesthetic outcomes can still be achieved with fewer short-term complications without the use of ADM [4, 5].

This chapter will examine the controversy as to whether or not acellular dermal matrices provide a substantial benefit to surgical and aesthetic outcomes in the setting of nipple-sparing mastectomy and prosthetic breast reconstruction. A review of the various components of this operation is provided.

Nipple-Sparing Mastectomy

Nipple-sparing mastectomy can be performed in the setting of therapeutic or prophylactic mastectomy [6, 7]. Classic indications are based on breast and tumor characteristics that include mild to moderate breast volume and tumors with a diameter of less than 3 cm that are located at least 4 cm from the nipple areolar complex [8]. However, these parameters are being challenged, as strategies for nipple areolar preservation in women with large or ptotic breasts are now possible [9, 10]. In addition, larger tumors in excess of 3 cm may no longer be a contraindication as long as adequate margins are obtained [11].

Preservation of the entire skin envelope of the breast provides the plastic surgeon with a variety of reconstructive options. These will be dependent on the quality and viability of the mastectomy skin flaps. Assessment of the perfusion to the mastectomy skin flap and nipple areolar complex is achieved using clinical observation; however, fluorescent angiography can provide additional useful information [12]. When tissue perfusion is sufficient and skin thickness is adequate, either a direct-to-implant or two-stage reconstruction can be performed. The two-stage reconstruction involves placement of a tissue expander followed by replacement with a permanent implant. When tissue perfusion is compromised, a two-stage or delayed reconstruction is considered. The rationale for this is to minimize any pressure placed on the nipple areolar complex. Direct to implant reconstruction is usually performed in the setting of partial muscle coverage in order to release the inferior insertion of the pectoralis major muscle and to permit a hand-in-glove fit of the permanent implant within the skin envelope. Direct-to-implant reconstruction is not commonly performed in the setting of total muscle coverage because of the challenges associated with placement of a prefilled silicone gel implant under the pectoralis major muscle following mastectomy. Two-stage reconstruction can be considered with either partial or total muscle coverage techniques. With the direct-to-implant and two-stage procedures in the setting of partial muscle coverage, the use of acellular dermal matrix is often considered. With total muscle coverage, ADM is usually not necessary because the device is already completely covered. The purpose of ADM will be further described.

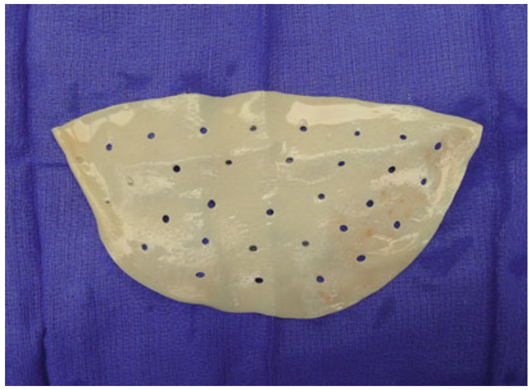

Fig. 13.3 Acellular dermal matrix (AlloDerm) in its typical form that is contoured, perforated, and ready to use (LifeCell Corporation, Bridgewater, NJ)

Acellular Dermal Matrix

Acellular dermal matrix is cadaveric skin derived from human, porcine, or bovine sources [13]. It is processed to remove all cellular elements such as fibroblasts, erythrocytes, leukocytes, and bacteria and to retain noncellular elements such as collagen, hyaline, elastin, and fibronectin. ADM has the capacity to recellularize and revascularize when in contact with adjacent host tissues [14]. The role of ADM in the setting of prosthetic devices is to provide coverage of the implant or tissue expander. This is achieved in two ways. The first is in the setting of partial muscle coverage by maintaining coverage of the device from the divided inferior edge of the pectoralis major muscle to the inframammary fold [15–18]. The second is in the setting of prepectoral coverage where ADM is used to line the subcutaneous mastectomy skin envelope and to compartmentalize the device [19]. The primary function of the ADM in both settings is to provide additional soft tissue support, compartmentalization, and prevention of window-shading or upward movement of the pectoralis major muscle. It is beneficial in the setting of immediate direct-to-implant as well as two-stage prosthetic reconstruction.

Acellular dermal matrices come in a variety of shapes and sizes and are manufactured by a variety of companies (Fig. 13.3). Not all ADMs are created or perform equally. The processing and sterilization methods vary amongst the different companies (Table 13.1). A thorough review is not possible within the context of this chapter; however, when selecting an ADM, surgeons should review the relevant data and literature, study the performance profile, and be aware of the mechanism of action. Readers are encouraged to review the referenced manuscripts for a complete breakdown of the various ADMs [13, 20–24].

The essential component of ADM is the extracellular matrix. The ability of an ADM to revascularize and recellularize when adjacent to vascularized tissue is dependent upon the integrity of the extracellular matrix. The integration of ADM to the mastectomy skin flap requires a certain degree of inflammation for wound healing to occur. Once integrated, the ADM will provide long-term tissue support without resorption or conversion to scar or capsule. Histologic examination of ADM following implantation into the breast demonstrates repopulation with red blood cells and fibroblasts with retention of the elastin [25, 26]. There is a clear line of demarcation between scar tissue and the ADM.

A common clinical observation following the use of prosthetic devices and ADM is that the amount of scar tissue formed along the surface of the ADM adjacent to the prosthetic device is reduced compared to when ADM is not used [2]. The physiologic basis for this is that there are specific cell-signaling mechanisms that limit the amount of collagen deposited on the surface of the ADM adjacent to the device. The host

Table 13.1 The characteristics of various acellular dermal matrices are listed

	AlloDerm *(RTU)*	Flex HD	DermaMatrix	AlloMax
Source	Human	Human	Human	Human
Cross-linking	None	None	None	None
Decellularization and processing	Proprietary	Hypertonic bath	Hypertonic bath	Acetone, hypo/ hypertonic bath, H_2O_2
Sterilization (SAL)	Radiation (10^{-3})	Detergents (aseptic)	Detergents (sterile)	Radiation (10^{-6})

AlloDerm (LifeCell, Bridgewater, NJ), Allomax (Bard, Warwick, RI), Dermamatrix (MTF, Edison, NJ), Flex HD (Ethicon, West Sommerville, NJ)
RTU ready to use, *SAL* sterility assurance level

response to the ADM is that of "host recognition" because of the intact extracellular matrix that allows for incorporation and regeneration. Thus, capsular contracture appears to occur less frequently when ADM is used. The mechanics can be explained based on principles regulating wound contraction given that it is reduced in the setting of a full thickness skin graft. Although ADM is not a skin graft in the true sense because it lacks the cellular elements of a full thickness skin graft, it does possess the mechanical properties of a full thickness skin graft. When a full thickness skin graft is placed on a raw skin surface, it will inhibit wound contraction by inhibiting the activity of myofibroblasts that are necessary for contraction to occur. When ADM is used, collagen deposition occurs at the junction of the graft and the tissue surface and is not exaggerated [25, 26]. For capsular contracture to occur around a breast implant, a spherical capsule must be present. When ADM is used, the spherical nature of the capsule is disrupted, thus capsular contracture is rarely observed in nonradiated patients.

Several experimental and clinical studies have attempted to explain this phenomenon of reduced scar formation. In an experimental study, silicone sheets were implanted into the dorsum of 20 rabbits [27]. In ten rabbits, the silicone sheets were wrapped in ADM and in another ten rabbits, silicone sheets were not wrapped in ADM. The periprosthetic tissue was analyzed at 13 weeks. The ADM cohort demonstrated thin capsule with minimal cellularity or inflammatory infiltrates, whereas in the non-ADM cohort, the capsule was thick with increased cellularity. In another experimental study, implanted devices that were partially wrapped in ADM demonstrated less capsule formation than devices that were not wrapped in ADM [28]. These two studies suggest that capsule formation is minimized in the setting of ADM. The effect of radiation therapy on ADM incorporation has also been studied [29]. Komorowska-Timek demonstrated that ADM (AlloDerm, LifeCell Corporation, Bridgewater, NJ) decreases radiation-related inflammation in a murine model and may lessen the progression to capsule formation and ultimately capsular contracture.

In a clinical study, the histology of implanted ADM and native capsule was studied in 23 women following prosthetic reconstruction [25]. ADM histology demonstrated a lack of granulation tissue and vascular proliferation as well as a mild increase in collagen and inflammatory infiltrates. Capsule histology demonstrated abundant granulation with mild vascular proliferation as well as a moderate increase in collagen and inflammatory infiltrates. This study demonstrated that the presence of ADM appeared to attenuate the process of fibrosis. Explanations are debatable but are most likely related to the diminished inflammatory response. The association of prolonged inflammation leading to increased fibrosis is well known. Other studies have demonstrated that in women with silicone gel implants and capsular contracture, the capsules are characterized by vascular proliferation and the presence of a lymphocytic and mononuclear infiltrate as well as silicone particles [26]. This was not seen in the setting of ADM and silicone gel implants.

Based on the observation that periprosthetic fibrosis or capsular contracture may be minimized in the setting of ADM, some surgeons are advocating prepectoral placement of the device with total anterior coverage using ADM. The rationale is that the device will remain covered in the event of delayed healing and that the operation would be simplified by not having to elevate the pectoralis major muscle. The implications of this technique are that tissue support would be provided by the ADM, capsular contracture would be minimized because of the ADM, and that breast animation would be eliminated because the device is positioned above the pectoralis major muscle.

Surgical Techniques

Nipple-Sparing Mastectomy and ADM-Assisted Reconstruction

Nipple-sparing mastectomy with ADM can be performed through an inframammary, vertical infra-areolar or lateral incision. The choice between the various incisions is based on surgeon preference, tumor location, and nipple position. Laterally based incisions are usually designed in a lazy S fashion to prevent lateralization of the NAC that sometimes occurs with scar contracture. Inframammary incisions are made from the midline and extend laterally to a length of 6–8 cm. Vertical infra-areolar incisions are recommended when a mild to moderate amount of nipple elevation is desired. All approaches will provide ample access to the breast parenchyma to ensure that an adequate mastectomy has been performed.

Patients are marked preoperatively while standing. Following completion of the mastectomy, the skin flaps are assessed for viability and perfusion. Tissue perfusion is assessed using direct observation for arterial and venous bleeding from the cut edges as well as color and capillary refill of the mastectomy skin flaps. When questionable, fluorescent angiography can be considered to assess perfusion using infrared spectroscopy and indocyanine green. The decision between DTI and 2-stage reconstruction is made based on volume requirements, tissue thickness and perfusion, and patient/surgeon preference.

Partial Subpectoral/DTI

Direct-to-implant (DTI) reconstruction is often considered for women with mild to moderate breast volume following nipple-sparing mastectomy [2, 3]. The argument for DTI is that no skin has been excised; therefore, there is no need for tissue expansion. Partial subpectoral coverage is often performed because the divided and elevated inferior edge of the pectoralis major muscle allows for excellent projection of the permanent implant. Acellular dermal matrices play a critical role in these cases in order to adequately compartmentalize the implant, control the position of the pectoralis major muscle, and to provide additional tissue support.

There are several technical variations in the setting of partial subpectoral coverage and direct to implant reconstruction using ADM. The described technique is one that is commonly performed by the author. Figures 13.4, 13.5, 13.6, and 13.7 illustrate a patient having nipple-sparing mastectomy and direct-to-implant reconstruction using an ADM (AlloDerm—LifeCell Corporation, Bridgewater, NJ). A range of permanent implants is considered; however, only 1–3 are typically selected based on bio-dimensional planning. Following completion of the nipple-sparing mastectomy, the inferior border of the pectoralis major muscle is divided and the subpectoral space is created. The superior edge of the ADM is sutured to the

Fig. 13.4 Preoperative view of a woman with mild breast volume prior to nipple-sparing mastectomy

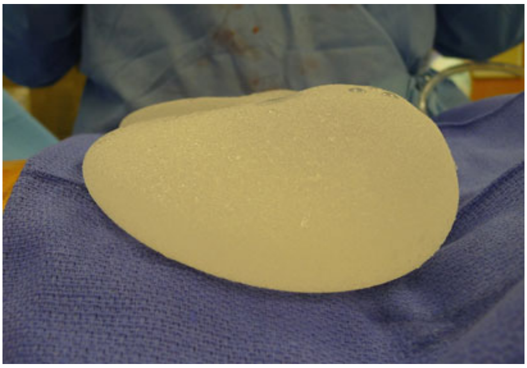

Fig. 13.5 A shaped permanent silicone gel implant is selected based on biodimensional planning

Fig. 13.6 The bilateral nipple-sparing mastectomy is performed through a lateral areolar incision. The ADM and the shaped silicone gel implant are inserted, oriented, and compartmentalized

inferior border of the pectoralis major muscle. A template of the implant is used to determine where to suture the lateral edge of the ADM to the chest wall. Once determined, the implant is inserted and positioned along the medial cul-de-sac and the desired inframammary fold. The ADM is trimmed so that it will lie along the inferior and lateral mastectomy skin flaps and adequately compartmentalize the implant. The inferior and lateral edges of the ADM are sutured to the chest wall using absorbable sutures.

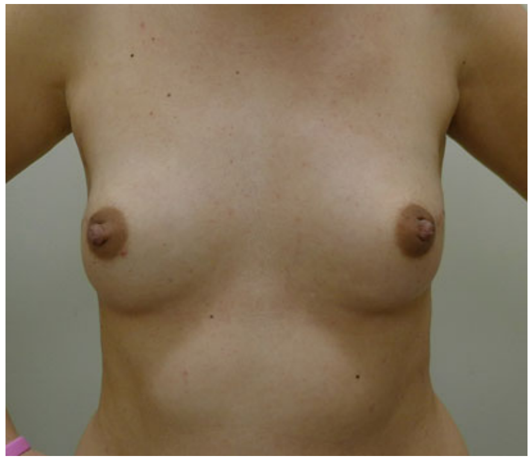

Fig. 13.7 Postoperative view at 6 months demonstrating excellent symmetry, volume, and contour

Partial Subpectoral/2-Stage

Two-stage reconstruction is defined as placement of a temporary tissue expander followed several months later by a permanent implant [17, 18, 30, 31]. A commonly asked question is why use a tissue expander in the setting of nipple-sparing mastectomy because the skin envelope is intact. There are several explanations; the first being that the mastectomy skin flaps may be thin and that perfusion to the skin and nipple areolar complex is questionable or uncertain. Placing a prefilled implant may cause additional pressure on the nipple areolar complex further compromising perfusion and possibly resulting in nipple areolar necrosis. A tissue expander is useful because it can be minimally filled avoiding undo pressure on the compromised skin flaps. Another reason is that selection of an optimal permanent implant is challenging given that there is an assortment of shapes, volumes, fillers, and textures. Selection of the optimal permanent implant is best made during the second stage.

As with DTI, there are several technical variations of the two-stage technique using ADM. The two-stage technique using ADM can be performed immediately or as a delayed reconstruction. With a delayed reconstruction the use of ADM is considered when there is skin redundancy and the mastectomy defect can be recreated. When the skin envelope is tight, ADM may not provide the same benefits. The described approaches are commonly performed by the author. Figures 13.8, 13.9, 13.10, and 13.11 illustrate a patient having nipple-sparing mastectomy and immediate 2-stage prosthetic reconstruction using ADM. Figures 13.12, 13.13, 13.14, and 13.15 illustrate a patient that had unilateral nipple-sparing mastectomy and will have delayed 2-stage reconstruction using ADM. Following completion of the nipple-sparing mastectomy,

Fig. 13.8 Preoperative view of a woman with mild to moderate breast volume prior to nipple-sparing mastectomy

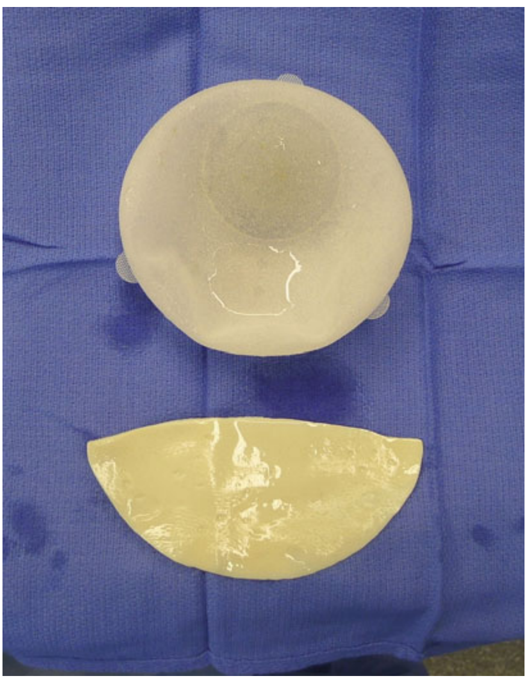

Fig. 13.9 The tissue expander (Allergan style 133 MV, Irvine, CA) and the contoured ready-to-use ADM (AlloDerm) are depicted. The dimensions of the ADM (small, medium, large) are selected based on the base width of the tissue expander

Fig. 13.10 The bilateral nipple-sparing mastectomy is performed through an inframammary incision. The ADM and the shaped silicone gel implant are inserted, oriented, and compartmentalized

Fig. 13.11 Postoperative view at 1-year demonstrating excellent symmetry, volume, and contour

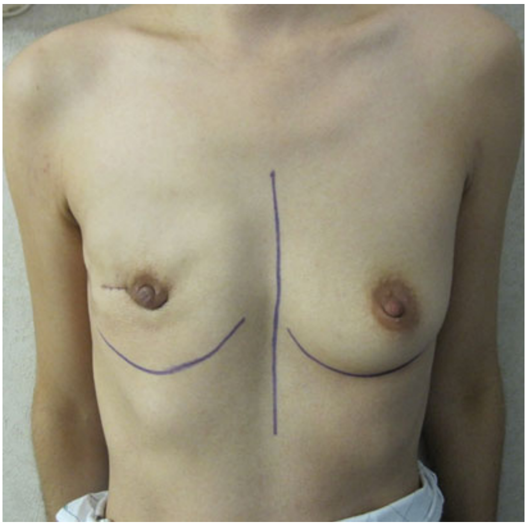

Fig. 13.12 Preoperative photograph following right nipple-sparing mastectomy

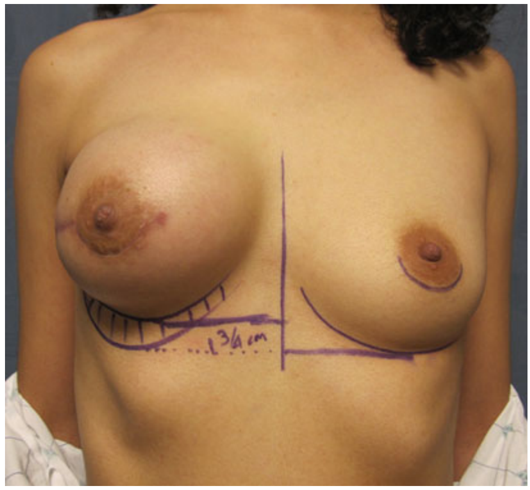

Fig. 13.14 The patient has been fully expanded and will have right implant exchange, lowering of the right inframammary fold, and a left augmentation mammaplasty for symmetry

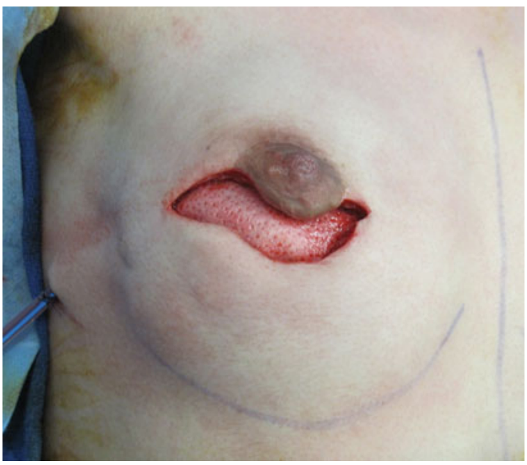

Fig. 13.13 The partial subpectoral plane has been recreated following by compartmentalization of the tissue expander using ADM

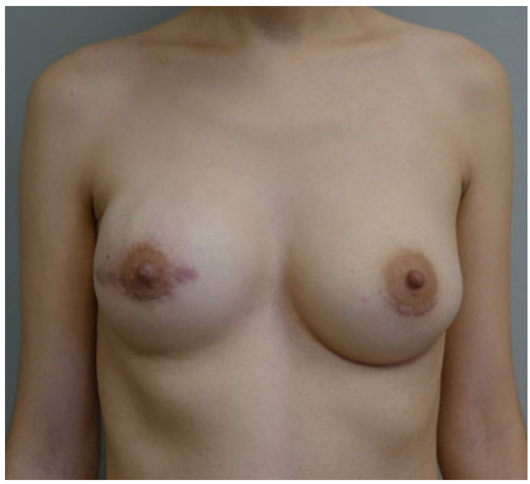

Fig. 13.15 Postoperative view at 1-year demonstrating good volume and contour symmetry

the inferior border of the pectoralis major muscle is divided and the subpectoral space is created. The superior edge of the ADM is then sutured to the inferior border of the pectoralis major muscle. A tabbed tissue expander is obtained, positioned along the medial border and inframammary fold, and sutured to the fascia of the chest wall. The ADM is draped over the tissue expander and the inferior edge is sutured to the chest wall at the inframammary fold. All air is evacuated from the tissue expander and replaced with saline. The tissue expander is typically filled to 40–60 % of capacity intraoperatively. The remainder of the expansion occurs in the office. The exchange to a permanent implant typically occurs at 3 months.

Prepectoral/1 or 2 Stage

A relatively new approach for prosthetic breast reconstruction is the prepectoral placement of a permanent implant or tissue expander [19]. The rationale for this is that by leaving the pectoralis major muscle undisturbed, animation deformities of the breast will be eliminated and postoperative pain and muscle spasm will be minimized. An absolute requirement for this approach is that the mastectomy skin flaps be thick and well perfused. The use of fluorescent angiography is frequently considered to assess tissue perfusion. Delayed healing of the skin flaps could result in device exposure and reconstructive failure. The mastectomy itself can be skin- or nipple sparing. The use of ADM is highly recommended for this approach in order to adequately compartmentalize the device, to provide additional tissue support, and to provide a barrier between the skin and the device. Larger sheets of ADM are usually used with this technique because the entire anterior surface and sometimes posterior surface of the device is covered.

Total Subpectoral/2 Stage

Some surgeons prefer total subpectoral coverage of the device following mastectomy [4, 5, 32]. This can be performed in the immediate and delayed setting following nipple-sparing mastectomy. The rationale for this is that by covering the entire device with vascularized muscle, poorly perfused mastectomy skin flaps will have a lesser impact on the outcome. Delayed healing for the skin usually does not result in exposure of the device or reconstructive failure. Given that the device is completely covered with muscle, ADM is usually not necessary during the initial operation. In most cases of total muscle coverage, a tissue expander is used rather than a permanent implant because the subpectoral space is relatively tight and requires a low volume device. Patients typically require gradual expansion in the office at weekly intervals. During the second stage, the tissue expander is exchanged for a permanent implant. The inferior border of the pectoralis muscle is sometimes released to enhance projection. In some cases, a sheet of ADM can be placed along the lower pole of the breast for additional tissue support and to reduce the incidence of capsular contracture.

Analysis of Outcomes

An ongoing debate with prosthetic reconstruction is total muscle coverage without ADM versus partial muscle coverage with ADM [4, 5, 30]. Both methods are safe, effective, and capable of delivering excellent outcomes. The question has focused on whether one is better than the other in terms of breast aesthetics and patient satisfaction. In the ideal setting, a comparison of aesthetic outcomes following total versus partial muscle coverage of a prosthetic device would entail a randomized, prospective study. However, this would be a formidable task because enrollment in a bilateral setting may be limited and a unilateral study would not provide a direct comparison.

In a recent case of nonsynchronous bilateral breast cancer, a woman had bilateral nipple-sparing mastectomy and direct-to-implant reconstruction [33]. The two operations were three years apart. Of note is that the right and left breast reconstructions were identical in all aspects except that total muscle coverage was performed on the left breast and partial muscle coverage with ADM was performed on the right (Figs. 13.16, 13.17, and 13.18). The postoperative

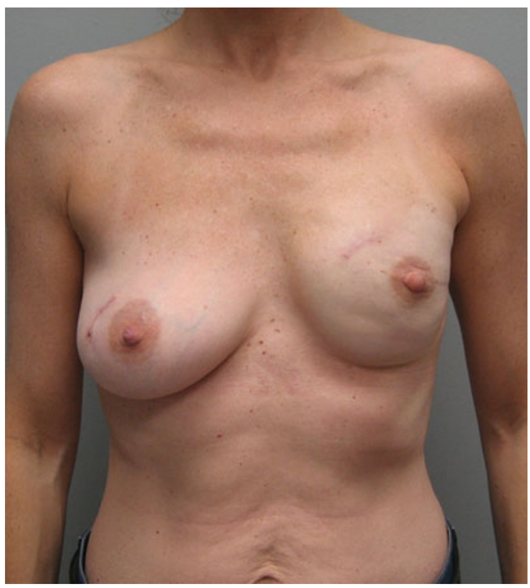

Fig. 13.16 Preoperative image of a woman following left nipple-sparing mastectomy and direct-to-implant reconstruction (300 cc Allergan style 20) in a total subpectoral position. A new diagnosis of right cancer has been made

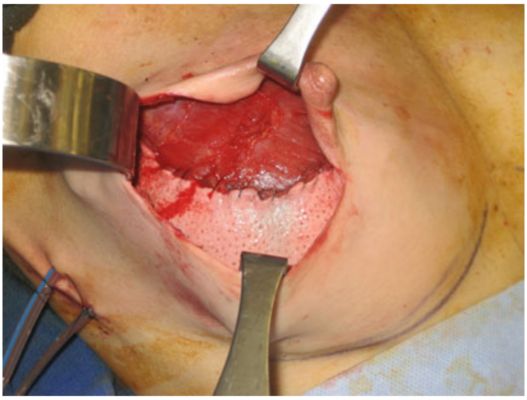

Fig. 13.17 Following the right nipple-sparing mastectomy, a direct-to-implant reconstruction (300 cc Allergan style 20) is performed in the partial subpectoral position using ADM

Fig. 13.18 Postoperative view at 2-year demonstrating excellent contour on the right and good contour on the left

outcomes for both were excellent albeit different. The differences are that the inframammary and lateral mammary folds are naturally configured on the right compared to the left. These differences are attributed to partial pectoralis major muscle coverage and the use of ADM allowing for improved lower pole projection, defined lateral breast contour, and less breast compression. Total muscle coverage has a tendency to compress the lower and lateral aspect of the breast/implant with blunting of the lateral and inframammary folds.

The benefits of total versus partial muscle coverage with or without ADM are becoming increasingly understood; however, evaluation of aesthetic outcomes has been mixed. Preminger et al. demonstrated no difference in terms of the number of postoperative expansions and aesthetic outcome [4]. Sbitany et al. demonstrated that partial muscle coverage with ADM resulted in increased intraoperative expansion, fewer postoperative expansions, and improved aesthetic outcomes [30]. Reisch et al. reviewed 605 prosthetic breast reconstructions in the setting of nipple-sparing mastectomy of which 70 % were performed using ADM and 30 % had total muscle coverage [34]. Radiation therapy was performed in 88 breasts demonstrating a trend towards increased complications (19.3 %, vs. 12.8 %, $p=0.099$) and a significant increase with implant loss (6.8 % vs. 1 %, $p=0.001$) when compared to no radiation. Removal of the nipple areolar complex secondary to malposition or positive oncologic margins was no different in the radiated and nonradiated cohorts. Retention of the nipple areolar complex in patients with radiation therapy was 90 % (79 of 88), and reconstruction failure occurred in 8 %.

The benefits of ADM in the setting of prosthetic breast reconstruction have been well documented. Salzberg et al. in an 8-year follow-up study following direct-to-implant reconstruction using ADM has demonstrated an overall complication rate of 3.9 % with capsular contracture rate of 0.4 % [2]. Complications did not differ between prophylactic and therapeutic mastectomy. Radiation therapy resulted in a fourfold increase in the complication rate. Colwell et all have reviewed 280 breasts following direct to implant reconstructions using ADM and compared outcomes to 101 breasts following 2-stage reconstructions with total muscle coverage without ADM [3]. Total complications were similar between the two cohorts (13.6 % vs 14.7 %, $p=0.777$). Ibrahim has demonstrated that overall aesthetic scores are improved by 12 % when ADM was used in prosthetic breast reconstruction compared to when it was not [35]. Specific improvements included breast contour (35.2 %), implant placement (20.7 %), lower pole projection (16.7 %), and inframammary fold definition (13.8 %)

A cost evaluation of ADM is relevant based on the expense of the material. Colwell demonstrated that a single-stage reconstruction using ADM is cost-neutral relative to the two-stage reconstruction without ADM because a second operation is not needed with the 1-stage technique [3]. Jansen et al. has demonstrated that single-stage reconstruction using ADM is cost-effective compared to two-stage without ADM in the Canadian health care system [36]. The cost benefit is increased or decreased based on the amount of ADM used and the length of the operation. De Balcam et al. in a similar study demonstrated that single-stage reconstruction using ADM is cost-effective compared to two-stage reconstruction in a Medicare-based system [37]. The cost benefit diminishes when complications are increased. In the United States, approximately 90 % of prosthetic reconstruction is performed in two-stages [38]. Krishnan et al. has demonstrated that two-stage reconstruction can be cost-effective based on quality-adjusted life years [39]. This becomes evident if complications are minimized resulting in an improvement in quality of life when ADM is used.

Conclusions

In summary, ADM has provided a significant benefit in the setting of prosthetic breast reconstruction. Its utility following nipple-sparing mastectomy has facilitated our ability to achieve predictable and reproducible outcomes. Aesthetic outcomes are improved, capsular contracture is reduced, and complication profiles are similar with or without ADM.

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Prepectoral Reconstruction with Acellular Dermal Matrix (ADM) Strattice®

14

Roland Reitsamer

Background

Conservative mastectomy techniques as nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) are more or less replacing the conventional mastectomy methods as modified radical mastectomy or simple mastectomy without compromising the oncologic safety. These conservative mastectomy techniques with conservation of the complete skin-envelope including the nipple-areola complex (NAC), or conservation of large parts of the skin envelope but loss of the NAC, can be performed easily when the tumor does not involve the skin or the NAC, or when the NAC has to be removed. An integral part of this procedure is the immediate reconstruction of the breast either expander- or implant-based or autologous tissue-based breast reconstruction. The conserved skin envelope has to be filled immediately with a volume replacement, otherwise the skin would shrink and would be lost for a delayed reconstruction. Single-stage direct-to-implant (DTI) breast reconstruction is a perfect option for patients who do not want their breast size to be changed, or patients who will have postmastectomy radiation therapy. The optimal implant placement after NSM has still to be determined and depends on various factors such as skin quality as well as on patients' wishes and preferences. The choice for the subpectoral implant placement for breast reconstruction originates from the reports of subpectoral implant placement in aesthetic breast surgery for breast augmentation, although no data exist comparing pre- and subpectoral implant placement in breast reconstruction after mastectomy. In aesthetic breast surgery several planes for implant placement are available, the subpectoral, the subfascial, and the subglandular plane. In breast reconstruction there are few alternatives. The subpectoral implant placement with complete muscle coverage using parts of the serratus muscle and the fascia of the rectus muscle with many variations results in a moderate cosmetic outcome, is painful for the patient and the surgical procedure is more complex. The partial implant coverage with parts of the pectoralis major muscle and partial coverage of the implant with acellular dermal matrix of the lower pole of the implant results in much better cosmesis, especially in patients with mild to moderate ptosis, but many disadvantages remain. These well-known disadvantages are the dissection and elevation of the pectoralis major muscle, the breast animation deformity during contraction of the pectoralis major muscle

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Table 14.1 Pros and cons for prepectoral and subpectoral implant placement

Prepectoral implant placement		Subpectoral implant placement	
Pro	Con	Pro	Con
Pectoralis major muscle intact	Visibility	Less visibility	Dissection of the pectoralis major muscle
No loss of strength	Palpability	Less palpability	Loss of strength
No breast animation	Rippling	Less rippling	Breast animation
Less pain			Painful surgery
No implant displacement			Implant displacement

(PMM), the reduction of muscle strength, postoperative pain, and a longer recovery period (Table 14.1). The insertion of the ADM to cover the lower pole of the implant should stabilize the dissected pectoralis major muscle and operate as a hammock for the implant. On the other hand, especially in less toned women, the thickness of the pectoralis major muscle is very thin, sometimes millimeters, and is very smooth, resulting in a thin layer of tissue covering the implant in the upper pole, when the implant is placed subpectorally. In a consequence of the variance in the origin of the PMM and therefore in the size of the PMM, the coverage with the PMM can vary significantly [1, 2]. In those the subpectoral implant placement does not add much to the anticipated good cosmesis. If half or up to two thirds of the implant has to be covered in the lower pole by an ADM, the question arises why not to cover the implant completely with ADM and leave the pectoralis major muscle entirely intact. We performed a series of 70 NSMs and direct-to-implant breast reconstruction with a prepectoral implant placement and covered the implant completely with a porcine ADM, Strattice®.

Patients and Methods

In 49 patients and 70 breasts NSM and single-stage direct-to-implant breast reconstructions with prepectoral implant placement and complete coverage with ADM was performed. The mean age of the patients was 47 years (min 26, max 74 years). 21/49 patients were treated with bilateral mastectomy, and 28/49 patients were treated with a unilateral mastectomy. Eleven patients were BRCA 1 and/or BRCA2 gene mutation carriers. Nine of those patients were diagnosed with unilateral breast cancer and had a bilateral NSM. Two of the mutation carriers received bilateral risk-reducing mastectomy. Ten of 21 patients with bilateral NSM were diagnosed with unilateral invasive breast cancer and chose a contralateral risk-reducing mastectomy due to fear of a second breast cancer in the other breast or due to strong family history of cancer without BRCA gene mutation. Twenty-eight of 49 patients with unilateral NSM were diagnosed with invasive multicentric breast cancer or extensive DCIS or were patients with recurrent breast cancer in the same breast. Eight patients had NSM after preoperative chemotherapy. Twelve patients had received some form of radiotherapy, six of 12 patients had radiotherapy after NSM and DTI reconstruction. Six of 12 patients were diagnosed with recurrent invasive breast cancer or recurrent DCIS and had a history of radiotherapy. The mean age of the patients was 47 years (range 26–74 years), the mean volume of the removed breast was 291 ml (range 59–875 ml) and the mean implant weight was 300 g (range 135–540 g). Nipple-sparing mastectomy was performed in all patients. In most patients, the inframammary fold incision was chosen, which is the standard incision for most patients if possible [3]. In some cases lateral S-shaped incisions, vertical incisions, or periareolar incisions were performed, depending on the former incision for lumpectomy or segmentectomy, or when skin excision was necessary due to close or positive margins (Table 14.2).

Table 14.2 Age, breast volume, implant weight, incision type, radiotherapy

Age mean, years	47
Age min, years	26
Age max, years	74
NSM bilateral, *n* patients	21
NSM unilateral, *n* patients	28
Breast volume excised mean, ml	290
Breast volume excised min, ml	59
Breast volume excised max, ml	875
Implant weight mean, g	300
Implant weight min, g	135
Implant weight max, g	540
Incision type	
Inframammary fold incision, *n* breasts (%)	55 (78.6 %)
Periareolar with extension, *n* breasts (%)	3 (4.3 %)
Vertical incision, *n* breasts (%)	7 (10.0 %)
Lateral s-shaped incision, *n* breasts (%)	5 (7.1 %)
Radiotherapy	
Radiotherapy after NSM + reconstruction	6
NSM + reconstruction after prior radiotherapy	6

Technique

For NSM the injection of tumescent solution was used in most cases. After injection of 20–40 ml of tumescent solution (5 Units vasopressin/100 ml of saline solution) per breast, the skin envelope was dissected from the breast gland carefully with blunt scissors. The dissection of the breast gland from the pectoralis major muscle was performed by electrocautery. After removal of the complete breast gland, the volume and weight of the breast gland were measured and the implant size could be determined. As most patients wanted their reconstructed breasts looking natural and like their original breasts, we used anatomical implants and implant sizes resembling the removed breast volume. The pectoralis major muscle was left entirely intact and the pocket was washed with antibiotic solution. Then the ADM was prepared to cover the implant and keep the implant in place. We used the porcine ADM Strattice™ (LifeCell™ Corporation, Bridgewater, NJ, USA) for total implant coverage. Since pliable matrices in the desired size were not available in Europe, two sheets of Strattice™ 8x16 cm were joined by suturing the long sides of the two sheets with interrupted Vicryl® 3/0 sutures after thorough washing of the ADM. The enlarged 16x16 cm ADM was incised twice on every edge and trimmed as illustrated in Fig. 14.1. This type of incision allows the creation of four straight flaps (to be fixed by sutures) and four angular flaps at the corners (to be wrapped around the implant). This large sheet of ADM was then placed to create the implant pocket. The superior straight flap of the ADM was fixed primarily to the fascia of the PMM or the overlying tight connecting tissue with three interrupted sutures after marking the optimal suture sites from outside. The next step was to fix the medial straight flap of ADM to the fascia with 3 sutures. Then the implant with the appropriate size was placed prepectorally beneath this ADM envelope. We used exclusively highly cohesive anatomically shaped silicone gel-filled implants (Allergan®, Inc., Irivine, California, USA; Natrelle 410®). The angular ADM flaps were wrapped around the implant medial-cranially and medial-caudally as well as lateral-cranially and lateral-caudally, so that a complete ADM-covered implant pocket was achieved. Then three sutures fixed the lateral straight flap, and in the final step three interrupted sutures were used to fix the caudal straight flap to the fascia to define the inframammary fold. During all the steps of implant fixation attention has to be turned to the position of the pocket in the breast and according to symmetry with the contralateral breast. With this suture technique the implant can be kept in an exact position and an implant malposition can be prevented. One suction drain was inserted and a double layer wound closure was performed with Monocyrl® 4.0 interrupted sutures and Monocryl® 5.0 running sutures for skin closure. After wound dressing all patients were adequately supplied with a surgical compression bra.

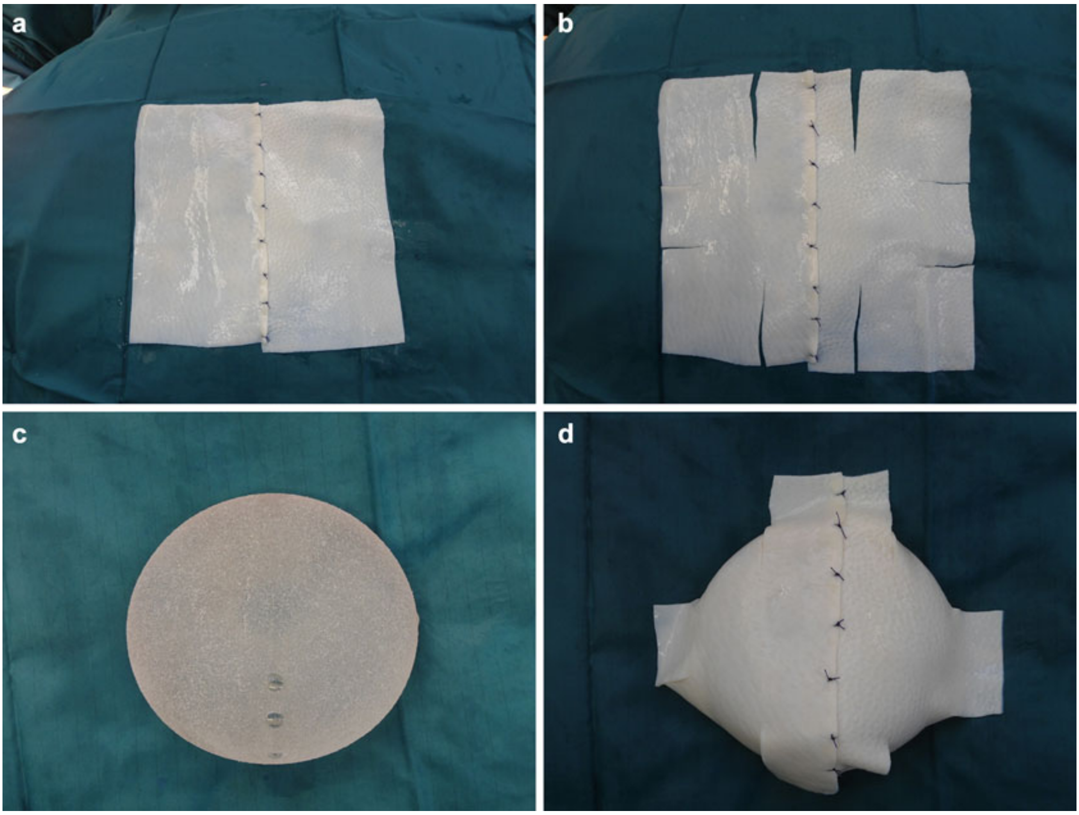

Fig. 14.1 (**a–d**) ADM trimming and implant wrapping. Two sheets of ADM 8 × 16 cm joined by interrupted Vicryl® 3/0 sutures, incised and wrapped around the implant

Results

In total 70 breasts were reconstructed by using the described procedure. After informed consent all patients decided against PMM detachment or dissection, and asked for prepectoral implant placement with complete ADM coverage.

Postoperative complications (Table 14.3) included minimal nipple necrosis without further intervention followed by complete healing in 4 breasts, and hematoma with evacuation in 4 breasts. In one patient the implant had to be removed 4 weeks after radiotherapy due to massive swelling, edema, and pain. Breast pain was not recorded in the other patients and no analgesics were required after surgery. Arm-shoulder mobility showed no restrictions and no motion-associated pain was reported. Mean duration of drainage was five days.

Cosmetic results were excellent after a median follow-up of 16 months (min 3 months, max 34 months). Patients were fully satisfied concerning the cosmetic outcome (Fig. 14.2). Breast animation could not be observed when the patients contracted their PMMs, there were no signs of jumping breasts. The breasts were smooth, and no capsular contracture Baker grade III or IV could be observed. Implant displacement occurred in none of the patients. The implant rims were visible and palpable in the upper poles of the breasts in three very thin patients, and rippling could be observed in two other very thin patients, but even those patients were pleased with the cosmetic result.

Six patients received postoperative radiotherapy to one breast. Except for the one patient with the implant removal, the other five patients had no radiotherapy-induced side effects (Fig. 14.3).

Table 14.3 Complications

	Radiotherapy	No radiotherapy	Total	%
Minor complications				
Minimal nipple necrosis	1	3	4	5.7
Major complications				
Hematoma	3	1	4	5.7
Implant removal	1		1	1.4
Total	5	4	9	12.8

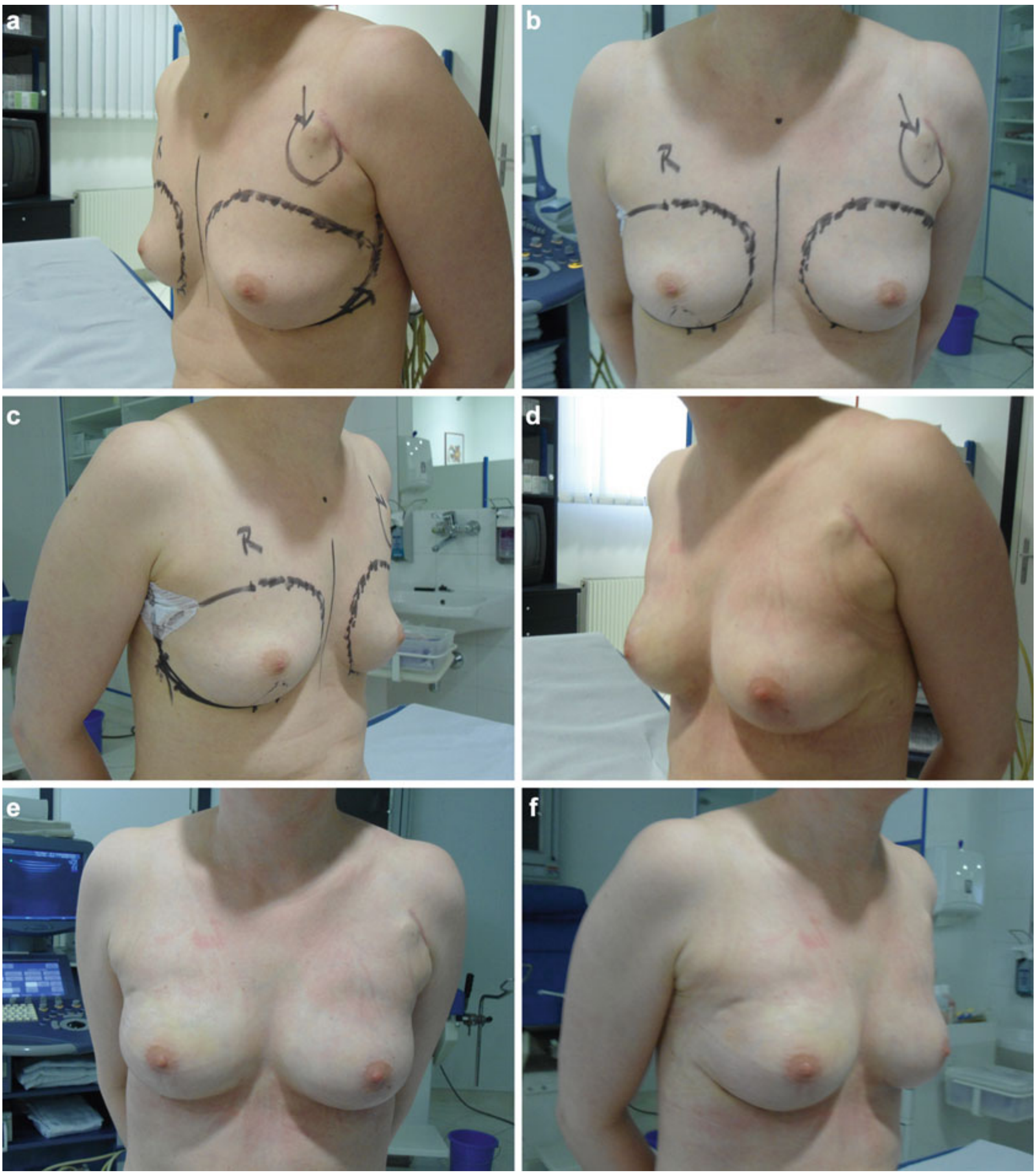

Fig. 14.2 (**a**–**c**) Preoperative photos of a 36-year-old woman with stage I triple-negative breast cancer and BRCA1 mutation after primary systemic therapy. (**d**–**f**) Postoperative photos after bilateral NSM and DTI-breast reconstruction with prepectoral implant placement and complete ADM coverage. No radiation therapy indicated

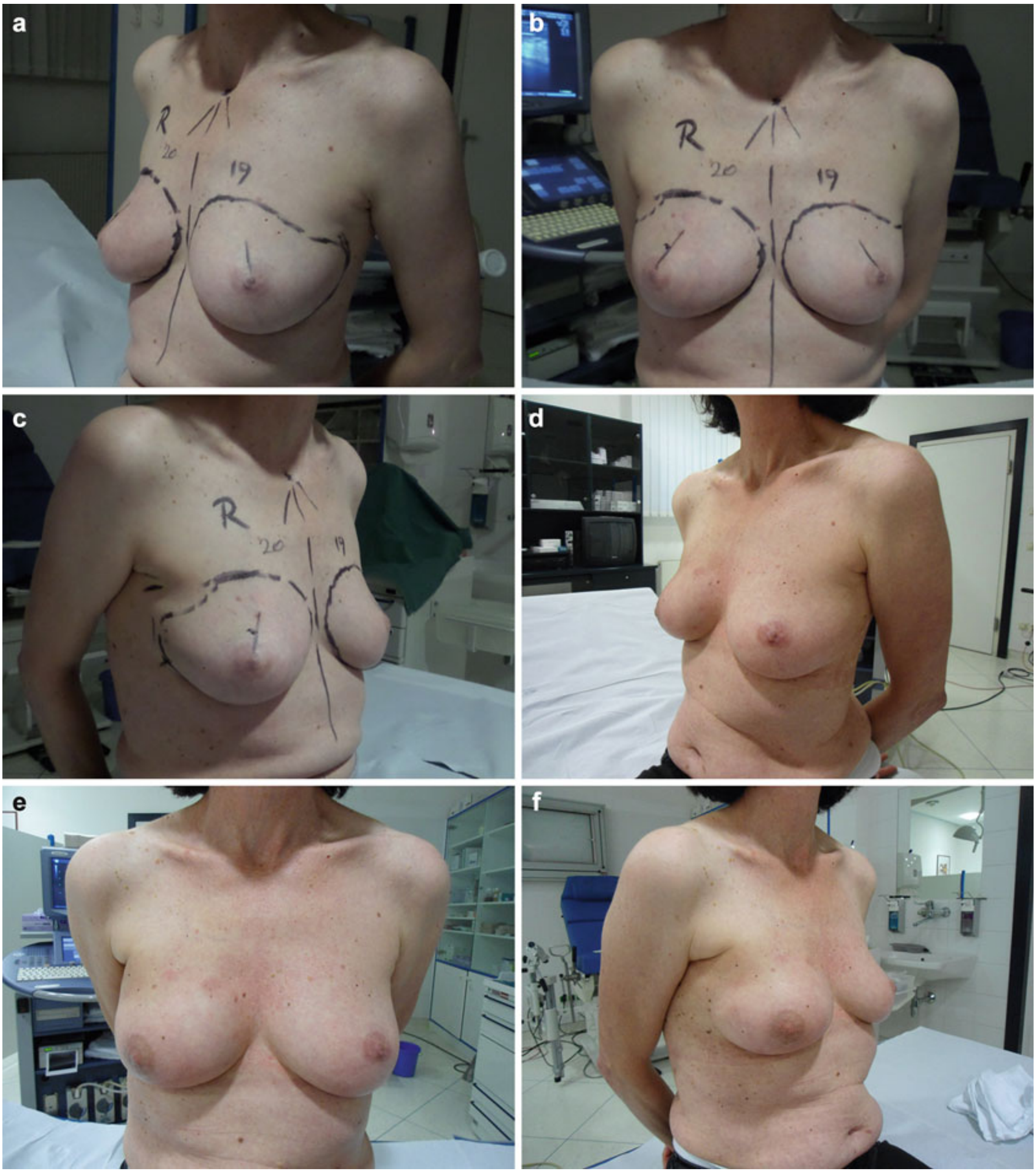

Fig. 14.3 (**a**–**c**) Preoperative photos of a 42-year-old woman with stage II right breast cancer. (**d**–**f**) Postoperative photos taken 12 months after completion of right NSM and DTI-breast reconstruction with prepectoral implant placement and complete ADM coverage and postmastectomy radiation therapy to the right breast

Capsular contracture was not observed, and cosmetic results were excellent at the short-term follow-up. Only one of the six patients who had radiotherapy to the breast prior to NSM developed minimal nipple necrosis with complete healing, the other five patients had no wound healing problems.

Discussion

NSM and implant-based breast reconstruction is an evolving technique, superseding conventional mastectomy techniques. As early as in the seventies Hüter J et al. discussed the question on subcutaneous or subpectoral prosthesis positioning and single-stage breast reconstruction [4, 5]. Older studies using older generation implants for breast reconstruction showed poor results, high complication rates, and high capsular contracture rates [6–8]. The subpectoral implant placement was the preferred placement to improve the cosmetic results. However, the subpectoral implant placement of implants for breast reconstruction after NSM is an unnatural position. The healthy female breast is overlying the PMM. For cosmetic reasons alone, the subpectoral implant placement was standard of care for many years. The arguments for subpectoral implant placement are the reduced visibility and palpability of the implant edges in the upper pole of the reconstructed breast, and the avoidance of rippling which makes the reconstructed breast less beautiful. The subpectoral position should give the breast a more natural look and putatively prevent capsular contracture. The disadvantages of subpectoral implant placement were accepted in favor of the cosmesis. Pain and discomfort after detachment of the PMM are well-known postoperative complaints [9]. Animation deformities or breast distortions during PMM contraction following subpectoral breast implant placement are a well known entity, but its significance and prevalence remain unclear [10, 11]. Every motion of the arms results in PMM contractions pushing the implants down and laterally over time. Activities as weight lifting or exercises are problematic for this placement. More and more women decide against the detachment or dissection of the PMM, after exhaustive preoperative information. They dislike the muscle function impairment, they dislike the breast animation and they dislike postoperative pain and prolonged recovery. De Haan et al. reported on substantial strength loss of 20 % in women with subpectoral prosthetic breast reconstruction and they provide thorough information to the patients about the possible postoperative muscular deficit [2].

There are no data supporting subpectoral implant placement being superior to prepectoral implant placement for breast reconstruction. Morbidity reducing techniques for autologous reconstruction are preferred in general as free TRAM flaps compared to pedicled TRAM flaps and DIEP flaps compared to TRAM flaps. Morbidity reduction is a strong argument for prepectoral implant placement. The dissection of the PMM impairs the muscle function and causes unnecessary postoperative pain. There is no evidence for a preferred technique of pectoralis major dissection, or to what extent the muscle should be dissected to achieve the best cosmetic results. Usually the ADM is sutured to the inferior edge of the PMM after its dissection, covers in a loose manner the lower half or two thirds of the implant and is fixed to the fold, when the subpectoral implant placement is performed. The hypothesis that the ADM stabilizes the PMM was never verified. It is a contradiction that the implant should lie in an ADM hammock loosely without tension and concurrently this loose ADM stabilizes the PMM. When the PMM retracts after dissection or when the PMM contracts with arm movement, the ADM will be pulled up together with the implant and possibly dislocate the implant. On the other hand the PMM has no stabilization at all as the PMM retracts as far as possible as long as the ADM is still loose overlying the implant, again resulting in breast animation deformity.

Another argument for subpectoral implant placement is the putative formation of capsular fibrosis around the implant. Capsular fibrosis is reported to be higher in smooth breast implants compared to textured breast implants [12–14], and there are some reports that the additional use of human ADM (Alloderm®) could further reduce the capsular contracture rate [15]. Furthermore there are reports on reduced capsule formation in patients with Alloderm® envelope and following radiation [16]. Alloderm® may slow the progression of capsule formation, fibrosis, and contraction via a decreased radiation-related inflammation.

The total wrapping of breast implants with ADM as a preventive tool against capsular contracture was experimentally performed in rats, with promising results [17]. Schmitz and colleagues observed a positive effect of total ADM envelope by a reduced rate of inflammation and proliferation and hypothesized a decrease of capsular contracture in long-term periods. Cheng et al reported on complete implant coverage by ADM as a treatment of capsular contracture for patients who developed capsular contracture after subpectoral breast implant reconstruction [18]. In contrast to our approach, Cheng and colleagues placed the ADM covered implant subpectorally and not prepectorally. Also, they used the human ADM Alloderm® in contrast to the porcine ADM Strattice®. Nevertheless, the results are very promising, none of the patients developed recurrent capsular contracture after a mean follow-up of 9.2 months. The prevention of capsular contracture formation with the application of ADMs predestines the prepectoral approach and complete ADM coverage. In our experience no capsular contracture Baker grade III or IV were observed in patients who received radiotherapy.

There are only few reports on prepectoral implant placement [19–24], with different approaches to cover the implant, either with ADMs or with titanized polypropylene meshes. The study from Casella et al. [21] using TiLoop® Bra either in a standard subpectoral or in a prepectoral approach and complete coverage could not find differences according surgical complication rates in the short-term follow-up. Further follow-up, cosmetic results, evaluation of pain, or cost evaluation are not yet available. The use of complete ADM coverage with the function as a regenerative matrix reinforces the skin and keeps the implant in place. The ideal ADM should be smooth and pliable but firm enough to keep the implant in place. The ADM serves as soft tissue support, by acting as a tissue regeneration interlayer between the skin and the implant especially in thin patients with thin mastectomy flaps. The ADM prevents breast implant displacement and minimizes or avoids the implant edge prominence. The development of form-stable silicone gel-filled breast implants and the advent of acellular dermal matrices enable the prepectoral implant placement with complete wrapping of the implant and therefore the reconstruction of a natural looking soft breast without detaching the PMM. Ideal candidates for this technique are patients with small to moderate non ptotic breasts and good soft tissue skin envelope.

Conclusion

Prepectoral implant placement for breast reconstruction after NSM is a novel and feasible technique by using highly cohesive anatomically shaped silicone gel-filled implants and porcine ADM for complete implant coverage. This technique allows a natural appearing reconstructed breast for the full satisfaction of the patients. The disadvantages of the subpectoral implant placement by the detachment of PMM, as the muscle function impairment, breast animation deformity, postoperative pain, and prolonged recovery, can be avoided by this technique. Short-term follow-up is promising, long-term follow-up has to be performed.

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15 Subcutaneous Reconstruction Without Acellular Dermal Matrix

Arthur H. Salibian, Jay K. Harness, and Donald S. Mowlds

Introduction

Subcutaneous breast reconstruction after nipple-sparing mastectomy (NSM) using expander/implant has taken a back seat in breast reconstruction because of issues related to implant exposure and undesirable outcomes such as capsule formation. The use of acellular dermal matrix (ADM) or other synthetic material for a single-stage subcutaneous implant reconstruction (see Chap. 14) has renewed the discussion on the efficacy of subcutaneous implantation after nipple-sparing mastectomy [1–3]. We have previously reported our experience with subcutaneous staged expander/implant reconstruction after NSM without the use of acellular dermal matrix [4] and have updated our experience since then (see Chap. 8). For more than 10 years, subcutaneous implantation has been our primary method of reconstruction for patients with different breast sizes, including patients with large ptotic breasts (see Chap. 7) who require a mastopexy in conjunction with nipple-sparing mastectomy. Here we discuss the advantages of the subcutaneous reconstruction as it relates to breast shape, implant positioning, ease of expansion, and cost-effectiveness. The advantages of the subcutaneous reconstruction are contrasted to those of submuscular reconstruction for an informed decision as to the method of choice.

Patient Selection

Nipple-sparing mastectomy with "thick" mastectomy flaps, meaning the retention of full thickness subcutaneous fat, has been our preferred surgical treatment for breast cancer patients using immediate subcutaneous expander/implant reconstruction. All patients are considered candidates for subcutaneous reconstruction except those with tumors involving the nipple-areola or the breast skin, and those patients in whom large areas of breast subcutaneous fat have to be thinned for tumor clearance. In patients with very

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large breasts who are to undergo mastopexy-nipple-sparing mastectomy, tumors close to the skin of the inferiorly based dermal-fat flap carrying the nipple-areola are also a contraindication to nipple-sparing mastectomy, as flap subcutaneous fat thinning may lead to nipple-areola loss. Additional contraindications to NSM include inflammatory breast cancer and bloody nipple discharge.

Patients with breast sizes varying from small to large (A cup to D cup) are considered candidates for a staged subcutaneous reconstruction. Patients with large breasts and grade III ptosis who desire a lift are advised to have a mastopexy at the time of nipple-sparing mastectomy. Patients with very large breasts are strongly recommended to have a buttonhole mastopexy to reduce breast size and improve implant positioning. This particular group of patients who are candidates for a mastopexy-nipple-sparing mastectomy are told that a small amount of normal breast tissue beneath the areola will be preserved during the mastectomy to enhance the circulation of the nipple-areola, but will be removed later when the implant is exchanged in the second stage. The patients are also told that the subareolar breast tissue will be submitted for pathologic examination in the first and second stages to rule out cancer involvement.

Requirements of Subcutaneous Reconstruction

The key to subcutaneous breast reconstruction is thick mastectomy flaps that preserve the full thickness of subcutaneous fat to "protect" the implant and sustain the circulation to the nipple-areola [5]. Preservation of the entire fat superficial to the anterior mammary fascia allows the resection of the subareolar breast tissue without compromising the dermal circulation to the nipple-areola. To remove all the subareolar breast tissue safely, the subdermal tissue resection should not exceed 16 cm^2, otherwise the nipple-areola may necrose. Large areolae with diameters greater than 5 cm should not be thinned down to the dermis for fear of losing the skin. One option here is to leave some breast tissue attached to the areola to preserve its subdermal circulation and remove the tissue later during the second-stage reconstruction. Localized subdermal or subcutaneous thinning of the breast flaps superficial to underlying cancers is feasible but should be performed judiciously to avoid nipple-areola loss. In our experience, breast flaps may be thinned subcutaneously as much as 25 cm^2, and to a lesser extent subdermally, provided the thinned areas are not close to the areola.

An important step in subcutaneous reconstruction is the management of the expander. The expander (Mentor, Irvine, CA), with its three fixation tabs, is fixed in place over the pectoralis major muscle with absorbable sutures keeping the medial tab one cm from the midline and the lower tab 5 mm above the inframammary fold. Expander inflation in the first stage is kept to a minimum to allow the skin to drape over the expander without tension. Postoperative expansion is also kept to a minimum to avoid overstretching the skin and worsening existing ptosis. Women with small breasts (A cup) who want to increase the size of the breast by two cups (C cup) may require stretching of the skin beyond the original surface area.

Lastly, during the second-stage implant exchange a near-circumferential capsulotomy and undermining of the subcutaneous flap is done without disturbing the inframammary fold. The final implant covers a larger subcutaneous area than the expander requiring an implant that is on the average twice the size of the expander fill volume. Wide subcutaneous undermining and insertion of larger implants does not compromise the circulation to the nipple-areola because of the increased collateral skin circulation.

Advantages of Subcutaneous Reconstruction Without Acellular Dermal Matrix

Acellular dermal matrix for expander/implant reconstruction following nipple-sparing mastectomy has been used to "protect" the implant, improve breast shape, fill the expander rapidly, maintain the inframammary fold, and minimize capsule formation [6–10]. In our experience thick mastectomy flaps that retain the full thickness of subcutaneous fat provide equal implant protection. Instances of implant exposure are usually due to excessive flap thinning with subdermal removal of breast tissue beneath the areola. Thick flaps also provide adequate "protection" in patients who have received preoperative or postoperative radiation (Fig. 15.1) except in the rare setting where the radiation burn injury involves the full thickness skin and underlying soft tissue.

Rapid expansion for improving breast shape with acellular dermal matrix is considered advantageous when partial muscle coverage is compared with total muscle coverage that blunts the lower half of the breast [11, 12]. Subcutaneous expansion is as fast, if not faster than submuscular expansion with a cellular dermal matrix, because the muscle does not require expansion and the lower portion of the breast readily assumes the full rounded shape of the underling expander with very little expansion. This leaves the upper half of the breast that does not require expansion ready for augmentation with a final implant that is twice the size of the expander fill volume (Fig. 15.2). Also, in subcutaneous reconstruction the pectoralis muscle does not need to be detached from the sternum to improve the cleavage nor does the muscle have be expanded in its upper portion or the tail of the breast region, as these areas can be readily augmented with subcutaneous implantation (Fig. 15.3). The major drawback of submuscular reconstruction is the difficulty in expanding the infraclavicular portion of the muscle that often leaves a step-off contour deformity along the upper border of the implant requiring fat injection [13].

Subcutaneous expansion is reliable in defining the inframammary fold if thick mastectomy flaps are used and the fold ligaments [14] are not disrupted during the mastectomy and second-stage reconstruction. In thin individuals (BMI = 21) with relatively large implants, it is preferable to anchor the chest skin at the inframammary fold to the rib periosteum with nonabsorbable sutures during the second-stage reconstruction to avoid implant migration. Finally, subcutaneous reconstruction without acellular dermal matrix carries less morbidity and is more cost-effective.

Capsular Contracture in Staged Subcutaneous Breast Reconstruction

One of the reasons for the acceptance of submuscular breast reconstruction with acellular dermal matrix, rather than the supramuscular method, is the reduced rate of capsular contracture [15]. Clinical evaluation, corroborated with laboratory studies, has shown decreased inflammatory

Fig. 15.1 Preoperative radiation therapy. (*Left*) Fifty-seven-year-old patient who had been previously treated with left partial mastectomy and radiation therapy. The patient underwent bilateral nipple-sparing mastectomy and staged subcutaneous reconstruction with 400 ml silicone implants. (*Right*) Result at 21 months

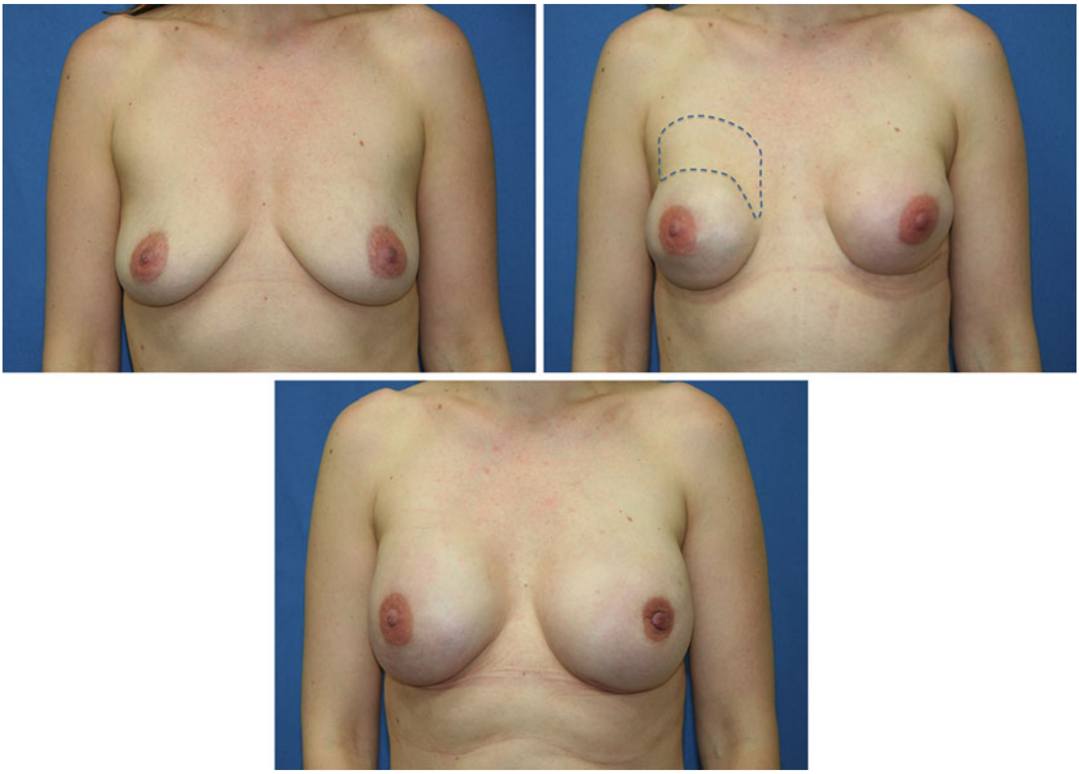

Fig. 15.2 Moderate inflation of tissue expander. (*Above*, *left*) Thirty-eight–year-old patient with left breast carcinoma who underwent bilateral nipple-sparing mastectomy. (*Above*, *right*) Expanders inflated up to 240 ml. The final implant will cover a larger area requiring a larger implant to fill the upper and medial portions of the breast (*Blue broken line*). (*Below*) Reconstruction with 550 ml silicone gel implants at 16 months

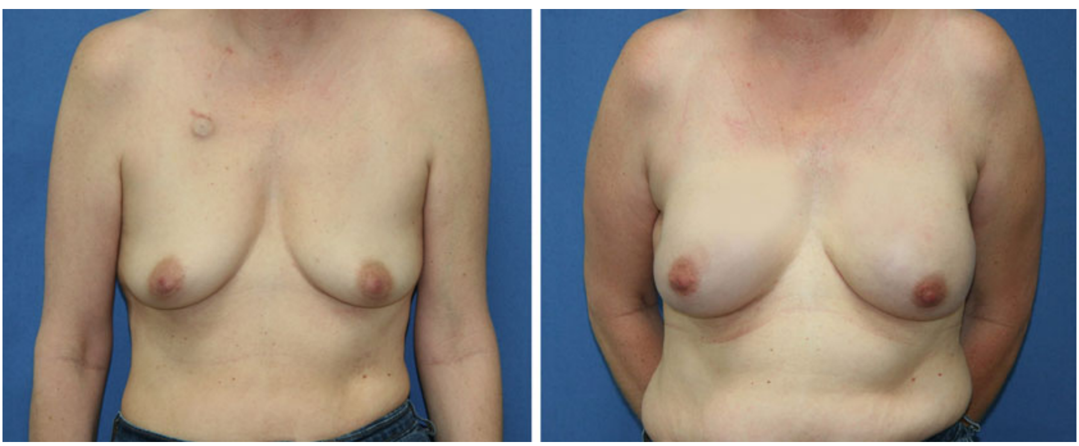

Fig. 15.3 Suprapectoral reconstruction. (*Left*) Fortnine-year-old patient with left invasive ductal carcinoma who underwent bilateral nipple-sparing mastectomy and staged suprapectoral reconstruction. (*Right*) Result of reconstruction with 525 ml silicone gel implants at 4 years

response to acellular dermal matrix that results in a thinner capsule and less capsular contracture [16, 17]. In spite of its disadvantages in staged suprapectoral breast reconstruction, capsular contracture has certain advantages in the ptotic breast that cannot be overlooked. If the expander is placed subcutaneously and expanded minimally, capsule formation may be desirable to reduce the skin surface area and "lift" the breast to improve the ptosis. Most patients with medium or large breasts and Regnault grade II/III ptosis benefit from the "lift" provided by capsular contracture.

Capsular contracture rates are time dependent with Baker grade III/IV capsular contractures typically developing several years after the completion of reconstruction. Our average 33.5-month follow-up breast capsular contracture rate for Baker grade III/IV contractures was 3 % [4]. This capsular contracture incidence will probably increase with longer follow-up periods. The overall advantages and disadvantages of capsular contracture should be considered in making a decision whether to place the implant subpectorally or subcutaneously.

Complications

Major complications in subcutaneous reconstruction such as postoperative bleeding, infection, expander exposure, and explantation are comparable to submuscular reconstruction. In subcutaneous reconstruction skin loss can be avoided if the breast flaps are kept thick and subcutaneous fat thinning around the nipple-areola, as previously mentioned, is limited to 16–25 cm^2. Major skin loss following subcutaneous mastectomy or extensive radiation damage is treated with latissimus dorsi myocutaneous flap transfer. For minor skin loss, the eschar is excised in the operating room and the wound closed primarily leaving the expander in place to complete the reconstruction in two stages. Patients who develop a deep wound infection following the mastectomy will require removal of the expander to allow the wound to heal for several months before reconstructing the breast with a permanent implant. Direct subcutaneous permanent implantation is feasible because the skin does not require expansion, other than a radical capsulotomy, to restore its original surface area.

Other relatively minor complications in subcutaneous reconstruction include implant dystopia and rippling. With thick mastectomy flaps implant dystopia and rippling is uncommon. We have seen implant migration in thin women (BMI = 21) with implants larger than 400 ml. This deformity can be corrected with fixation of the chest skin along the inframammary fold to the rib periosteum with nonabsorbable sutures. To avoid this complication, we routinely tack the skin down to the rib during the second-stage implant exchange in thin women who desire large implants. Rippling in thick mastectomy flaps is minor and is treated with implant exchange or low volume lipofilling.

Subcutaneous One-Stage Implant Reconstruction After Nipple-Sparing Mastectomy

Single-stage immediate subcutaneous breast reconstruction with acellular dermal matrix or synthetic mesh has produced excellent results in small and medium size breasts (see Chap. 14) [18]. Direct permanent implant reconstruction is not advised for large and ptotic breasts because placement of a large implant at the time of mastectomy may compromise the circulation to the nipple-areola. Furthermore, in ptotic breasts it is difficult to position the nipple-areola at the apex of the implant mound if the one-stage subcutaneous method is used. In contrast, when using the two-stage expander/implant reconstruction and allowing the skin to contract over the expander, the nipple-areola is raised physiologically because of the capsule formation for better positioning of the nipple-areola over the breast mound.

Another advantage of the two-stage reconstruction has to do with patients requiring postoperative radiation therapy based on the pathology findings of the breast specimen and/or axillary lymph nodes. Radiation instituted after the final gel implant is in place will cause the skin to shrink

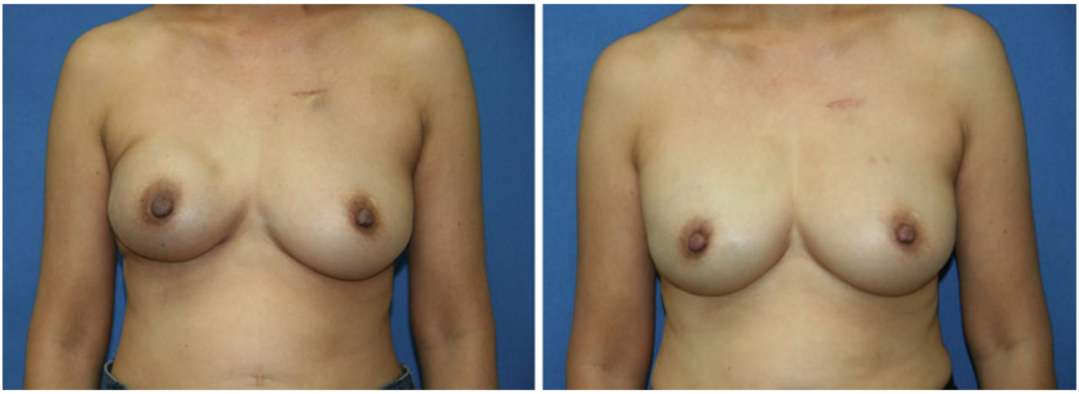

Fig. 15.4 Postoperative radiation therapy. (*Left*) Fifty-nine-year-old patient with right nipple-sparing mastectomy for invasive ductal carcinoma showing expander in place 6 months after completion of radiation therapy. (*Right*) Result of subcutaneous reconstruction (425 ml implant) at 28 months

permanently, reducing the size of the breast and distorting its shape. In the two-stage reconstruction, on the other hand, postoperative radiation can be given with the expander in place, followed 6 months later with insertion of the permanent implant for a better aesthetic result (Fig. 15.4).

Conclusion

The subcutaneous method of expander/implant reconstruction using thick flaps without acellular dermal matrix has been our choice for reconstruction following nipple-sparing mastectomy because of advantages related to ease of reconstruction, breast shape, decreased morbidity, and cost-effectiveness.

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16 Nipple-Sparing Mastectomy in the Previously Radiated Patient

Eleni Tousimis and Lindsay Potdevin

Introduction

A surgeon's experience with performing nipple-sparing mastectomy (NSM) in previously radiated patients has been historically very limited. There are few patients that recur after lumpectomy and radiation [1]. Of this small subset of patients, many have had long term complications from the previous radiation including preoperative asymmetry, poor skin quality, fibrosis, and tethered lumpectomy scars (Fig. 16.1). With these preoperative deficits along with a known higher complication rate associated with operating on radiated skin, most surgeons would opt for excising the nipple areolar complex and performing either a skin-sparing mastectomy with reconstruction or a total mastectomy without reconstruction.

As the use of nipple-sparing mastectomy is becoming more widespread, the selection criteria have been broadening significantly. Most surgical practices are shifting toward including more complex patients including patients with macromastia, ptosis, tumors less than 2 cm from the nipple, older patients, patients with positive nodes, and those receiving neoadjuvant chemotherapy [2, 3]. A recent publication from Mayo Clinic showed that 7.8 % of their patients undergoing nipple-sparing mastectomy had received preoperative radiation therapy whereas it was previously considered a relative contraindication in their practice [2].

Patients who decide to save their nipple areolar complex have been shown to have a higher patient satisfaction when they undergo nipple-sparing mastectomy versus skin-sparing mastectomy [4]. Patients with previous radiation who have preoperative asymmetry and poor skin quality must be informed that they will potentially have persistent asymmetry postoperatively and that previously radiated skin carries a higher risk of postoperative complications such as infection, flap necrosis, high-riding nipple, asymmetry, and implant loss [5]. Careful patient selection, preoperative planning, meticulous technique, perioperative antibiotic coverage, and maintenance of the blood supply are important in order to reduce the risk of complications.

Pathophysiology of Radiation and Surgical implications

Radiation can obscure normal tissue planes, cause reduced tensile strength, decrease elasticity of the skin and impair wound healing [6, 7]. It can also

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Fig. 16.1 Preoperative asymmetry after right lumpectomy and radiation

cause inhibition of revascularization which results in reduced blood supply and subsequent tissue hypoxia. This can impair the normal inflammatory response to wound healing, which can in turn predispose the surgical site to bacterial invasion [6, 7].

Radiation treatment causes excitation and ionization of electrons, which results in direct damage to DNA as well as the production of free radicals. These free radicals can damage cell membranes, proteins, and DNA which ultimately causes apoptotic cell death.

The effects of radiation are divided into early and late effects. Early effects occur within the first 10 to 14 days after starting treatment. They are caused by vascular permeability, vessel wall edema and thrombosis, fibroblast injury, insufficient collagen production, inability to encourage maturation, reduced response to stimulatory effects of local growth factors, and reduced neovascularization. The late effects are seen more than 3 months after starting treatment and include atrophy, contraction, loss of vessels, fibrous tissue replacement, and damage to melanocytes, altering skin pigmentation [7]. In radiated tissue, TGF-beta receptors are upregulated and become chemotactic for mast cells, fibroblasts, monocytes, and macrophages. TGF beta 1 is considered a major stimulant of radiation fibrosis [6].

Impact of Time Interval Between Radiation and Surgery

Previously, many surgeons felt that the longer the time from the radiation, the longer the time the skin had to repair and recover and the fewer the complications. However, there has been insufficient data examining the effect of length of duration from radiation to complications to draw this conclusion [8]. In 2011, Khansa et al. found no relationship between time interval from radiation to final mastectomy and reconstruction outcome [9]. In the sarcoma literature, there was no correlation between preoperative radiation and time to surgery with wound complications in patients undergoing lower extremity resections [10]. Many have proposed that there may be a genetic predisposition in how a patient responds to radiation therapy [11].

Outcomes After Reconstruction in Previously Radiated Patients

Several studies have shown that the failure of reconstruction is much higher in patients who have been treated with previous radiation, at a rate of 19 % versus around 5 % in those who have never been radiated [12–14]. The surgical outcomes of nipple-sparing mastectomy in previously radiated patients are unpredictable due to the side effects of radiation on the skin. Several recent studies have reported on these decreased outcomes. A study in 2011 from Khansa et al. looked at 113 patients who had undergone breast conservation therapy followed by mastectomy with reconstruction. The overall complication rate in this group was 36.5 % compared to 27.1 % in those who had never had radiation. They ultimately found that the only statistically significant complication was an increased rate of mastectomy skin flap loss in breasts that had been radiated (12.4 % vs. 6.8 %, $p=0.024$) [9].

The following year in 2012, Hirsh et al. reported on a series of 71 breasts from 66 patients that had undergone prior breast conservation therapy followed by mastectomy with tissue expander reconstruction. They found an overall rate of major complications requiring surgical intervention including loss of implant or reconstruction with autologous flap reconstruction of 28.2 %, with an 8.5 % rate of minor complications. The overall rate of successful completion of reconstruction with expander exchange for implant was 62 % [15].

Technical Surgical Aspects and Pearls

Patients with radiated skin do not tolerate even the slightest complication such as infection, extreme tension on skin flaps, hematoma, or ischemia. Since the outcomes may not be ideal and there is a higher rate of complications in previously radiated patients, appropriate patient selection, careful preoperative planning, and surgical technique are of utmost importance. Patient with smaller breasts, lack of severe ptosis, and minimal skin changes after radiation are more ideal for this procedure. It is important to work closely with the reconstructive surgeon during the preoperative planning stage. The imaging work up should include a mammogram and possible sonogram, as well as a preoperative MRI in order to assess the distance of the tumor to the skin and nipple areolar complex (Fig. 16.2a, b). This facilitates the planning of the surgical incision.

All patients who undergo breast reconstruction should receive perioperative antibiotics with gram-positive coverage. When technically feasible, an inframammary fold (IMF) incision is preferable as it has been associated with decreased complications (OR, 0.018). A large incision measuring at least 12 cm in length can be used for adequate exposure and decreased tension on the flaps [16]. In nonradiated patients, the IMF incision is usually the length of the width of the surgeon's hand, or at least 9 cm, starting at the medial aspect of the areola and extending laterally. In a previously radiated patient, it is preferable to extend the incision at least 12 cm (Fig. 16.3a, b). If a previous lumpectomy scar is tethered, or the cancer is near the lumpectomy scar, then this skin may need to be excised and incorporated into the new incision, depending on its location.

Meticulous dissection is important for all patients undergoing nipple sparing mastectomy in order to preserve the blood supply to the flap as well as the nipple areolar complex. This is technically more challenging in patients undergoing an inframammary fold incision where the length of the flap is even longer and the watershed area inferior to the nipple is more compromised. The flap is made slightly thicker at the skin incision to prevent necrosis of the skin edges. It is important to identify and develop the layer between the anterior fascia of the breast and the patient's sub-

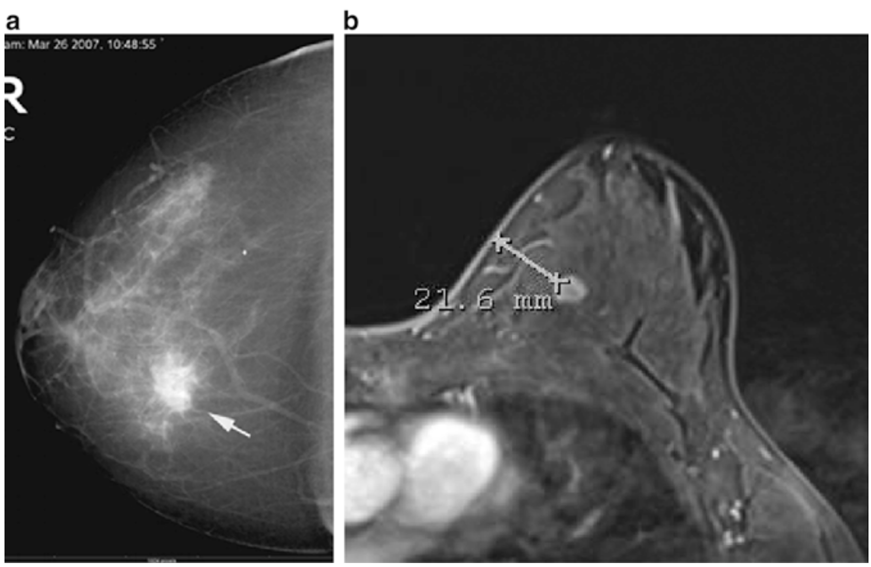

Fig. 16.2 (**a**) Mammogram showing location of cancer in relation to skin and nipple areolar complex. (**b**) MRI showing location of cancer in relation to skin

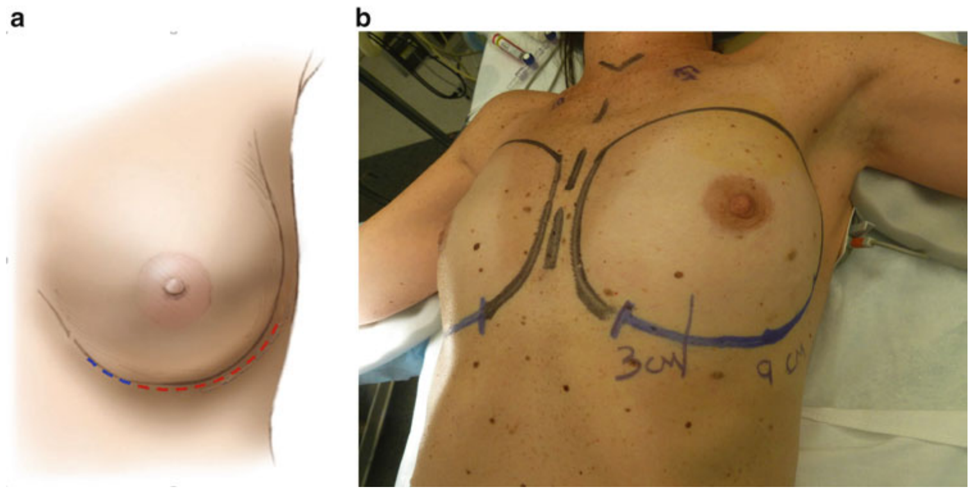

Fig. 16.3 (**a**) Nonradiated skin, perform approximately 10 cm incision length along IMF (*red line*), however, in radiated skin extend incision to at least 12 cm for maximal exposure and less flap tension (*blue line*). (**b**) Shows extension of IMF in a previously radiated patient for better exposure

cutaneous layer. This anterior plane is a relatively avascular plane with only small vessels in the patient's Cooper's ligaments connecting the breast tissue to the skin. The boundaries of the mastectomy are the clavicle superiorly, the sternum medially, the latissimus laterally, and the sixth rib inferiorly. The posterior plane is between the pectoralis major muscle and the posterior aspect of the breast. We routinely remove the posterior fascia of the breast along with the specimen.

The largest blood supply to the breast comes from the second intercostal perforator off the internal mammary artery, followed by the lateral thoracic artery (Fig. 16.4). Preservation of the second intercostal artery is highly recommended in order to maintain perfusion to the flap (Fig. 16.5). We also recommend preserving the venous plexus in the subcutaneous layer to ensure adequate perfusion to the flap and prevent venous congestion.

When operating on radiated patients, it is important to minimize tension on the flaps both intraoperatively as well as postoperatively. We use noncorrugated lighted retractors to assist with creation of the flaps, and periodically remove the retractors to alleviate tension from the flaps thus giving them a chance to reperfuse (Fig. 16.6). When performing the dissection behind the nipple, the assistant's finger is used to provide gentle upward traction.

Oncologic Safety of NSM

Controversy has long surrounded performing NSM in patients with cancer fearing that retained breast tissue behind the nipple areolar complex may harbor a future breast cancer. However, several retrospective studies comparing local recurrence in skin sparing versus nipple sparing patients reveal a similar local recurrence rate in the two groups. A large study on 657 breasts in 428 patients undergoing nipple sparing mastectomy revealed a recurrence rate of 2.4 % after 3 years follow up [17]. In the most recent largest study of 982 patients undergoing NSM, ten patients had locoregional recurrences. However, none of these recurrences occurred in patients who had been treated with previous radiation at a mean follow up of 24 months [18]. A recent meta-analysis of 27 studies in 2013 showed an overall local regional recurrence rate of 2.8 % in patients undergoing NSM [19]. The largest study to date of nipple sparing mastectomy in radiated patients followed for 22 months revealed no local recurrences in 43 patients with previous radiation [12].

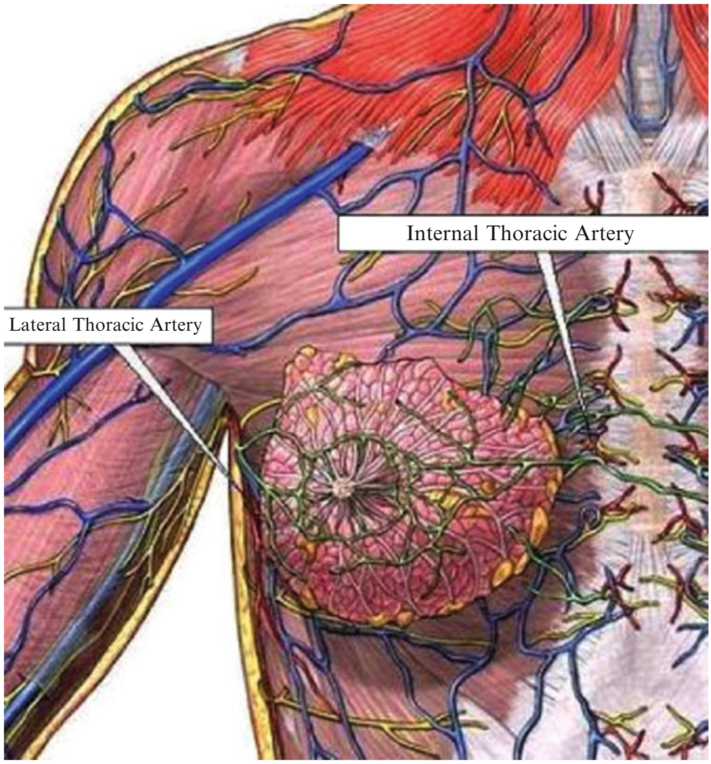

Fig. 16.4 Blood supply to breast

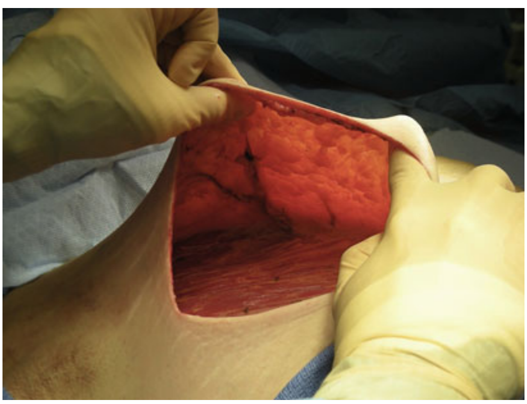

Fig. 16.5 Intraoperative photo shows largest blood supply to the breast, the second intercostal perforator

Fig. 16.6 Intraoperative photo shows extended incision along the IMF with good exposure and no tension on flaps

Outcomes and Associated Complications

The most common complications in patients who undergo nipple-sparing mastectomy and reconstruction after previous radiation include infection, flap necrosis, capsular contracture, fibrosis, asymmetry, nipple malposition, and a higher revision rate. Several studies in recent years have reported on complications and outcomes in this patient population (summarized in Table 16.1). Colwell et al. found that preoperative irradiation was a positive predictor for nipple necrosis with

Table 16.1 Literature review from 2004 until 2015 showing risk of complications in previously radiated patients undergoing NSM

Study	# of patients	Infection (%)	Capsular contracture (%)	Nipple (N) or flap (F) necrosis	High-riding nipple/ asymmetry (%)	Implant loss (%)	Overall complication rate (%)
Spear et al. [5]	13	7.8	7.8	7.8 % (partial N)	53.9	7.8	30.8
Alperovich et al. [21]	24	n/a	0	7.6 % N, 11.5 % F	n/a	8.3	33.3
Sbitany et al. [14]	63	57.1	n/a	3.2 % N, 11.1 %F	n/a	20.6	n/a
Tang et al. [18]	69	n/a	n/a	4.3 % N, 11.6 % F	n/a	2.9	21.7
Huston et al. [20]	20	n/a	n/a	18.7 % N	n/a	n/a	n/a
Reish et al. [12]	88	7	9.3	7 % N 9.3 % F	n/a	4.7	30.2

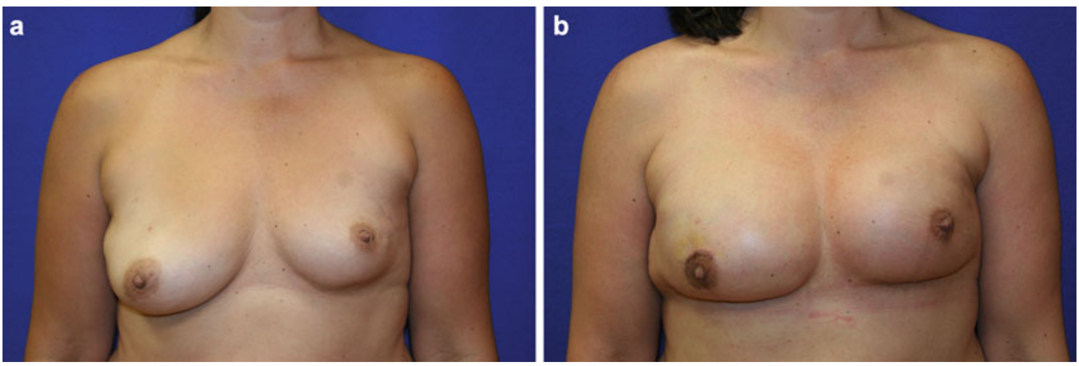

Fig. 16.7 (**a**) Status post left lumpectomy and radiation with significant asymmetry and (**b**) Postop bilateral NSM with persistent left high-riding nipple

an odds ratio of 4.86 compared to patients who had no radiation [16]. In a large review of 318 patients undergoing nipple-sparing mastectomy, 20 were identified who had been treated with previous radiation [20]. This review found a 30.0 % rate of postoperative nipple-areola complex ischemia, compared to the group of NSM without prior lumpectomy or radiation ($n=187$) which had a NAC ischemia rate of only 18.7 %.

In 2014, our institution followed 13 patients who had undergone NSM after previous radiation or prior mantle radiation for an average of 3 years [5]. The overall complication rate was 30.8 % and included skin ischemia, infection, and hematoma. About half of all patients experienced a high-riding nipple on follow up (Fig. 16.7a, b). In addition, 30 % of patients required surgical revision for correction of malposition, and only 7 % had capsular contracture. In conclusion, 88 % maintained their reconstruction. Spear et al. [5] stressed the importance of using selection criteria in this subset of patients. Patients with smaller, non-ptotic breasts, normal nipple position, minimal skin changes, breast asymmetry, and scar contracture were more favorable (Fig. 16.8a, b). Another study found that in selectively chosen patients with healthy skin post radiation, the rate of complete nipple necrosis was only 3.8 % in 24 patients followed for 20 months. Eleven percent of these patients experienced flap necrosis requiring operative intervention [21] (Fig. 16.9).

In 2014, a large study from UCSF reported on 63 breasts that had been previously irradiated who had NSM and were followed for an average

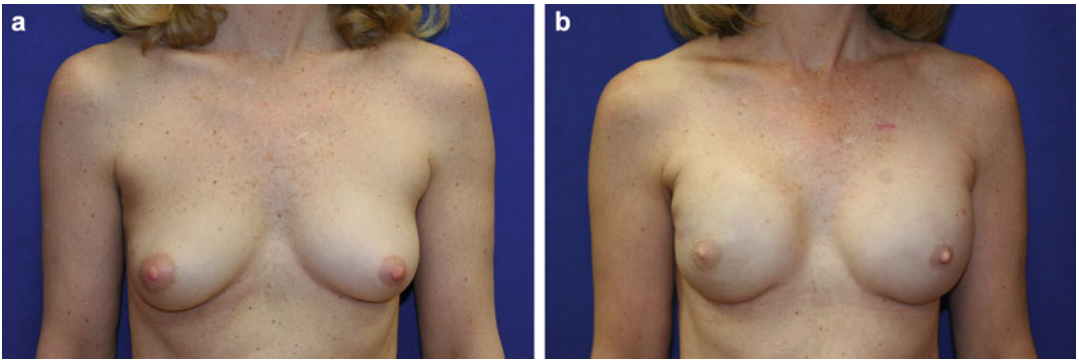

Fig. 16.8 (**a**) Status post right lumpectomy and radiation with little asymmetry and minimal side effects from radiation. (**b**) Postop bilateral NSM after right breast conservation therapy with IMF incision

Fig. 16.9 Postoperative photo showing flap necrosis

of 21 months [13]. Twenty-seven percent had postoperative infection requiring oral antibiotics, 20 % required intravenous antibiotics, and 9 % required surgical intervention. There was also a higher incidence of incisional breakdown (24 % vs. 7.2 %), expander or implant exposure (11.1 % vs. 4.5 %), and expander or implant removal (20.6 % vs. 5.1 %) in these patients. They did, however, find that rates of partial or complete nipple (1.6 % and 1.6 %, respectively) or skin (3.2 % and 7.9 %, respectively) necrosis was not significantly different between the two groups. Interestingly, they also found that the use of acellular dermal matrix (ADM) for the reconstruction of this patient cohort increased the risk of skin flap complications and NAC necrosis, likely due to poorer incorporation of the ADM into the irradiated tissue as well as the decreased ability of this tissue to handle tension from the larger expander pocket created. This group has thus changed their practice to minimize expansion in these patients when the tissue expander is placed. Our group favors using a larger piece of ADM to accommodate for the tight pectoralis muscle from previous radiation.

Another large subset of 69 breasts of patients at a single institution who had undergone NSM after radiation therapy reported the overall rate of complications in these patients was 21.7 %, compared to 10.2 % in patients who had no radiation [18]. There was an increased rate of skin necrosis (11.6 % vs. 4.5 %), nipple loss (4.3 % vs. 0.9 %), and early complications requiring surgery including necrosis, hematoma, and infection (18.8 % vs. 7.1 %). Their multivariate regression analysis determined the use of periareolar incision to be an independent risk factor for complications requiring surgical revision, as well as age >55 years, breast volume >800 cm^3, and smoking.

Another large series of 43 patients who received preoperative radiation before NSM with a mean follow-up of 22.7 months reported an overall complication rate in these patients of 30.2 %, compared to 16.6 % for patients without radiation [12]. These complications included nipple areolar complex necrosis in 7 % (vs. 3.9 %), skin flap necrosis in 9.3 % (vs. 5.4 %), infection, hematoma, seroma, and explant secondary to complications of 4.7 % (vs. 1 %) (Fig. 16.10).

Fig. 16.10 Flap necrosis and loss of implant

They also found a significantly higher rate of secondary procedures for capsular contracture and fat grafting for patients with preoperative RT at 9.3 % (vs. 2.3 %), and 25.6 % (vs. 3.9 %), respectively.

Patient Satisfaction After Nipple Sparing Mastectomy

Several papers have reported on increased patient satisfaction associated with NSM. In 2009, Didier et al. conducted a survey to determine whether preservation of the nipple areolar complex was associated with higher patient satisfaction, body image, and psychological adjustment [4]. Those patients who had preserved their nipple areolar complex had significantly less difficulty looking at themselves undressed and being seen by their partners. They also had fewer feelings of mutilation and higher satisfaction with both appearance and nipple sensitivity. The researchers observed that preserving the NAC helped 93 % cope with their disease and its consequences. In the group of skin sparing mastectomy patients who did not save their NAC, 89 % regretted that decision. Peled et al. report patient satisfaction data after administering the BREAST-Q questionnaire to 28 patients undergoing NSM [22]. They found that the vast majority of patients were satisfied with their nipple appearance postoperatively (89 %), however there was much less satisfaction with nipple position (56 %) and sensation (40 %).

The literature for patient satisfaction in NSM in patients who have undergone previous irradiation is limited. In 2011, Khansa et al. found that both general and aesthetic satisfaction rates did not significantly differ between 113 patient who had a history of breast-conservation therapy prior to breast reconstruction and 419 patients who did not have radiation (general 66.7 % vs. 66.8 %, aesthetic 63.3 % vs. 66.5 %) [9] (Fig. 16.11a, b).

Conclusions

A surgeon's experience with performing nipple sparing mastectomy in a previously radiated patient is very limited because tumor recurrences are rare, and many patients after radiation have poor skin quality, preoperative asymmetry, and fibrosis. The complication rate in these patients is higher than patients without previous radiation and many will require revision surgery for nipple or implant malposition and capsular contracture.

Patient selection is crucial in these challenging cases and close collaboration between the breast surgical oncologist and reconstructive surgeon is important to decide incision placement and type of reconstruction. Review of all preoperative imaging is also a key part in planning these operations. In addition to mammogram and sonogram, an MRI is useful to address the distance of the tumor to the skin and nipple areolar complex.

Perioperative antibiotics, an extended IMF incision when oncologically feasible, meticulous dissection with a tension free approach, avoidance of unnecessary tension on the flaps, and preservation of blood supply is imperative to avoid ischemia of skin flaps and nipple areolar complex.

Many studies have shown that patient satisfaction is high in patients undergoing nipple sparing mastectomy. However, it is important to counsel patients who undergo this procedure in the setting of previous radiation that the complication rate is higher in this setting due to the physiologic effects of previous radiation on the skin and that cosmesis may not be ideal requiring additional surgery.

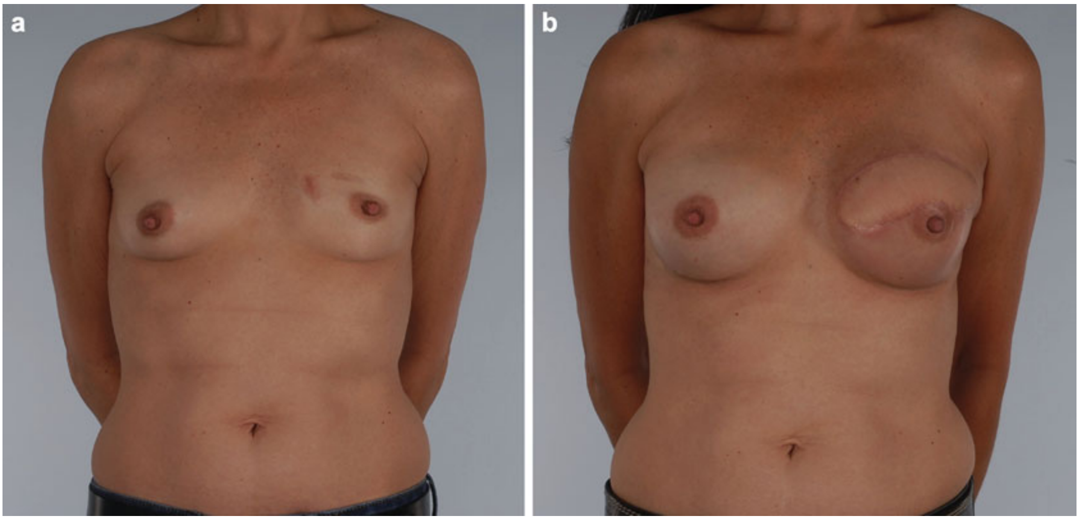

Fig. 16.11 (**a**) Patient status post lumpectomy and radiation with upper inner quadrant recurrence. (**b**) Status post bilateral nipple sparing mastectomy with left excision of skin due to recurrence and reconstructed with latissimus flap and tissue expander. This patient exhibited high patient satisfaction and good symmetry

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Experience with Postmastectomy Radiation Therapy in Nipple-Sparing Mastectomy

17

Hani Sbitany

Introduction

Surgical techniques for performing complete mastectomy have undergone significant evolution since the 1970s, when a shift away from traditional Halsted radical mastectomy techniques occurred [1]. The general trend has been increased preservation of the breast skin envelope, while maintaining the same thorough excision of underlying breast parenchyma [2]. This was initially a rapid change, in the mid 1970s, when the radical mastectomy, with complete removal of the chest wall skin, breast parenchyma, pectoralis major and minor, and axillary lymph nodes, was replaced by more skin preserving techniques [3]. Additionally, spin-sparing techniques did not involve removal of the chest wall muscles [4]. The skin-sparing mastectomy has offered improved aesthetic outcomes, with preservation of greater amounts of the original breast skin envelope and thus shape, while maintaining low recurrence rates [5, 6].

Recently, techniques incorporating complete nipple-areolar preservation have been shown to be equally safe from an oncologic perspective [7, 8]. Furthermore, nipple- sparing mastectomy has allowed for a further improvement of aesthetic outcomes with postmastectomy reconstruction, as the entire original breast shape and envelope can be maintained, with no removal of the breast skin [9]. Given these advantages, the use of nipple-sparing mastectomy (NSM) techniques has increased significantly in the surgical prevention and treatment of breast cancer.

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Adjuvant Radiation Therapy in Traditional Mastectomy

The surgical inclusion criteria for NSM was initially very well defined [10]. These inclusion criteria involved tumors less than 4 cm, and over 2 cm from the nipple/areola complex. Furthermore, the low rates of nipple and skin necrosis in these patients have led to excellent reconstructive outcomes [11]. However, increased experience with the technique has led to expanded patient inclusion for NSM, and thus more advanced tumors are being treated with this procedure [12]. Additionally, patients with tumors closer to the nipple-areola complex (NAC) are also being offered NSM, if MRI shows no direct involvement with the nipple, as this is a sensitive predictive test of actual clinical involvement [13, 14].

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With these expanded indications for the procedure, there has been an increase in patients undergoing NSM being treated with adjuvant therapies, including external beam radiation therapy [15, 16]. This treatment increases the risk for surgical complications, due to the effects of the radiation therapy on the remaining soft tissue envelope of the breast [17]. These effects include radiation fibrosis and increased potential for wound dehiscence, as well as capsular contracture in prosthetic breast reconstruction patients.

The clinical outcomes of skin-sparing mastectomy (SSM) in the face of postmastectomy radiation have been well defined. Nava et al. described outcomes of mastectomy and immediate prosthetic breast reconstruction with tissue expander placement [18]. In those patients undergoing radiation to the temporary tissue expander, followed by exchange for permanent implant after radiation, the implant removal rate due to complications (primarily infection and capsular contracture) was 40 %. Conversely, those patients undergoing radiation to the permanent breast implant, following completion of all reconstructive operations, experienced an implant removal rate of 6.4 %.

Despite the lower rate of explantation with delivery of radiation to the permanent implant, this procedure is less commonly performed, as the rates of significant capsular contracture are much higher, and achieving excellent aesthetic reconstructive outcomes are thus more challenging [19]. Furthermore, this technique is usually not an option for women who have undergone neoadjuvant chemotherapy as part of their treatment. These women must also usually undergo radiation therapy soon after their mastectomy, which may not allow time for both the tissue expansion and the exchange operation.

With delivery of radiation to the temporary tissue expander, the secondary exchange operation of the expander for permanent implant allows for removal of hypertrophic capsule built up during radiation therapy, and thus improved aesthetic outcomes with lower capsular fibrosis rates.

Given these factors, the majority of reconstructive surgeons routinely proceed with radiation to the temporary tissue expander. This is then followed by tissue expander exchange for permanent implant, and removal of scar tissue and radiation fibrosis following radiation completion.

Adjuvant Radiation Therapy in Nipple-Sparing Mastectomy

Preservation of the nipple and areola, through NSM, introduces a new set of caveats in the setting of postmastectomy radiation therapy. The nipple and areola are in many cases thinned more aggressively during mastectomy than the remaining skin, due to the manual inversion of the nipple and excision of all its parenchyma [20, 21]. If this area is thinned further, it is more susceptible to breakdown during radiation therapy, resulting in nipple necrosis or skin necrosis.

The author's institutional experience with NSM and prosthetic breast reconstruction in the setting of radiation has exhibited much higher complication rates in the radiation therapy group [22]. The overall explantation rate of prosthetic devices in this series of NSM followed by postmastectomy radiation to the tissue expander, was 17.7 % (113 breasts). This is compared to a 5.1 % explantation rate in the nonradiated NSM patient cohort (727 breasts). Rates of prosthetic implant infection requiring oral antibiotics for resolution, in the postmastectomy radiation cohort, was 26.5 %, while 22.1 % of cases required IV antibiotics for successful treatment.

Interestingly, this series found that preservation of the nipple-areola complex is safe in this population, with 0 % rate of complete nipple necrosis, and 3.5 % rate of partial nipple necrosis, in the setting of postmastectomy radiation therapy. It is the author's experience that the NAC skin performs similar to the remaining mastectomy skin flap through radiation, and thus if it has healed prior to XRT initiation, carries no increased risk of radiation-induced necrosis (Fig. 17.1a, b). The overall rates of any amount of mastectomy skin flap necrosis were 3.5 % (partial thickness) and 11.5 % (full thickness) in the radiated population, compared to 1.7 % (partial thickness) and 3.7 % (full thickness) in the nonradiated population.

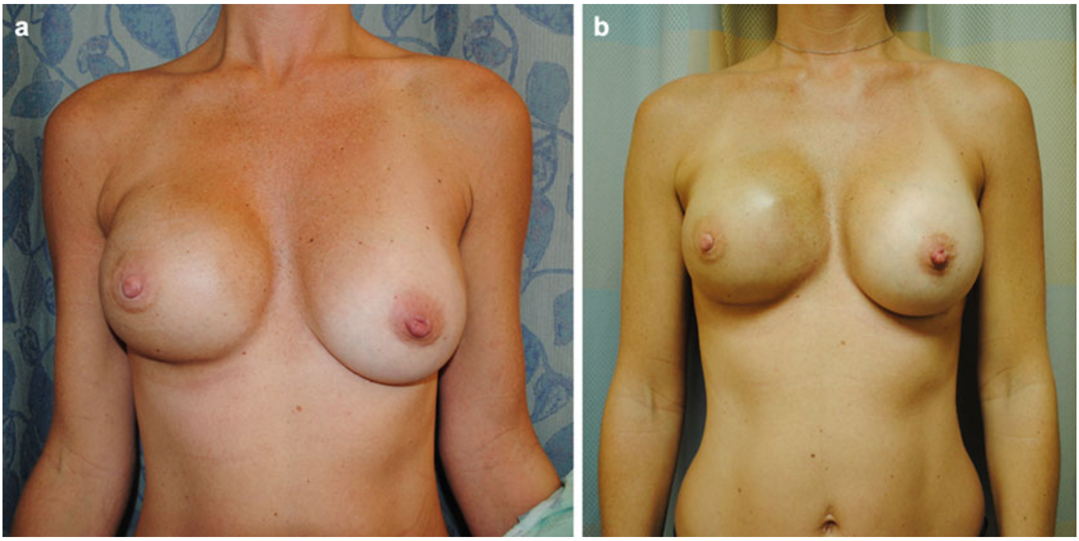

Fig. 17.1 (**a**) Thirty-nine-year-old female with right breast invasive ductal carcinoma, following right nipple-sparing mastectomy, tissue expander placement, and post-mastectomy radiation therapy. The right breast has healed and the nipple has tolerated postmastectomy radiation therapy. (**b**) The patient 2.5 years after exchange of her right breast tissue expander for permanent silicone implant, and small left breast augmentation

These findings clearly illustrate the higher complication rates of prosthetic breast reconstruction following NSM, in the setting of post-mastectomy radiation therapy. However, the 17.7 % explantation rate in this population is a reduction from the 40 % explantation rate reported previously by other groups radiating tissue expanders prior to implant exchange [18]. The improvement in the author's outcomes over time, is largely attributed to the increased experience of surgical oncologists performing NSM. With this increased experience, the ability to adequately remove the nipple parenchyma while preserving vascularity of the NAC skin has improved, thus offering enhanced resistance to complications in the setting of radiation.

Use of ADM in the Setting of NSM and PMRT

An additional protective effect in reduction of complications in the setting of XRT, even with the addition of NSM, is seen with the addition of acellular dermal matrix (ADM) to assist in coverage of the tissue expander at time of placement [23]. These matrices are aseptically processed sheets of human cadaveric dermis that retains its collagen matrix and allows for host cell repopulation and revascularization [24]. The use of ADM to fully or partially cover the tissue expander at time of placement following mastectomy, particularly along the lower pole of the device for support and stability, has become a common technique among reconstructive surgeons (Fig. 17.2). Numerous studies have now illustrated that the use of these devices carries a safety profile similar to those achieved with traditional full submuscular coverage of the prosthetic devices [25, 26].

It has previously been established that ADM maintains integrity and functions well in the setting of radiation therapy [24]. Additional data has now shown that the use of ADM for assistance in tissue expander coverage following NSM, offers a reduced complication rate in the setting of postmastectomy radiation [22]. When compared to the population of NSM patients undergoing tissue expander placement and radiation without ADM coverage of the device, those with ADM assisted device coverage exhibited lower rates of infections requiring operative

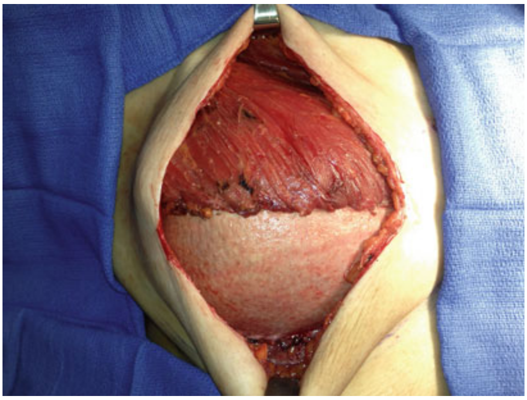

Fig. 17.2 Acellular dermal matrix placed at time of mastectomy over tissue expander, for lower pole coverage and support of the tissue expander

intervention (RR 4.30 vs. .48, $p = 0.041$) and lower rates of expander/implant loss (RR 4.46 vs. 2.41, $p = 0.262$).

This clinically protective effect of ADM in the setting of XRT is likely multifactorial, and related in part to the improved physical support of the expander along the lower pole, in the area where it places the most weight and tension on the skin flaps during radiation, once it has been filled. This hammock of ADM likely offloads some of the weight of the expander, thus resulting in less pressure on the lower pole skin flaps, and thus less risk of breakdown or wound dehiscence, and resulting prosthetic device exposure.

This reduction in complication and explantation rates of prosthetic devices conferred by ADM in the setting of NSM and XRT has also been illustrated by other high volume centers performing these procedures [27, 28]. When comparing immediate prosthetic breast reconstruction with the use of ADM assisted tissue expander coverage vs. no ADM use, Seth et al. reported a statistically significant reduction in total complications and infection with the use of ADM [27]. When performing immediate tissue expander coverage with ADM in breasts undergoing postmastectomy radiation therapy, Spear et al. reported a 21.4 % explantation rate [28]. Again, this is lower than the findings reported by Nava et al. (40 % explantation rate) when using full submuscular coverage without ADM assistance, prior to radiation delivery [18].

In all cases, consistent and reproducible results have been achieved in this setting. These findings have led the author's group to consistently utilize ADM for tissue expander coverage at the time of mastectomy in all cases in which postmastectomy radiation is known or anticipated.

Effect of Mastectomy Incision Location on Outcomes

Another technical aspect of surgery, in the setting of postmastectomy radiation, that has been found to significantly affect outcomes, is the mastectomy incision location. Clinical evidence has shown that the inframammary incisions used for NSM and reconstruction result in a higher wound dehiscence and complication rate when subjected to radiation therapy, relative to all incisions on nondependent locations of the breast [29]. These include periareolar and lateral/radial incisions.

The increased rate of complications seen with the inframammary (IMF) approach, in the setting of radiation, is likely due to the weight of the full tissue expander or implant sitting directly on the incision. This increased weight places additional stress directly on the IMF incision. Furthermore, with the IMF incision, the mastectomy skin just above the incision, on the lower pole of the breast, is relatively poorly perfused, given its distance from branches of the internal mammary artery perforators. Furthermore, the skin in this location receives minimal perfusion from the abdominal perforators, given the interruption of this blood supply by the incision location.

These factors account for the reduced ability of the inframammary incision to withstand complications relative to other incision locations, in the setting of radiation. For this reason, the author's preference is a periareolar or lateral radial incision for mastectomy and reconstruction, when postmastectomy radiation is anticipated.

Timing of Expander Exchange for Permanent Implant

The timing of tissue expander exchange for permanent breast implant, following completion of radiation therapy, must also be carefully considered. There are proponents of performing this exchange operation early after completion of radiation therapy, before radiation fibrosis fully occurs. Surgeons in favor of this timing maintain that the skin and capsule are still soft and malleable at this point, allowing for improved tissue handling and healing.

However, the skin in this acute period following completion of radiation therapy is in an acute inflammatory state [30]. This state is not conducive to healing following surgery. Published evidence has supported this finding. It has been shown in clinical series, that waiting at least 6 months following completion of radiation, prior to performing the expander exchange for implant, reduces complication rates from 22.4 to 7.7 % in this population [31]. The most common complications encountered are wound dehiscence and cellulitis.

These reduced complications with prolonged waiting periods greater than 6 months following radiation completion, are likely explained by two major factors. First, in vivo studies have shown that endothelial damage from radiation, causing reduced dermal blood flow, occurs between 2 and 6 months after radiation, and levels off after this [32]. Second, imaging studies have shown that the breast edema and skin thickening induced by radiation therapy, peak at 6 months after treatment initiation, then reduce from this point forward [33].

As a result, it is advisable to wait 6 months or longer, following completion of radiation therapy, before performing the implant exchange operation. At that time, a second consideration in operative planning is incision placement. The original mastectomy incision will consist primarily of radiated scar tissue, which will offer reduced healing potential over the prosthetic device. It is advisable at this operation to consider a new counter incision in a separate location of the breast.

The optimal incision location following radiation is the lateral breast, approximately 5 mm below the inframammary fold. In this area, the tissue is of abdominal origin. Thus, there is a thicker area of fascia, subcutaneous tissue, and skin, that may be used in closure. Although this area is usually in the radiation field, it has not been previously incised, so is devoid of scar tissue. Furthermore, the multilayer closure is more durable to withstand full thickness dehiscence. Reusing the original mastectomy incision, at any location on the breast, results in closure of a very thin, often 1- or 2-layer closure of radiated scar tissue under tension.

Given this, it is encouraged to plan the original mastectomy incision with the exchange incision in mind. The preferred location, when PMRT is anticipated, is a periareolar incision for the mastectomy and tissue expander placement, and a lateral incision just below the IMF for the exchange operation. The author's experience has shown that this offers the lowest morbidity rate.

Aesthetic Outcomes with NSM and XRT

Aesthetic outcomes with NSM and prosthetic reconstruction have been mixed. In general, patients report a loss of nipple projection and pigmentation on long term follow up, without radiation [8]. Satisfaction regarding nipple/areola aesthetics remains mixed among these patients. The addition of radiation therapy increases loss of projection and hypopigmentation of the NAC. Furthermore, reduction of areola diameter is routinely experienced, making NAC asymmetry common in unilateral reconstruction cases [11].

Following radiation, positional asymmetries in the NAC are exceedingly difficult to correct, given the radiation fibrosis of the breast skin [34]. This is primarily due to the inability of transposition flaps, used for NAC positional changes, to heal properly. Additionally, the skin fibrosis results in reduced ability to transpose and rotate skin significant distances.

Thus, great care must be taken to fix the nipple at the time of mastectomy in the correct location and allow it to heal to the underlying tissue, in the first few postoperative weeks. Thus, it is routine practice now to suture the NAC to underlying pectoralis muscle or acellular dermal matrix at the time of mastectomy, with a dissolvable suture. Once the NAC heals in the correct position, it is unlikely to be displaced during radiation therapy, or require significant repositioning after completion of radiation.

Operative Algorithm for Prosthetic Reconstruction with NSM and PMRT

Given all these factors, the author has developed an operative algorithm for patients undergoing NSM and prosthetic reconstruction in the setting of PMRT. All patients undergo immediate tissue expander placement with the addition of acellular dermal matrix to assist in expander coverage. For the mastectomy, the periareolar incision is used preferentially, given previous data findings that this offers a lower dehiscence rate in the setting of PMRT. If the patient has mild breast ptosis preoperatively, then this periareolar incision can be planned as a small crescent mastopexy with modest skin removal, allowing for NAC elevation.

A tissue expander with suture tabs is used in these patients, to prevent migration of the expander induced by tissue contraction during radiation. These patients are fully expanded prior to radiation therapy, and usually over expanded, to allow for additional tissue laxity during the exchange operation. It is important to avoid expander deflation of the radiated side during PMRT. Keeping the expander inflated does not interfere with radiation delivery, and also avoids reexpansion of the radiated breast following completion of PMRT [35]. It is the expansion and reexpansion of a radiated soft tissue envelope that causes much of the wound breakdown and keeping the expander inflated allows for avoidance of reexpansion.

Finally, following completion of PMRT, the author waits a minimum of 6 months prior to the exchange operation. The author's institution has shown this to offer a reduced wound dehiscence risk, relative to proceeding sooner [31]. At this exchange operation, a new incision, just below the lateral inframammary fold is used preferentially. This allows for multilayer operative closure in an area of thick, abdominal subcutaneous tissue and skin, which has not been previously incised, and thus does not contain scar tissue. Using this algorithm, consistent outcomes have been achieved in this challenging patient population [22].

Effects of Axillary Node Dissection on Outcomes

Another consideration that must be made when considering prosthetic reconstruction following NSM is the axillary lymph node status. There is clear data showing that the combination of radiation therapy, and primary axillary lymph node dissection (ALND), significantly accelerates complication rates in this patient population. Specifically, risk of implant loss in this population stands at 13 % following second-stage expander/implant exchange in NSM patients [36].

When compared with sentinel lymph node biopsy (SLNB), full primary axillary lymph node dissection carries a significantly increased risk of implant loss (RR 3.8), independent of all other risk factors [36]. With the addition of radiation, these patients need to be counseled strongly on their risk, and encouraged to consider either breast conservation with oncoplastic reconstruction, or autologous reconstruction following NSM [37, 38].

Unlike ALND, similar data has shown that hormonal therapy does not carry a significant effect on implant failure rates [36]. Thus, patients on these adjuvant treatments can safely undergo prosthetic reconstruction following NSM.

Autologous Reconstruction in the Setting of NSM and PMRT

Given the increased morbidity rate of prosthetic reconstruction in the setting of radiation following NSM, a viable alternative is autologous breast reconstruction. It has been shown that autologous reconstruction offers lower complication rates in the setting of postmastectomy radiation, compared to prosthetic reconstruction [39]. Furthermore, vascularized autologous flaps can be safely radiated, with the only statistically significant side effect observed being volume contraction [40].

Immediate autologous reconstruction can be safely performed following NSM, although reported rates of partial NAC necrosis are higher than that seen following immediate tissue expander placement. This is likely a result of the larger flap placing tension and stretch on the healing and acutely devascularized skin of the breast and NAC, thus leading to venous congestion and skin ischemia.

To deal with this, and still provide well-vascularized autologous reconstruction, alternative strategies have been developed to minimize acute skin stretch. The author has employed a technique in which a tissue expander is placed immediately at time of NSM [41]. Following this, rapid expansion is employed to achieve desired size after the NAC safely heals without excessive underlying tension. Then, the expander is replaced with an autologous flap. This technique is a variation of the delayed-immediate reconstruction technique described for preservation of the skin envelope following skin sparing mastectomy, in anticipation of radiation [42]. This allows for maintenance of the mastectomy skin envelope and improved NAC survival, while avoiding radiation delivery to the autologous flap.

In the setting of NSM, this technique also avoids acute stretch on the NAC skin at the time of NSM. This has been shown to result in reduced NAC ischemia and necrosis rates when compared to immediate autologous reconstruction at the time of NSM. The author's series showed a 29 % rate of NAC partial or complete necrosis with immediate autologous reconstruction, versus a 0 % rate with initial tissue expander placement followed by secondary exchange for autologous flap [41].

When radiation is used with this technique, over the filled tissue expander, it is the author's preference to wait 12 months prior to exchange for a flap after the completion of radiation. Data has shown that waiting at least 12 months after completion of radiation results in lower flap thrombosis rates, versus proceeding sooner [43]. This is likely a result of recovery from radiation damage of the recipient vessels on the chest.

Conclusion

Prosthetic breast reconstruction following nipple-sparing mastectomy, in the setting of postmastectomy radiation delivery, carries a higher complication rate. However, this technique can be safely performed with the use of certain techniques, which have been shown to lower morbidity rates. These include the use of ADM, the use of certain incision locations, and specific timing schemes for the operations planned around radiation delivery. Alternatively, the use of autologous reconstruction can be used for lower complication rates in patients who are judged to be good candidates for these procedures.

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Management of Complications Following Nipple-Sparing Mastectomy

18

K.C. Chu and Albert Losken

Introduction

Nipple-sparing mastectomy offers many advantages over skin-sparing mastectomy given preservation of the breast skin and nipple-areolar complex. Some of the main benefits include a more natural appearing breast without the need to reconstruct the nipple-areolar complex, better aesthetics, and often a one-stage procedure. The disadvantage, however, is the higher potential for complications. These complications can often be minimized with careful attention to surgical technique and strict patient selection.

Management of Complications After Nipple-Sparing Mastectomy

Although nipple preservation is increasingly prevalent during both therapeutic and prophylactic mastectomies, there is a relative paucity of written data on the management of complications following this procedure. Amongst the largest published series of institutional experiences with nipple-sparing mastectomy (NSM), overall complications rates are described as being comparable to those following skin-sparing mastectomy with nipple sacrifice. NSM-specific complications and their implications can be categorized into short- and long-term groups.

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Short-Term Complications

Nipple Ischemia

The nipple-areolar complex (NAC) is vascularized by branches of the internal mammary, anterior and posterior intercostal, and lateral thoracic arteries [1]. Studies have demonstrated an apparent association between incision location and nipple necrosis. Inframammary fold incisions carry the lowest risk of nipple ischemia, though periareolar incisions less than one-third of the areolar circumference have also been found to be safe [2, 3]. Factors typically associated with ischemic complications of the nipple-areolar complex include preexisting macromastia and/or ptosis, smoking, central coring of the nipple, and extended periareolar or trans-areolar incisions [4–6]. Nipple ischemia is felt to be less common when autologous reconstructions are performed as the NAC could almost act as a full-thickness graft if sitting on a well-vascularized flap,

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The definition of nipple ischemia varies widely, resulting in a similarly varied range of reported prevalence from 1 to 30 % [2, 4, 7–9]. Sequelae of NAC ischemia include superficial nipple necrosis, partial nipple loss, and complete nipple loss. Superficial nipple necrosis manifests with blistering, partial thickness epidermolysis, and sloughing of skin that eventually heals with local wound care (Fig. 18.1). Most cases of nipple ischemia are of such minor severity. However, expectant observation during the period of demarcation benefits from experience, especially in the presence of an underlying expander or implant. In the majority of cases, superficial nipple necrosis has little impact on eventual cosmetic outcome, with some patients developing minor nipple discoloration. Amongst the largest published series of NSM, superficial nipple necrosis rates are reported at 5 % [3].

Partial nipple necrosis risk has been reported at 1.7 % [3]. The area of involvement can be surgically excised generally with primary closure. Larger nipple-areolar complexes are more forgiving, and results may be improved with delayed tattooing. However, nipple malposition may develop due to scar retraction, and in some cases complete excision with delayed nipple reconstruction may achieve a more predictable result. Total nipple necrosis requiring surgical excision is considered a relatively rare complication, but removal rates as high as 4.3–7.4 % in the postoperative period have been reported [7, 10].

Mastectomy Skin Flap Necrosis

Flap elevation in NSM can be successfully performed with sharp or cautery techniques. Skin flap necrosis after mastectomy can occur due to excessive thinning, retraction injury, and/or thermal

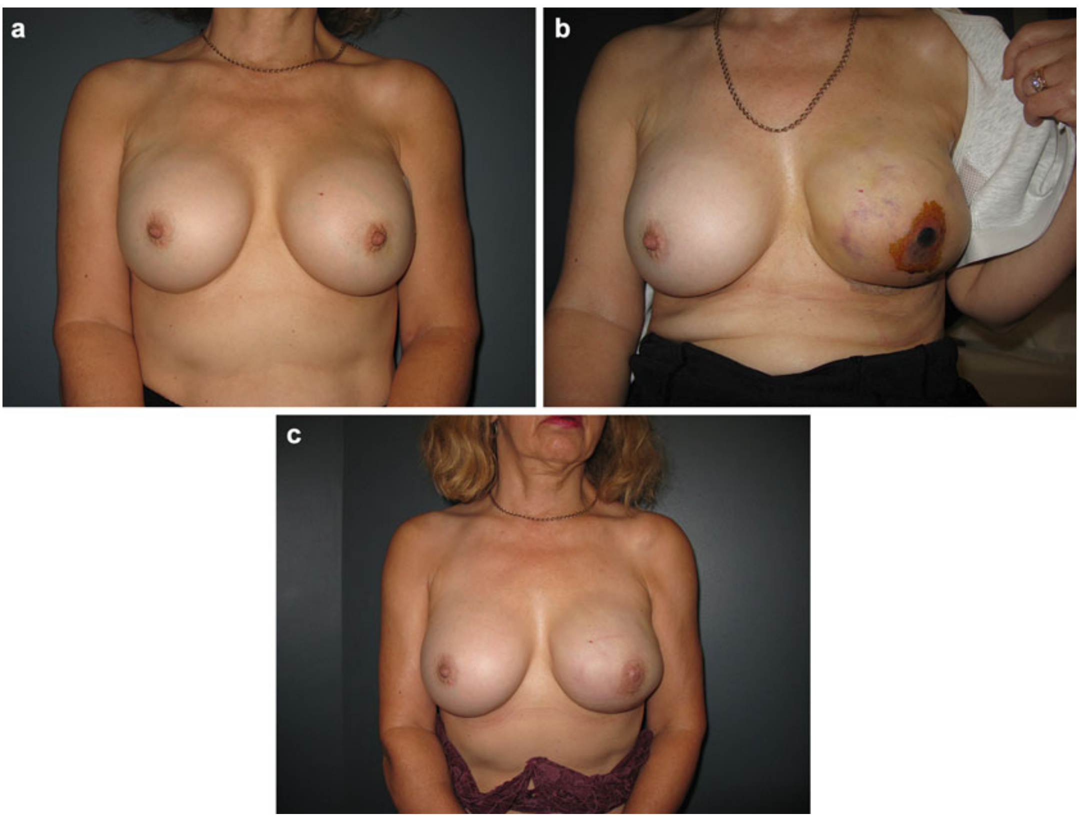

Fig. 18.1 This is a 63 year old female with left sided breast cancer (**a**). She underwent left nipple sparing mastectomy and direct-to-implant reconstruction (**b**). Her result is shown 1 year following reconstruction with preservation of nipple shape (**c**)

injury. Reported prevalence ranges from 3 to 20% [2, 11]. Potential negative consequences of mastectomy skin flap necrosis include delay for receipt of adjuvant chemotherapy and radiation therapy, as well as device infection, exposure, and/or failure. Earlier publications suggested slightly higher skin flap necrosis rates using NSM compared with skin-sparing mastectomy, though these observations likely reflect technical learning curves [12–14].

Management of skin flap ischemia does not differ drastically after NSM compared with conventional skin-sparing mastectomy. Use of indocyanine green with laser angiography may play a role in guiding intraoperative decision making with regard to mastectomy skin flap viability, but the validity of this technique may be compromised if epinephrine-containing tumescent solution is used to facilitate sharp subcutaneous dissection during NSM. Direct-to-implant reconstruction should only be carried out in the absence of marginal mastectomy skin condition; use of a non- or minimally inflated subpectoral expander will allow for greater flexibility in postoperative management. If concern for skin integrity arises postoperatively, expander deflation to accommodate the loss of skin envelope is often necessary to reduce stress and tension on the overlying skin. The use of topical vasodilators (such as nitroglycerin paste) has been described to improve viability of compromised skin, while antibiotic or antibacterial topicals, such as silvadene cream, are often used during the period of demarcation. Systemic antibiotic use varies widely amongst surgeons in this setting. After allowing for a short period of postoperative demarcation, full-thickness skin loss will require debridement and closure in particular in the setting of implant-based reconstruction. Implication for nipple position after excision of necrotic skin represents a unique challenge. In severe cases, excision of the nipple areolar complex with delayed nipple reconstruction may be a preferable option over attempted correction of subsequent malposition.

Management of mastectomy skin flap necrosis and nipple ischemia has traditionally been based on subjective judgment and clinical experience. The SKIN score system has recently been proposed as an externally-validated tool for assessment of severity and extent of mastectomy skin flap necrosis that is correlated with need for reoperative management. Each breast is assigned a letter grade based on depth of skin necrosis (A, no necrosis; B, cyanosis or erythema of skin suggestive of impaired perfusion or ischemic injury; C, partial thickness necrosis with at least epidermal sloughing; D, definitive full-thickness skin flap necrosis) and a numerical score based on the surface area of involvement (1, no necrosis; 2, 1–10% of breast or nipple-areolar complex skin; 3, 11–30% breast or nipple-areolar complex skin, or total nipple involvement; 4, >30% breast or nipple-areolar complex skin). For NSM, the latter numerical score is separately assigned for nipple-areolar skin; thus, the system can be applied to NSM to grade of nipple ischemia. Composite scores were shown to correlate strongly with need for surgical excision [15]. Although such systems do not eliminate the need for clinical judgment, they provide standardized language for comparison of outcomes and algorithms from which treatment plans may be based (Fig. 18.2).

Hematoma/Bleeding

Published prevalence of postoperative bleeding after NSM does not exceed that following skin-sparing mastectomy, but anecdotal evidence suggests that, depending on the incision used, attention to hemostasis in particular areas is critical. For instance, when NSM is carried out via an inframammary fold approach, bleeding can often be encountered in areas of difficult visibility such as the second intercostal internal mammary perforators and the perforating branches toward the clavicular head of the pectoralis major muscle (Fig. 18.3). Hematoma accumulation should be promptly evacuated, as retained blood may facilitate subsequent infectious sequelae and/or capsular contracture. In the authors' experience, bleeding typically occurs in the subcutaneous plane, and rarely does reoperation require reopening of the subpectoral space. Hemorrhagic complications following NSM are reported to be between 0 and 10% [3, 4, 8].

Infection

As with skin-sparing mastectomy, surgical site infection threatening reconstructive success, in particular in implant-based reconstruction, remains a point of concern. Even more so than

Fig. 18.2 This 45-year-old patient had left-sided breast cancer and underwent bilateral nipple-sparing mastectomies and implant reconstructions. She developed bilateral nipple ischemia and some mastectomy skin ischemia in the early postoperative period. She also likely had a right breast hematoma. This all resolved with local wound care and conservative management. Her result is reasonable symmetry with eventual survival of the nipple-areolar complex

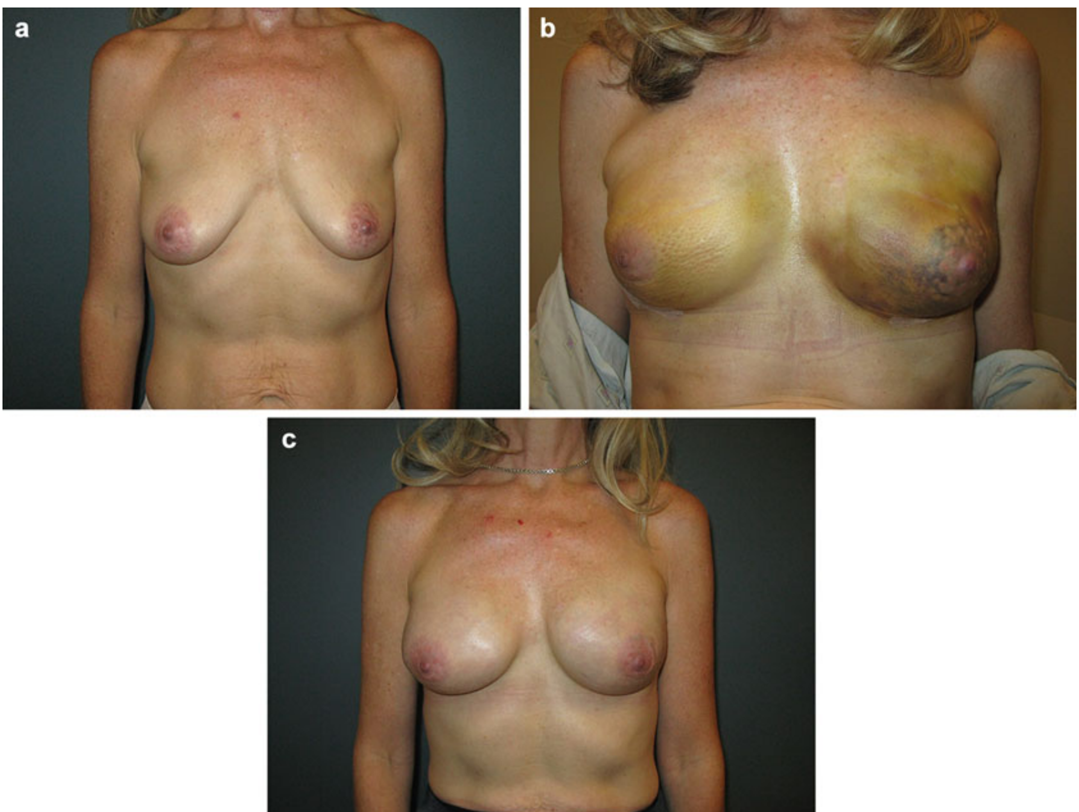

Fig. 18.3 This 36-year-old had a bilateral NSM and implant reconstruction with left breast hematoma. Since it was not expanding and the skin did not feel tight with vascular compromise, a decision was made to watch it conservatively and it resolved with time

with skin-sparing mastectomy, preferential use of acellular dermal matrix in NSM to allow precise pocket control and implant/expander positioning may contribute to seroma or infectious sequelae, though benefits in lower pole definition, increased initial fill volume, and enhanced device coverage are often thought to outweigh potential downsides. Infection management is not unique to NSM; systemic symptoms and presence of fluid of either serous or purulent quality may dictate clinician judgment with regard to appropriateness of oral or intravenous antibiotic therapy, operative management, and attempted implant replacement or salvage.

Long-Term Complications

Nipple Malposition

In contrast to conventional and skin-sparing mastectomy techniques, immediate reconstruction is a requisite component of successful NSM. Techniques to control nipple position during immediate reconstruction are critical to avoid subsequent malposition, as postoperative malposition is notoriously difficult to correct. Particular attention is needed in cases of higher body mass index, larger breast volume, wider breast base width, ptosis, and anticipated postoperative radiation, as these features may predispose to postoperative nipple malposition. The lateral radial incision may lead to lateral retraction of the nipple long-term. Any native nipple deviation will also be accentuated after mastectomy.

To this end, a number of intraoperative measures have been described. Securing the underside of the nipple to the pectoralis muscle in the desired location with an absorbable suture is feasible, but care must be taken to avoid further compromise of the blood supply to the nipple. Liberal use of suction drains to limit tangential movement of skin over the reconstruction is often preferred. Some surgeons favor use of external fixation devices such as surgical bras or clear occlusive skin dressings to minimize skin displacement. Optimizing expander selection, position, and fill will also facilitate proper nipple position. Maximal initial expander fill without compromise of mastectomy skin flap viability may help preserve satisfactory positioning. If the tissue expander or implant is positioned too medial for example, the nipple-areolar complex relative to the breast footprint will appear too lateral. This is difficult to correct and occasionally requires removal and repositioning of the tissue expander and repeat expansion with the device centered relative to the NAC.

The effort placed into nipple preservation for improved cosmetic outcome is potentially rendered futile if nipple-areolar complex malposition develops, but this adverse outcome is by no means infrequent. The most common displacement patterns are upward vertical malposition and lateral deviation, which have been observed in 69 and 75 %, respectively in smaller series [10]. In Small et al.'s cohort of 319 NSMs, malposition as measured by 1 cm or greater distance between actual and ideal nipple position occurred in 13.8 % of cases. Ideal nipple position was defined as either the point of maximal projection of the implant or the intersection of the mid-clavicular line and the inframammary fold in cases of implant malposition [16].

Once nipple malposition occurs, correction can be quite difficult. The first point of concern should be analysis of implant position and presence of capsular contracture. If implant malposition is due to capsular contracture, pocket revision with capsulotomy and/or capsulectomy should be performed prior to any attempt at nipple repositioning (Fig. 18.4). Inframammary fold elevation and lateral pocket release or capsulorraphy are the most common corrective maneuvers to address needs at post-NSM revision. If feasible, a less projectile or smaller implant may also be more forgiving. Need for nipple repositioning can then be reassessed and performed at the same operation or in a staged fashion.

Surgical correction of nipple position should not be attempted until 6 months to, perhaps more ideally, 1 year after initial reconstruction. Not all patients are candidates for reoperation. If the breast skin quality is thin or of poor vascularity as a result of delayed wound healing, radiation, or other causes, repositioning may be best avoided. Such might be the case when malposition occurs as a sequela of nipple ischemia.

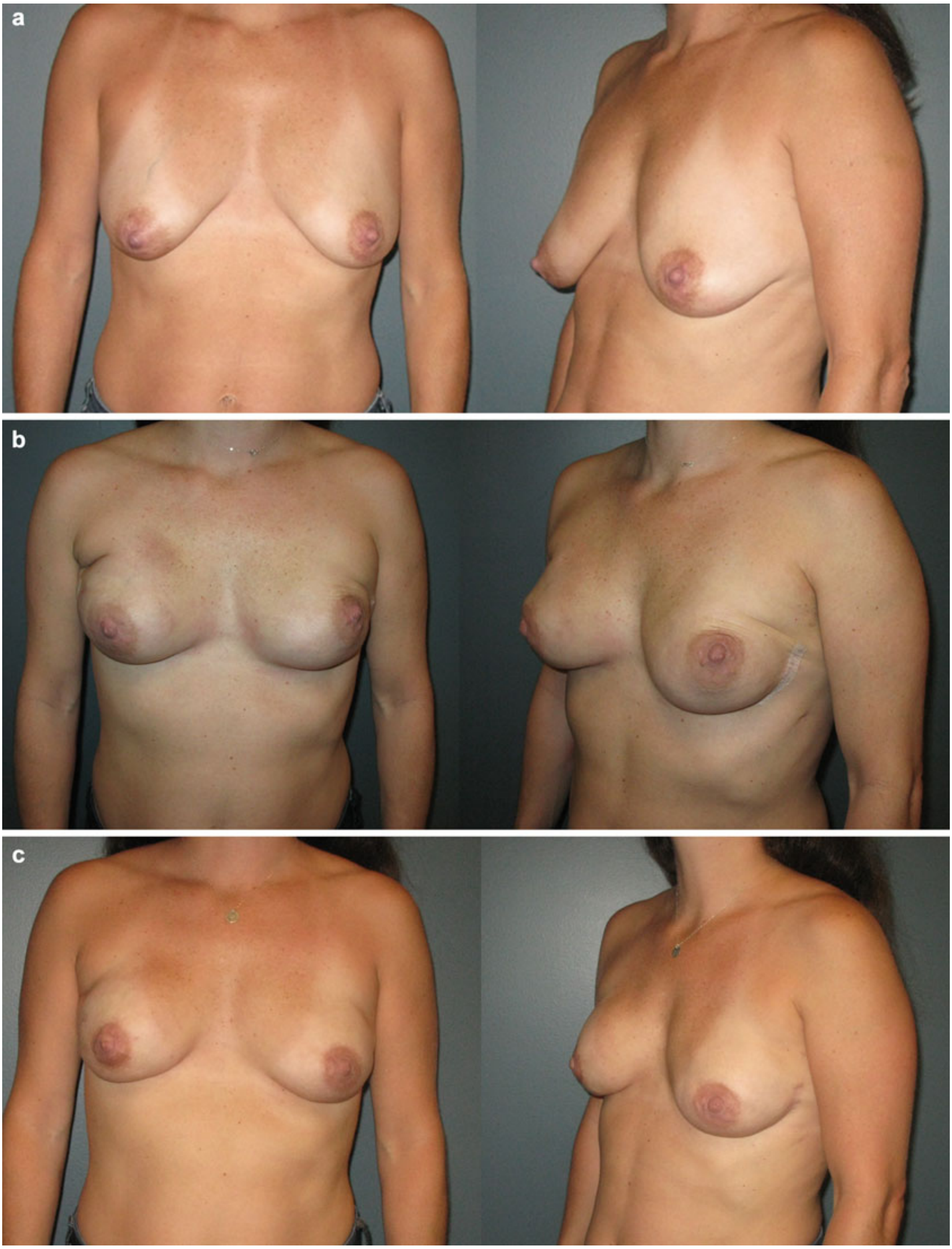

Fig. 18.4 This patient had lateral displacement of the left nipple-areolar complex after placement of a tissue expander. At the time of exchange she had the capsule completely removed in that location and disconnection of the skin envelope. This allowed correction of the nipple position

Crescent mastopexy is an option for addressing lateral and/or vertical malposition, though the degree and durability of correction can be less than satisfactory. Dilation of the areola is a possible undesirable outcome [16]. Using the concept of Z-plasties, reciprocal transposition flaps using the malpositioned areola and the skin from the new nipple position can be incised down to the level of the pectoralis muscle or implant capsule to allow for exchange in location [17–20].

For greater degrees of malposition, consideration may be given to excision of the nipple-areola complex and reapplication of the thinned nipple as a free graft. The areolar skin deficit may either be closed primarily or skin grafted as needed (Fig. 18.5). For severe cases of malposition, transposition of the

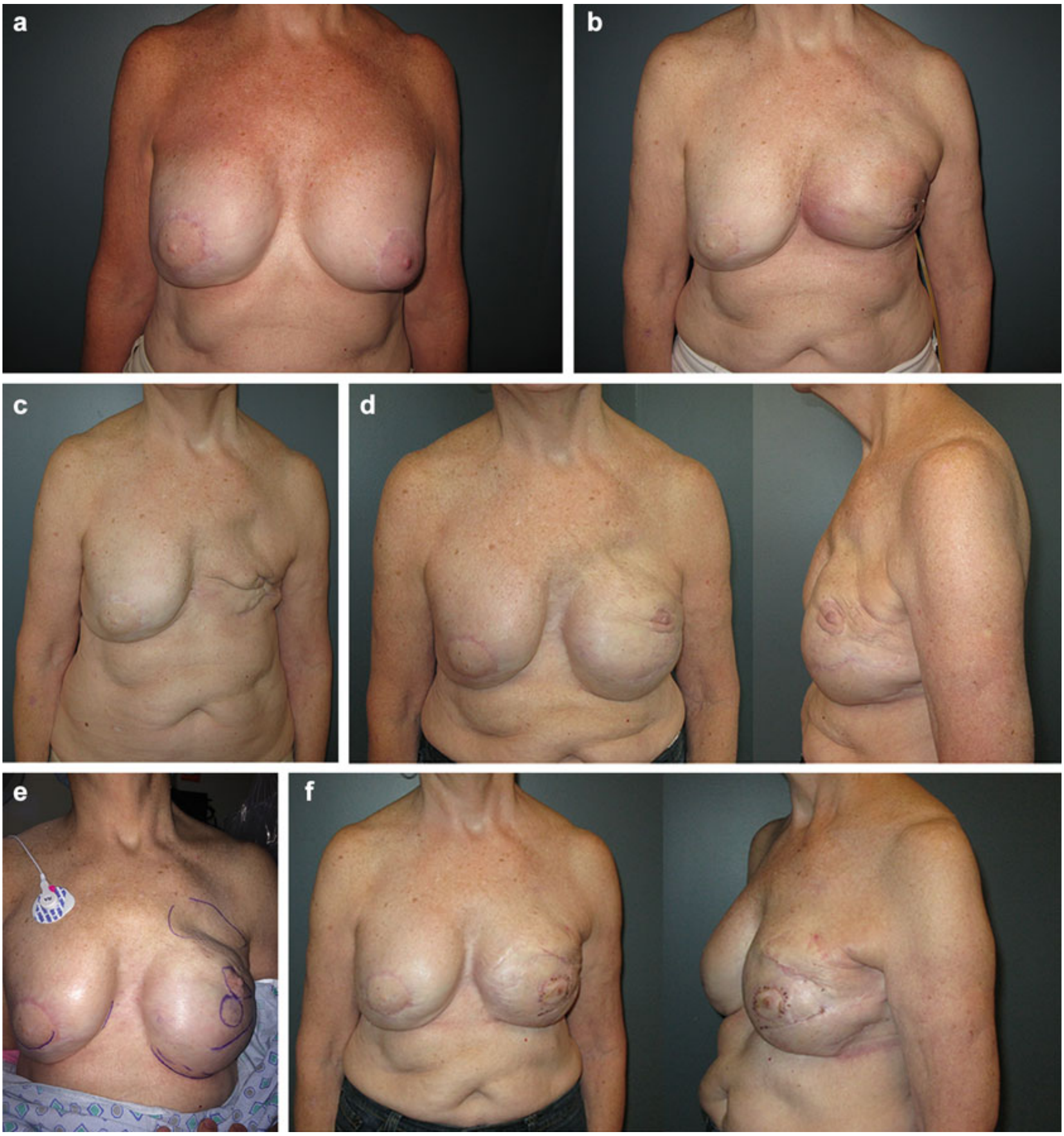

Fig. 18.5 This is a 50-year-old with a history of right breast cancer who had previously had a right mastectomy and latissimus dorsi reconstruction with implant. She then developed left breast cancer requiring a left nipple-sparing mastectomy and tissue expander reconstruction. Her expander was eventually removed due to an infection. After 6 months she had the expander replaced, expansion of the pocket and then had an implant placed. Unfortunately the nipple position was too high and lateral. For correction she had it removed and replaced as a full-thickness graft which corrected the symmetry

nipple via an inferior dermal pedicle has been described with success. Excess skin can be removed in the vertical or Wise reduction patterns [16]. Although implant-based techniques are most prevalent following NSM, some surgeons have suggested that autologous reconstruction offers the added benefit of allowing for secondary nipple-areolar complex repositioning with decreased concern for blood supply compromise [21].

Finally, the possibility of total nipple-areolar complex excision and delayed nipple reconstruction should be considered a reasonable reconstructive alternative. This straightforward approach will allow for precise nipple positioning, though care must be taken in designing new incisions relative to previous scars to avoid ischemia. Contralateral symmetry procedures such as mastopexies for nipple repositioning can improve the final reconstructive outcome.

Special Considerations

Direct-to-Implant Reconstruction

In patients with small breasts or prior augmentation, direct-to-implant reconstruction is well described following NSM. Although discussion of the full spectrum of considerations related to direct to implant reconstruction is beyond the scope of this chapter, the implications of this technique on potential complication profile deserve consideration. A recent meta-analysis suggested increased mastectomy skin flap necrosis rates following direct-to-implant reconstruction [22], though with proper patient selection the technique can be quite successful, obviating the need for serial expansions and subsequent staged operations. However, if mastectomy skin flap necrosis or nipple ischemia occur in the setting of direct-to-implant reconstruction, exchange to an expander with lower fill volume or total deflation may be necessary. In some large volume centers, a trend away from direct-to-implant reconstruction after NSM has taken place due to observed association with greater ischemic complications [3]. More studies also need to be done to examine the rates and types of revision following NSM with direct-to-implant reconstruction to clarify the benefit of this method.

Adverse Outcomes Following Radiation Therapy

As the indications for NSM are broadened, radiation in the preoperative or postoperative settings is becoming increasingly common. Studies examining radiated patients with NSM show increased capsular contracture, explantation rates, overall complications, and need for secondary revision procedures [23]. Implant malposition and excessively high nipple position represent the most common problems in long-term outcome [24]. However, early complications such as nipple ischemia, mastectomy skin flap necrosis, bleeding, and seroma have been found to be statistically equivalent [25]. Radiation that has occurred before or is planned after mastectomy no longer represents contraindications to NSM, but does hold implications for ultimate reconstructive outcomes that have not been systematically measured (Fig. 18.6).

Conclusion

Following NSM, nipple ischemia and mastectomy skin flap necrosis are potential short-term complications that may compromise outcomes. In the long run, nipple-areolar complex malposition represents one of the most problematic adverse outcomes that can also be difficult to correct. As is the case for most surgical procedures, prevention of complications via thoughtful planning and meticulous technique remains the optimal means of achieving predictable, satisfactory outcomes following NSM. As NSM continues to become increasingly popularized, however, appropriate management of short-term complications is essential to minimize long-term morbidity and unfavorable results, as surgical correction of the latter is notoriously difficult to achieve.

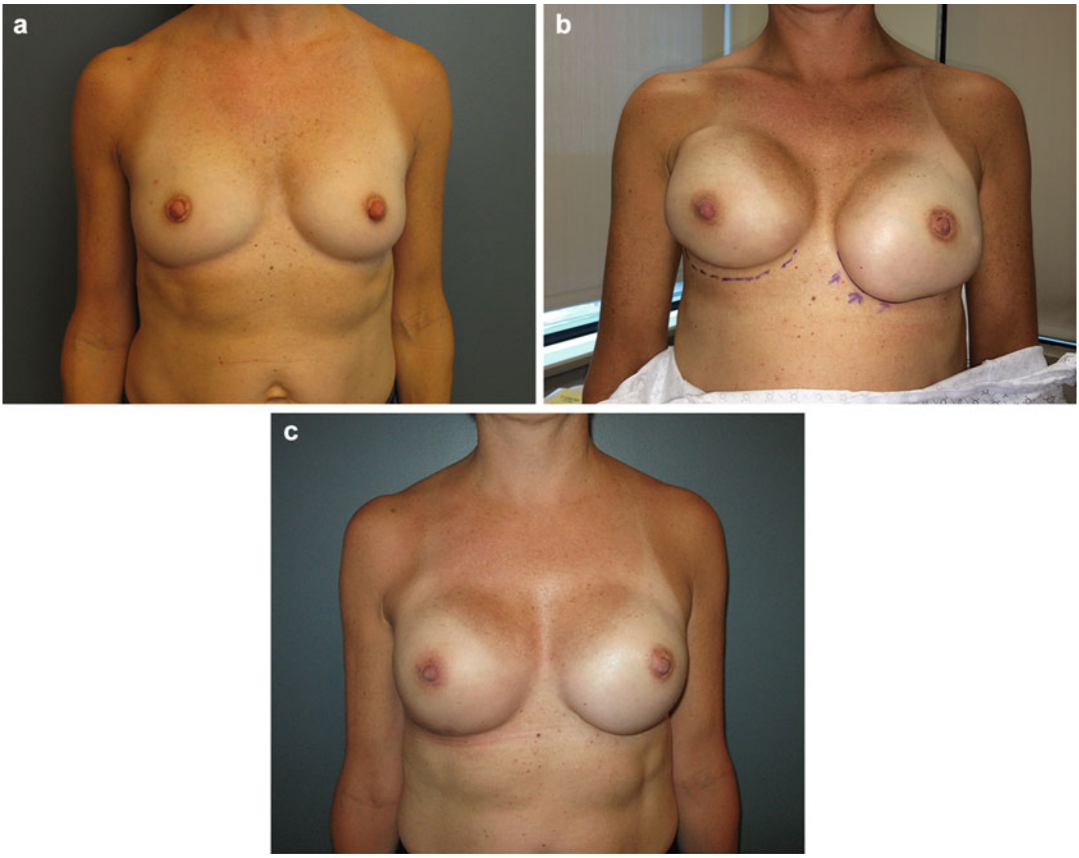

Fig. 18.6 This 39-year-old patient had a bilateral NSM and tissue expander reconstruction. Following radiation therapy on the right side her IMF was higher on that side and the expander pocket was too high. At the time of implant placement she had correction of the breast footprint with elevation of the left IMF and dropping of the right side. As long as the nipple position is reasonable the breast footprint can be easily adjusted

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19 Fluorescence Imaging in Breast Reconstruction: Minimizing Complications and Improving Outcomes

Troy A. Pittman, Chrisovalantis Lakhiani, and Kenneth L. Fan

Introduction

Over 200,000 women are diagnosed with breast cancer annually in the United States. Advances in detection, management, and adjuvant therapy now afford a 5-year survival rate approaching 90 % [1]. Nevertheless, surgery remains the mainstay of treatment and leaves an indelible mark on the patient. Although lumpectomy with adjuvant radiation (breast conservation therapy) remains a popular option, greater numbers of women with breast cancer who are eligible for breast conservation are electing to undergo mastectomy [2]. Improved imaging modalities and healthcare guidelines have led to a dramatic increase in the detection of early stage breast cancer and ductal carcinoma in-situ [3]. In addition, enhanced screening and genetic testing has improved surgeons' ability to detect high-risk patients and better care for those with pre-malignant lesions [2]. This has afforded surgeons the ability to offer more conservative surgical options, including nipple-sparing mastectomy (NSM) for treatment of the affected breast, as well as for contralateral prophylactic mastectomy [4]. As the treatment for breast cancer continues to evolve and improve, there is greater patient and surgeon interest in minimizing the morbidity associated with multiple operations, while improving breast cosmesis. To this end, nipple-sparing mastectomy combined with either immediate reconstruction with expanders or implants, or immediate reconstruction with autologous tissue, are necessary tools in the plastic surgeon's armamentarium in order to minimize the psychological morbidity associated with repeated operations, while maintaining the desired feminine aesthetic immediately following mastectomy.

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Safety of Nipple-Sparing Mastectomy

Nipple-sparing mastectomy (NSM) has been established as an oncologically safe surgical option compared to traditional or skin-sparing mastectomy in appropriately selected patients [5–8]; current guidelines include that the tumor be well-circumscribed, less than 3 cm, greater than 2 cm from the nipple-areola complex (NAC), not multicentric, and possess no lymphovascular invasion [8–10]. The NAC is a vital component and focal point of breast recognition. Preservation of the NAC in NSM has been shown to improve health-related quality of life outcomes compared to women who undergo skin-sparing mastectomy [11]. However, adoption

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of this technique has not been universally accepted due to technical concerns regarding NAC necrosis and even greater oncologic concern for cancer recurrence at the NAC necessitating removal for malignancy [5, 7, 8]. While the former has been reported to occur in 2.9–8 % of cases in recently published reports [5–8], these studies did not include the use of any intraoperative perfusion monitoring in order to assess NAC viability at the time of the mastectomy. Nevertheless, these concerns have not precluded one- or two-stage breast reconstruction following NSM, and several studies have demonstrated its safety and efficacy [9, 12–14]. Moreover, the oncologic safety of NSM has been proven in several studies, with a defined low complication rate [5, 7, 9, 10].

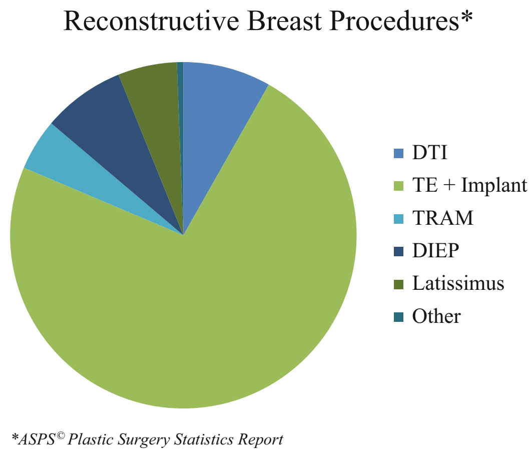

Fig. 19.1 Distribution of breast reconstruction procedures by type. *Courtesy of the American Society of Plastic Surgeons 2014* (*DTI* direct-to-implant, *TE* tissue expander, *TRAM* transverse rectus abdominis muscle, *DIEP* deep inferior epigastric perforator)

Implant Based Reconstruction Following Nipple-Sparing Mastectomy

Implant-based reconstruction is the most common technique for reconstructing the breast following mastectomy, accounting for approximately 80 % of all breast reconstructions currently performed. Of these, two-stage reconstructions involving temporary tissue expander placement followed by implant insertion compromise the majority (Fig. 19.1). The benefits of the two-stage approach include greater patient control in selection of final implant size, the ability to avoid undue tension on the overlying mastectomy flap and the opportunity for refinement of implant position at second stage. Since its introduction, surgical techniques have continued to improve, with a move away from total muscular coverage to partial submuscular coverage. The adoption of human acellular dermal matrices (ADM) as a sling for inferolateral coverage has further increased the plastic surgeon's ability to control final implant position, define the inframmary fold (IMF), and has been shown to reduce the risk of capsular contracture [15]. In addition, ADMs have been proven to become incorporated into the host by acting as a scaffold for cellular and vascular infiltration, allowing it to be resistant to infection and radiation [16].

As our understanding of patient selection has improved, there are greater opportunities for the plastic surgeon to offer direct-to-implant (DTI) reconstruction provided the vascularity of the skin flaps can be accurately assessed intraoperatively. Today approximately 15–20 % of women undergoing implant-based reconstruction receive a direct-to-implant operation [14]. DTI reconstruction allows for a one-stage reconstruction potentially avoiding the need for a second operation. DTI reconstruction has been shown to reduce cost and number of office visits, eliminate the need for uncomfortable tissue expanders, expedite time to radiation, and offers patients immediate aesthetic results [14, 17–20]. This single-stage procedure is also psychologically superior to two-stage reconstruction [21]. This offers an ideal reconstructive choice in select patients by recreating the breast at the time of mastectomy with a single operation. This technique has been attempted—and abandoned—in the past due to its technically demanding nature, issues with pectoralis muscle retraction, implant malposition, capsular contracture, and concern for implant exposure in thin-skinned individuals. These concerns have largely been obviated with the introduction of ADM. Using ADM for inferior and lateral pole coverage affords the surgeon the ability to maintain the pectoralis position, reliably delineate implant position in a single stage, and lower the risk of capsular contracture by inhibiting the foreign-body tissue response [14, 22, 23]. Furthermore, DTI reconstruction with human ADM has been shown to be a cost-efficient option, with a total cost less than that of traditional staged reconstruction without ADM [24]. Despite this, the inability to accurately assess skin flap viability immediately following the mastectomy raised concern over mastectomy skin flap or NAC necrosis limiting DTI reconstruction to carefully selected patients, specifically those with small breasts preoperatively and/or appreciably thick mastectomy skin flaps.

Overall concern for poor mastectomy flap perfusion can be addressed with the use of intraoperative indocyanine green (ICG) angiography (SPY *Elite*, Novadaq Technologies Inc., Mississauga, ON). The SPY *Elite* imaging system allows real-time, intraoperative clinical assessment of skin flap viability with a technology that provides qualitative and quantitative interpretation of skin flap perfusion.

The History of Fluorescence Imaging

Indocyanine Green (ICG) first saw its introduction to medicine during the 1950s. An executive from Eastman Kodak began helping Dr. Irwin Fox from the Mayo Clinic develop a dye biocompatible with blood. ICG exhibits a high affinity for serum albumin (98 %) and absorption near infrared (NIR) at 805 nm. Approved by the FDA in 1956, the Baltimore pharmaceutical firm Hynson, Wescott, & Dunning turned ICG from a substance unstable in aqueous solution to the lyophilized form used today. Shortly thereafter, ICG saw its first use for medical research in cardiology, measuring time varying dilution in whole blood as a way to evaluate cardiac output in valvular and septal defects [25]. The first attempts at using ICG for angiography was by Kogure and Choromokos in 1969 when they demonstrated infrared absorption angiography in the canine brain vasculature [26]. These efforts were further refined by Hochheimer [27] and Flower [28], who demonstrated the potential use of ICG in the aging and glaucomatous human eye [29, 30].

While ICG has been used for several decades in retinal angiography, fluorescein has been much more popular partly because it is visible without camera equipment [31]. Fluorescein remained the gold standard for evaluating superficial vascular structures in the fundus, identifying perfusion permeability, and proliferative abnormalities [29]. Nonetheless, ICG gives information of deeper lying blood vessels due to its NIR wavelength in which tissues are more translucent than in visual wavelengths without tissue chromophores interfering. Additionally, ICG does not stain tissues like fluorescein allowing multiple repeated images to be obtained in the same operative session.

The concept of fluorescence involves illuminating the tissue of interest with a light at the excitation (strong) wavelength (750–810 nm) while observing the fluorescing (weak) rays in the sensor (over 800 nm). Camera, filters, and a light source are required to prevent mixing of excitation and fluorescing rays to detecting sensors. Clinical value was initially hampered by the lack of photographic resolution and primitive technology to record the data. The introduction of digital angiography with highly weighted cameras in the NIR wavelength, partnered with high speed imaging provided clinicians with the ability to translate data into clinical use [32].

In 2005, the FDA approved the ICG angiography SPY for coronary angiography. Indocyanine green can be either used to evaluate myocardial tissue perfusion by imaging an area of interest around a coronary vessel or direct imaging of the graft by visualizing the lumen. Noncardiac surgeons soon saw the utility in a device that provided real time information regarding tissue perfusion. Shortly thereafter, SPY *Elite* received FDA clearance for use in plastic surgery, organ transplant, and gastrointestinal surgical procedures.

Indocyanine Green

ICG's advantages are its high affinity towards plasma proteins, specifically albumin, leading to confinement within the vascular space, low toxicity, short half-life in circulation, and rapid excretion, almost exclusively by the liver into bile. ICG has an excellent safety profile with a low incidence of adverse events [33]. Sodium iodide composes no more than 5 % of most ICG formulations, making the only true contraindication to its use patients with severe iodine and shellfish allergies.

After injection, ICG is bound within a few seconds to lipoprotein complexes and remains intravascular, with normal vascular permeability [34]. Exact wavelength of ICG excitation and fluorescence depends on the chemical environment and physical conditions, such as temperature and concentration [31]. Binding to blood proteins shifts the excitation peak from 780 to ~805 nm and the fluorescence peak to ~835 nm in several minutes.

With a half-life of 2.5–3 minutes, ICG is excreted exclusively by the liver via glutathione S-transferase without modification or reabsorption from the intestine [31]. There is negligible renal, lung, peripheral, or cerebrospinal uptake of dye [35]. This allows repeated administration within the same surgical procedure, in comparison with fluorescein which remains within the tissue for 12 h.

SPY *Elite* Imaging

The SPY *Elite* system is comprised of a near-infrared light source, a maneuverable imaging head and a digital camera. In the operating room, the articulating arm which contains the camera is positioned over the patient. ICG is then injected through a peripheral line by the anesthetist. As the ICG binds with albumin within vascularized tissue, a blush appears on the screen. Video of the procedure can be captured and quantification software is available to look at relative perfusion values. A digital display is present on two opposing screens allowing visualization by both the device operator and the surgeon (Fig. 19.2).

The maximum field that can be illuminated by the laser optical system is approximately $18.5 \times 13.5\ cm^2$. The cameras can capture images at 3.75–30 frames per second, with a recording time between 30 and 120 s. Coupled software (SPY-Q Analysis Toolkit) provides additional views, comparisons, analysis tools, including fluorescence intensity measurement algorithms. Gurtner et al. 2013 published technical recommendations of use of SPY in plastic surgery with guidelines on timing of evaluation [36].

Fluorescence Imaging in Breast Reconstruction

Since its introduction in 2007, intraoperative indocyanine green angiography using the SPY *Elite* system has been shown to be a reliable method for evaluating mastectomy skin flap and tissue flap perfusion [37]. A prospective trial evaluating its use in post-mastectomy breast reconstruction has demonstrated that it possesses a 90 % sensitivity for detection of tissue necrosis [38]. Furthermore, comparative cost studies have established that appropriate use of the SPY *Elite* system reduces the incidence of reoperation for ischemic complications, thereby reducing health-care related expenditure in prosthetic based breast reconstruction [37, 39, 40]. Moreover, the use of SPY *Elite* has also been shown to theoretically reduce the risk of capsular contracture, by selecting for only well-perfused skin flaps which are better able to combat sub-clinical infection [37].

In autologous tissue breast reconstruction using the deep inferior epigastric artery perforator (DIEP) flap or the transverse rectus abdominis (TRAM) flap, ICG angiography has proven its utility in identifying areas of poor flap perfusion and enhancing our understanding of flap microvasculature [41–43]. Notably, evidence from several studies have shown that the SPY *Elite* system is superior to clinical judgment alone in predicting areas of future flap necrosis [42, 43]. Moreover, its use has also been shown to produce a cost-savings benefit by reducing the need for reoperation due to flap necrosis or flap congestion

Fig. 19.2 SPY *Elite* imaging system

[44]. Although it can only provide information a few millimeters deep from the skin, one of the most significant advantages of ICG angiography is its ability to calculate intrinsic transit time through the vascular anastomosis and thereby provide real-time information regarding the risk for venous congestion [42, 45]. The main limitation of ICG angiography in microsurgical breast reconstruction is its inability to predict perforator location based on signal intensity readings [43]. Indeed, the functions of CT angiography and ICG angiography in autologous breast reconstruction planning are in contradistinction; whereas CT angiography has been shown to accurately assess size and location on perforating vessels, ICG angiography is able to evaluate the actual perforasome of a given vessel [45, 46]. Nevertheless, as understanding of DIEP flap vascular anatomy has improved, surgeons have recognized that perforators tend to arise in predictable locations, and the use of imaging (CT angiography) to identify perforator location is increasingly being abandoned. What has been found to be of greater importance is an understanding of DIEP/TRAM flap microsurgical perfusion patterns. Partly through the use of ICG angiography, these patterns have been clearly elucidated in the last decade [41, 47, 48].

Rapid and reliable DIEP flap harvest can be accomplished by attempting lateral dissection first in order to identify a lateral row perforator. When this fails, direction should then be turned to the periumbilical region, where perforators commonly originate within 5 cm of the umbilicus. Lastly, medial row perforator harvest should be attempted. It is now understood that lateral row perforators are better able to perfuse the hemiabdomen and follow the perfusion pattern described by Holm et al., in which Zones I and II compromise the entire hemiabdomen [41, 48, 49]. This is in contrast to the pioneering work of Hartrampf in which Zone II compromised the medial portion of the contralateral hemiabdomen [50]. This classic pattern of perfusion, however, is followed by medial-row DIEP perforators [48, 49]. This understanding of microvascular perfusion is further enhanced by intraoperative ICG angiography, which is able to detect areas of ischemia in the lateral and inferior aspects of the flap with high sensitivity. Lastly, the SPY *Elite* system affords the ability to evaluate dominance of the superficial or deep system for selection of appropriate vessel anastomosis [51].

At our institution the SPY *Elite* system is a vital adjunct to clinical decision-making when performing prosthetic or autologous breast reconstruction. Its merits include assessment of the NAC in nipple-sparing mastectomy, ability to determine feasibility of DTI reconstruction, predicting areas of mastectomy flap ischemia or congestion, and evaluation of arterial inflow and venous outflow in autologous tissue reconstruction.

Nipple-Sparing Mastectomy with Partial Subpectoral Direct-to-Implant Breast Reconstruction and Acellular Dermal Matrix (ADM)

Nipple-sparing mastectomy (NSM) with immediate direct-to-implant breast reconstruction represents the pinnacle of reconstructive surgery through which natural form, symmetry, and the feminine aesthetic can be immediately offered to the patient at the time of oncologic surgery. Preoperatively patients are extensively counseled regarding reconstructive options. Included in the preoperative consult is the fact that ICG angiography will be performed to assess skin flap viability for direct-to-implant reconstruction. Patients are counseled and informed that if there is questionable perfusion of mastectomy skin flaps, DTI reconstruction may be abandoned and a tissue expander will be placed at the discretion of the plastic surgeon. A specific advantage of the imaging system is the feature that allows printing of the SPY images in the operating room. This provides a hard copy of the images that can be included in the medical record and shared with the patient postoperatively, allowing them insight into the surgeon's intraoperative decision making.

At our institution, the majority of nipple-sparing mastectomies are performed via an inframammary fold (IMF) incision by the oncologic breast surgeons. This maintains NAC viability, allows for discrete scar placement, and minimizes nipple malposition postoperatively compared to peri-areolar or radial incisions. The SPY *Elite* system is used to interrogate the mastectomy skin flaps in order to assess skin flap viability before and after implant insertion. Although 10 cc of ICG are included in the SPY PAQ kit (along with a sterile drape and an aqueous solvent), only 3 cc need be used at once. This allows a total of three possible interrogations of the mastectomy skin flaps with a single kit.

There are times when the breast surgeons at our institution perform tumescent technique when performing mastectomy for hemostasis and assistance in dissection of mastectomy planes [52]. Tumescent has been previously shown to cause hypoperfusion voiding ICG readings [53]. We have confirmed this in our own practices anecdotally. Initially, we tested spy with 1 ampule (1 mg) of epinephrine in a 1 liter normal saline bag. We then decreased the doses to 0.7, 0.5, and 0.3 mg. While 0.3 mg does not seem to affect ICG readings significantly, the breast surgeons have noted it does not provide the desired hemostatic effect. We avoid direct-to-implant reconstruction and default to expander placement in cases where tumescence has been used, due to the unpredictability of mastectomy flap perfusion both clinically and with the SPY. At this time we are actively working on a technique where tumescent solution and SPY can be used in harmony.

Surgical Technique

At the completion of the nipple-sparing mastectomy, the patient is re-prepped with betadine and re-draped. The SPY *Elite* system is positioned next to the patient and draped with a sterile drape. Any packing is removed from the breast pocket and the skin flaps are returned to a tension free position. The articulating arm allows placement of the camera over the operative field. The operating room lights are turned off, and the mastectomy skin flaps are then interrogated using 3 cc of ICG with a 10 cc normal saline flush given by the anesthesia team. If there are no areas of poor-perfusion, the decision is made to proceed with DTI reconstruction (Fig. 19.3).

When performing a subpectoral reconstruction, a pocket is created beneath the pectoralis major muscle which covers the superior third of the implant. The pectoralis is raised from lateral to medial to the level of the clavicle, and is released from its origin along the sternal border for the inferior 2–3 cm. Next, ADM is opened and prepared. The ADM is then sutured to the inferior border of the pectoralis with a 3-0 Vicryl suture in a continuous running fashion. A degree of pleating is allowed while securing the ADM to the pectoralis medially in order to allow for medial pole fullness. The medial third of the ADM is then secured to the chest wall and IMF using 3-0 Vicryl simple interrupted sutures.

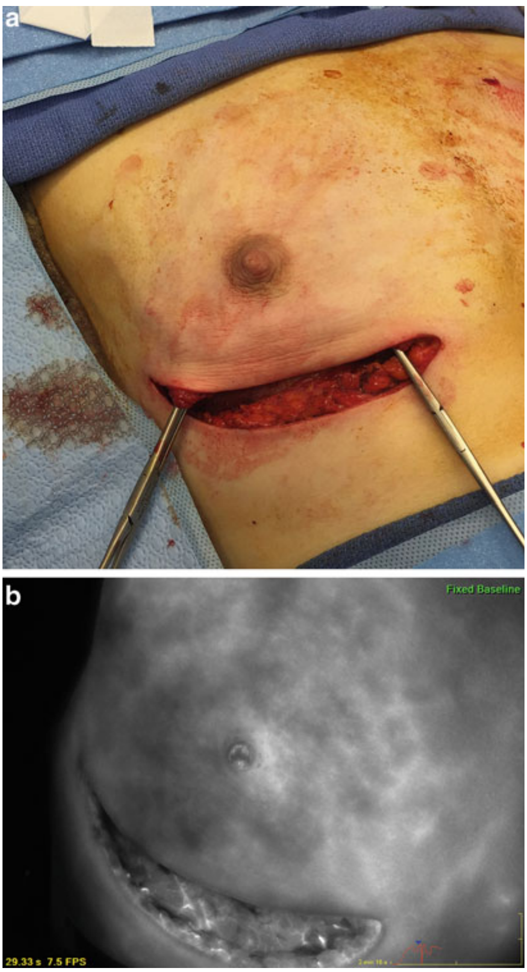

Fig. 19.3 (**a**) Clinical image of mastectomy flap immediately following NSM. (**b**) Corresponding SPY Image showing good tissue perfusion throughout the flap and NAC

In the situation where the vascularity of the flaps is in question, we proceed with the reconstruction: release of the pectoralis from its origin and sew the ADM to the caudal border of the pectoralis, followed by placement of a temporary sizer. In our experience, a marginal SPY image immediately at the end of the mastectomy may be due to over retraction of the skin flaps during the extirpative surgery. The SPY is then repeated with the sizer in place. In the situation where the SPY continues to appear marginal or nonfavorable (Fig. 19.4), the reconstruction is converted to a tissue-expander reconstruction with low or no intraoperative filling and closed primarily.

Provided that the SPY images show well-perfused flaps, the implant is removed from its packaging and allowed to soak in a triple antibiotic solution in its container (1 g cefazolin, 80 mg gentamicin, and 50,000 IU bacitracin). The breast pocket is then copiously irrigated with triple antibiotic solution as well. Surgeon's gloves are changed and the implant is inserted beneath the pectoralis/ADM construct using a one-touch technique. The inferior aspect of the ADM is next secured to the IMF using 3-0 Vicryl simple interrupted sutures, and laterally is secured to the chest wall just posterior to the lateral border of the implant in order to medialize the prosthesis and prevent lateral migration. A #7 Jackson-Pratt drain is next introduced through a lateral stab incision, and inserted between the ADM and the mastectomy flap.

The mastectomy skin flap incisions are tailor-tacked using staples, and re-interrogated using

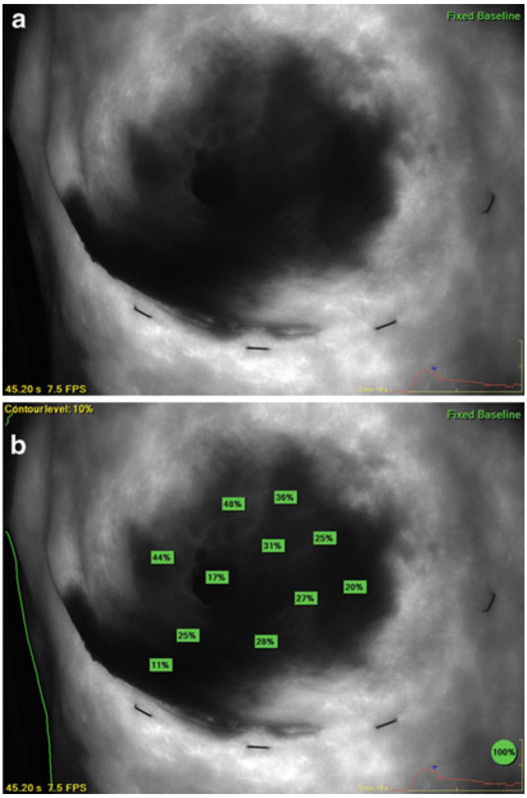

Fig. 19.4 (**a**) SPY Image showing poor perfusion of the mastectomy flap immediately following NSM. (**b**) Quantitative relative values indicating poor tissue perfusion. Note that the 100 % reference marker is placed over the sternum. In this case, DTI reconstruction was aborted and a tissue-expander was placed

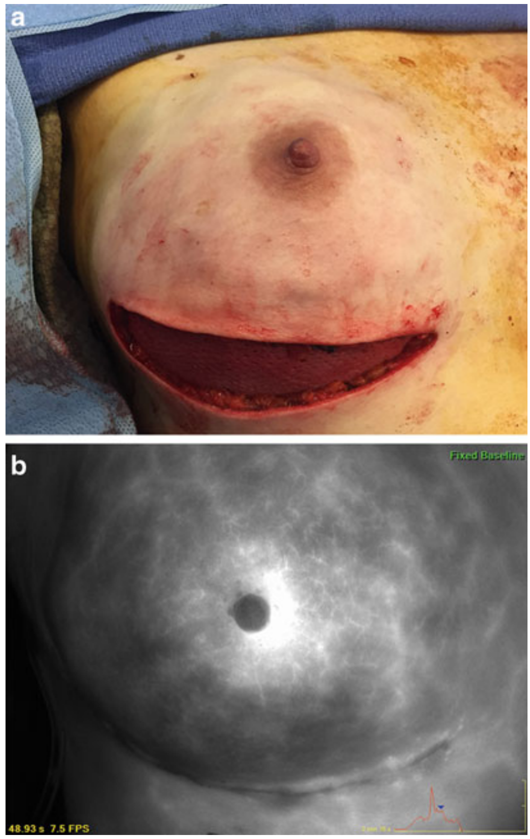

Fig. 19.5 (**a**) Clinical and (**b**) SPY image showing excellent flap perfusion following placement of implant in DTI reconstruction

the SPY *Elite* system (Fig. 19.5). Relative perfusion values can be obtained by placing a reference marker on tissue that is known to be well-perfused (we prefer an area over the sternum). Quantitative relative values are useful, not only to assess tissue perfusion, but also to assess for flap congestion caused by undue tension on the overlying flap by the implant. Any areas of ischemic perfusion at the incision site are excised at this time and the patient is closed primarily using 3-0 Monocryl deep dermal sutures, and a 3-0 Monocryl subcuticular pull-through suture. DermaBond (Ethicon, Somerville, NJ) is applied to the incision site in order to provide an occlusive seal and prevent bacterial entry into the wound. The drain is secured using a 3-0 Nylon suture, a BioPatch (Ethicon, Somerville, NJ) is placed in order to prevent bacterial migration through the drain-site, and the drain site is covered with a transparent film dressing. Finally, the patient is placed in a surgical bra prior to transfer to the surgical bed (Fig. 19.6).

Tips

- Resect all nonviable portions of skin near the mastectomy incision site.
- If there is questionable viability of the NAC or mastectomy skin flaps on SPY *Elite* angiography, proceed to staged reconstruction with tissue expanders even if the tissue may appear viable by clinical examination.

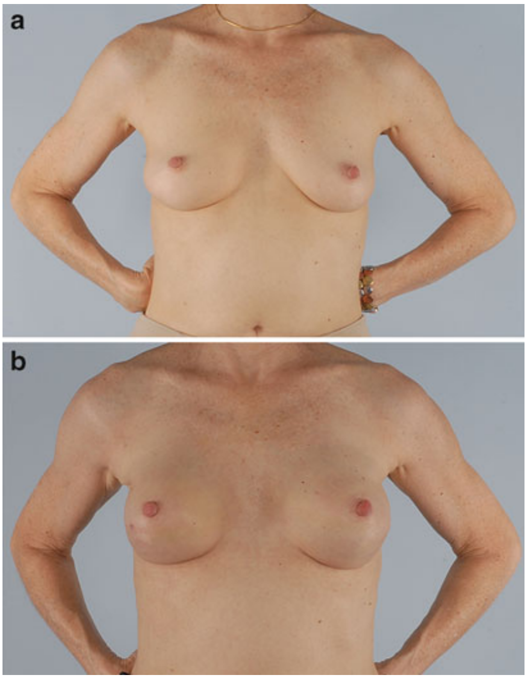

Fig. 19.6 Fifty-eight-year-old female with DCIS in right breast. Patient opted for bilateral NSM with DTI reconstruction. (**a**) Pre-op, (**b**) 6-months post-op

Nipple-Sparing Mastectomy with Immediate Tissue Expander Breast Reconstruction

Staged tissue expander reconstruction following nipple-sparing mastectomy is a reliable surgical option as either a primary surgical choice for patients who are poor direct-to-implant candidates (poor quality or atrophic skin, desire for final breast volume greater than initial bra size), or as a salvage option when skin flap ischemia is detected by SPY *Elite* imaging in a planned DTI reconstruction. As with subpectoral DTI reconstruction, the procedure involves creation of a subpectoral pocket with inferolateral expander coverage using human acellular dermal matrix. After intraoperative expansion. ICG angiography can be used to determine if overfilling resulting in ischemia or flap congestion has occurred. The expander can then be deflated in real-time while being imaged by the SPY *Elite* system in order to visualize reperfusion of the ischemic or congested segment (Fig. 19.7).

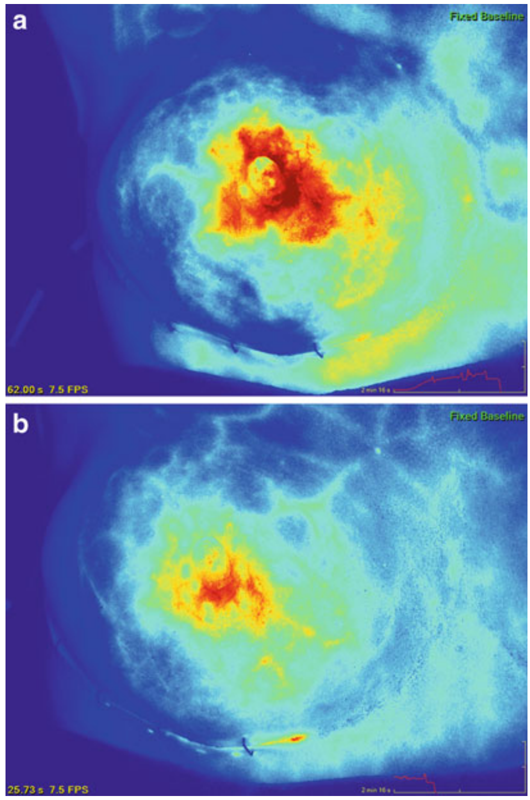

Fig. 19.7 (**a**) SPY Image taken after placement of tissue-expander. Note the central dark red area indicating flap congestion due to pressure from aggressively filling the expander. (**b**) After removing 100 cc from the expander the flap appears less congested

Tips

– Skin flaps should be visualized using the SPY *Elite* system following expansion. If areas of ischemia or congestion are noted on SPY *Elite* angiography, the expander should be deflated intraoperatively until reperfusion of the ischemic or congested segment is noted.

Nipple-Sparing Mastectomy followed by Autologous Breast Reconstruction

Deep inferior epigastric artery perforator (DIEP) flap breast reconstruction is both technically challenging and has a steep learning curve. Compared to TRAM flap reconstruction, it offers decreased donor-site morbidity and time to recovery. Paramount to successful DIEP flap reconstruction is selection of perforator(s) used to supply the flap in order to ensure maximal flap survival. In this regard, ICG angiography is a valuable adjunct to the reconstructive surgeon by providing in-vivo real-time information regarding flap perfusion and vessel patency.

CT angiography has been shown to be a useful tool in assessing abdominal perforators preoperatively [46]. Proponents for this technique cite decreased operative time, accurate preoperative assessment of long-intramuscular vessel course and potential decrease in muscle damage. However, preoperative CT imaging not only exposes the patient to additional radiation, but fails to give the surgeon information regarding the specific zonal perfusion of the skin (perforasome) from a given perforator. In our practice, we use the SPY *Elite* imaging system to assess flap perfusion both before and after isolation of the perforators.

ICG angiography use in autologous breast reconstruction has been shown to be effective at the following points: isolating perforators on the abdominal wall, determining which of those perforators will maximally perfuse the flap, assessing the relative dominance of the superficial or deep inferior epigastric artery system, evaluating the patency of arterial and venous anastomoses after flap transfer, and defining which areas should be discarded after flap inset, thus decreasing postoperative fat necrosis [42, 53, 54].

Surgical Technique

The patient is marked in the preoperative holding area. If a prior Pfannenstiel incision exists, the marking is placed below the resultant scar. The patient is prepped and draped in the usual sterile fashion. If the operation is performed with multiple reconstructive surgeons, exposure of the internal mammary vessels is performed simultaneously with flap harvest.

The inferior incision is made first and dissection carried to the anterior rectus sheath. If a superficial inferior epigastric artery and/or vein is encountered, every attempt is made to salvage them as they may represent the dominant blood supply to the flap in a minority of patients, or can be used to turbo- or super-charge the flap in cases of poor inflow or venous congestion, respectively. The superior incision is then made and again dissection carried to the anterior rectus sheath. In a bilateral reconstruction, flap harvest is then carried out in a lateral to medial direction. As the border of the rectus muscle is approached and perforators begin to emerge, the flap is then split vertically in the midline to create two hemiabdominal flaps. Dissection is carried out for each hemiabdominal flap in order to isolate relevant perforators. After this has been accomplished, the SPY *Elite* system is introduced in order to assess the location and contribution of the perforators and perforasomes (Fig. 19.8). A 3 cc bolus of ICG is given by the anesthesia team

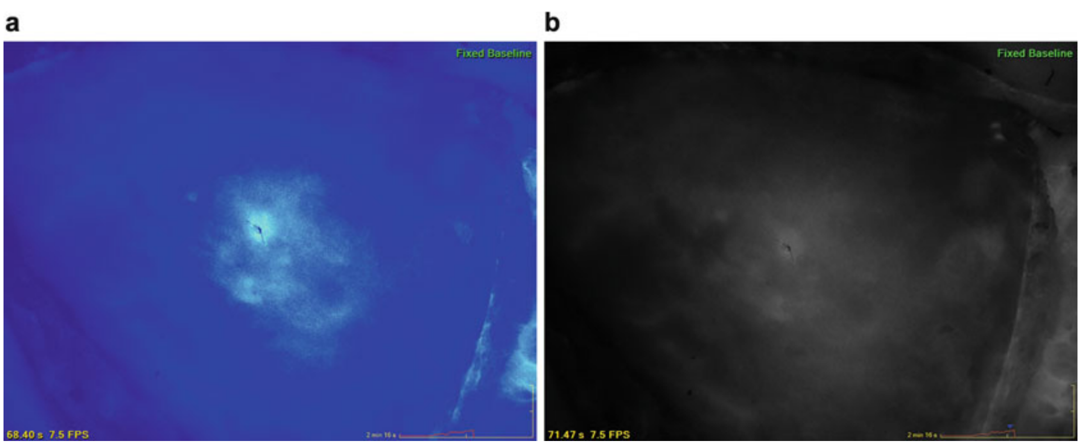

Fig. 19.8 SPY *Elite* used to locate perforator in DIEP hemi-abdominal dissection. (**a**) A 5-0 nylon suture is placed at the location of the perforator to assist in Doppler monitoring throughout the procedure. (**b**) The system interface can be changed after identification of the perforator to evaluate the perforasome associated with it

followed by a 10 cc normal saline flush. Individual perforators may be clamped in order to assess their relative contributions. The perforator(s), which demonstrate optimal flap perfusion is isolated, selected for harvest and marked with a 5-0 nylon suture while remaining perforators are ligated. In general, lateral-row perforators are preferred for hemiabdominal flap harvest, as they have been shown in physiologic studies to provide maximal perfusion to the entire hemiabdomen [48, 49].

Dissection then proceeds through the anterior rectus sheath and traces the perforating branch to its origin on the deep inferior epigastric artery, and proceeds inferiorly to the external iliac artery origin. The vessels are then ligated and the flap is irrigated with heparinized saline until clear venous outflow is observed. The flap is then transferred to the chest and vessels are prepared under the operating microscope. Donor deep inferior epigastric veins are first anastomosed to the internal mammary veins if both are present; otherwise a single venous anastomosis is performed. The donor artery is then sutured to the recipient internal mammary artery using 8-0 nylon suture in an interrupted manner. A Doppler probe is used to confirm flow.

The SPY *Elite* system is reintroduced in order to assess perfusion of the entire flap (Fig. 19.9). Areas of clear ischemia are marked for excision, with careful attention paid to the lateral and inferior most portions of the flap. The posterior aspect of the flap may also be examined at this time in order to assess subcutaneous fat perfusion and these areas may be excised in order to limit fat necrosis postoperatively.

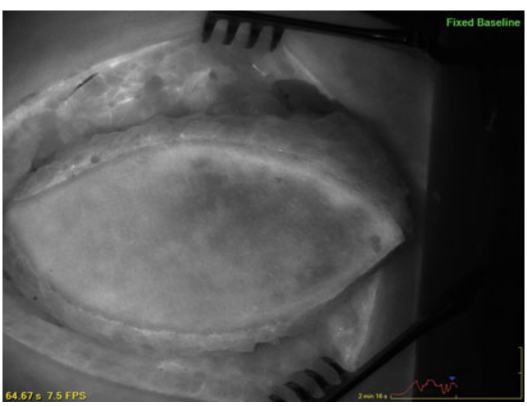

Fig. 19.9 SPY image showing good tissue flap perfusion after anastamosis and inset of DIEP flap

In addition to imaging the abdominal flaps, in cases of autologous reconstruction when NSM has been performed, it is essential to assess mastectomy flap and NAC viability. If ICG readings are equivocal and portions of the mastectomy flap are in the "gray zone" (25–45 % perfusion) [41], we often delay de-epithelialization of the abdominal flap and bury the skin flap until the necrosis has presented itself. This is an option unique to autologous reconstruction. Flap banking has been previously described and is commonly performed in our institution. It allows for demarcation and resection of questionably viable flaps before completion of reconstruction.

The flap is temporarily secured using penetrating towel clips to the chest wall and the flap is de-epithelialized with the exception of a small, externalized skin paddle used for monitoring. Twenty minutes after injection of the ICG, the SPY *Elite* system is used to assess delayed venous outflow. Clear egress of the ICG should be noted from the flap. If there appears to be high signal intensity within the entire distribution of the flap, this likely represents venous congestion (Fig. 19.10). At this point the venous anastomosis should be interrogated for kinking or thrombus. ICG angiography may then be used a third time and both the anastomotic sites should be evaluated, as well as the flap itself for venous egress.

At this point the flap may be inset with 3-0 Monocryl deep dermal sutures, and a subcuticular running suture with 3-0 Monocryl. The abdominal wall is closed in standard fashion using drains. The flap is finally reevaluated using the Doppler probe and a 5-0 nylon marking suture is placed so that it may be monitored postoperatively. An abdominal binder is placed on the patient and a forced-air warming blanket is placed over the reconstructed breast in order to minimize vessel constriction secondary to hypothermia.

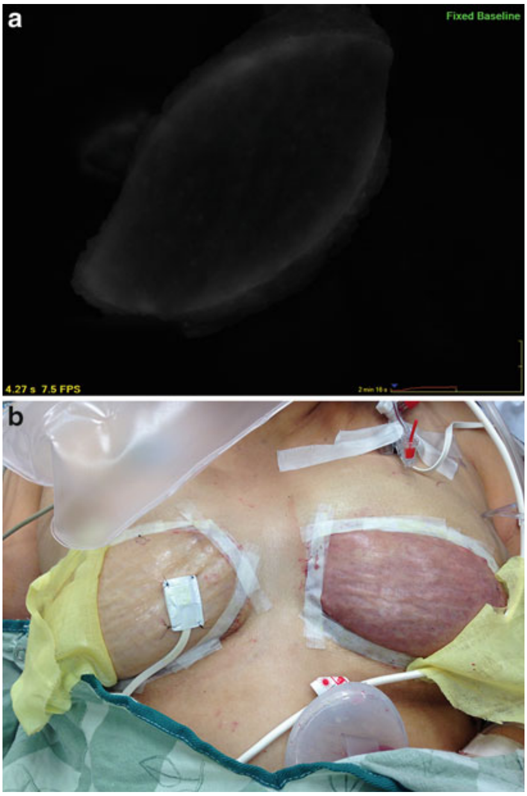

Fig. 19.10 (**a**) Image showing SPY 25 minutes after injection of ICG. Note the hyperintensity of the flap indicating congestion and stasis of the ICG. This was unrecognized as an issue intraoperatively given lack of clinical findings and the patient was transferred to the recovery room. (**b**) Shortly after transfer the flap began to clinically appear congested

Tips

- Clamping individual perforators and assessment with SPY at the time of flap harvest allows for selection of dominant perfusion to the DIEP flap.
- Ensure venous egress is evaluated using ICG angiography; venous congestion intraoperatively may represent a dominant superficial system if there is not a mechanical obstruction to outflow.
- It is essential to image the overlying mastectomy flaps. In the event that the overlying flaps appear ischemic or congested, delay de-epithelialization of the abdominal flaps.

Conclusion

Nipple-sparing mastectomy is the end of an evolutionary lineage beginning with the Halstead radical mastectomy, followed by the modified radical mastectomy and skin-sparing mastectomy. The challenge with NSM remains tissue perfusion to the nipple-areola complex and the central inferior skin of the breast.

The SPY Elite imaging system allows surgeons the ability to perform real-time assessment of tissue perfusion, enhances clinical decision making more accurately than physical exam alone and allows surgeons to anticipate potential problems in the post-op period.

The line between aesthetic and reconstructive breast surgery becomes blurred with increasing patient expectations. Patients are demanding superior aesthetic outcomes in fewer operations with shorter down time. The increasing desire for direct-to-implant reconstruction or immediate autologous reconstruction is in line with these patient's preferences and expectations. Given the higher rate of complications associated with immediate versus delayed reconstruction, surgeons are continually trying to find a balance between meeting patient's expectations and performing safe, reliable, reproducible breast reconstruction.

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20 The Science Behind Fat Grafting and Acellular Dermal Matrices

Steven J. Kronowitz

The Science of Fat Grafting (Lipofilling)

The increasing popularity of fat grafting is shown in the significant increase in articles being published on the subject over the last 20 years. One study examined the trends in fat grafting through a national survey of the ASPS members (456 respondents of 2584) [1]. Sixty-two percent of all respondents reported currently using fat grafting for reconstructive breast surgery. The most common applications for using fat grafting for breast reconstruction were as an adjunct to implants to disguise border or device and/or provide better shape, adjunct to tissue flaps for improving shape or correcting contour of flaps, and lumpectomy defects. Twenty-eight percent of all respondents reported currently using fat grafting for aesthetic breast surgery. Fifty-nine percent have not performed for aesthetic surgery and have no plans to perform in future. The most common applications for aesthetic surgery were as an adjunct to implant augmentation to disguise border of improved shape, as adjunct to mastopexy, and congenital deformities, like tuberous breast. When asked about potential obstacles to incorporation of fat grafting into clinical practice, 52 % strongly agreed or agreed that poor graft retention rates/or unreliable results are obstacles. Whereas 50 % strongly agreed or agreed that interference with mammography and cancer screening is an obstacle. Forty-nine percent strongly agreed or agreed the lack of evidence concerning the impact of fat grafting to the breast on breast cancer or recurrence is an obstacle.

Some important questions have also been raised regarding the safety of fat grafting in patients. Does fat graft lipoaspirate reactivate dormant tumor cells? Does fat grafting impair postoperative surveillance by mammography? Is postoperative imaging surveillance with fat grafting different from breast reduction? Does fat grafting increase the rate of locoregional recurrence of breast cancer? Is recurrence different between a mastectomy and BCT or with invasive and in-situ breast cancer? This chapter will address these important questions.

So, what happens when we use fat grafting in the breasts of our patients? The healing process of lipoaspirate has been studied in irradiated tissue models. In 2007, Rigotti elucidated the process of lipoaspirate healing of radiated tissue by a process mediated by adipose-derived adult stem cells [2]. Ultrastructural analyses of the lipoaspirate revealed a well-preserved stromal vascular component. However, well-preserved adipocytes were virtually absent. The cytologic characterization of the lipoaspirate by in-vitro

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expansion of the mesenchymal stem cells corresponded to that of bone marrow-derived mesenchymal stem cells. Rigotti injected lipoaspirate into radio-damaged subcutaneous tissue of humans that was fibrotic and microangiopathic. Photomicrographs of subcutaneous tissue, 1 and 2 months after lipofilling irradiated damaged tissue was characterized by signs of removal of the injected material along with signs of regeneration and two months after treatment, the injected material was completely gone, with complete absence of cellular debris. The overall picture showed that the regenerative phenomena were at an advanced stage. Four to six months after treatment, adipocytes were normal and microvessels exhibited normal ultrastructure. One year or more after treatment, the picture was substantially unchanged.

Postoperative breast surveillance imaging has been a concern with fat grafting. Is the concern over mammographic changes obscuring cancer detection different from breast reduction surgery? A study by Rubin and coauthors compared mammographic changes following fat grafting to the breast with those after breast reduction [3]. They studied 27 lipo-augmentation cosmetic patients and compared them with 23 breast reduction patients (Wise pattern, inferior pedicle). Scarring, benign calcifications, and masses warranting biopsy were all significantly less common in the lipotransfer group. Ratings were assigned by each of the eight radiologists to the two cohorts of 50 patients. There was a tendency to assign lower BIRADS (better) scores to patients undergoing lipoaugmentation when compared to breast reduction. Biopsy and 6-month follow-up rates were higher in the breast reduction cohort.

Probably the most important question is does fat grafting increase the rate of local recurrence of breast cancer? Although fat grafting continues to gain in popularity, little is known about the interaction between the fat graft and the prior oncological environment. The "tumor stromal interaction" or paracrine action of the injected fat may affect locoregional recurrence rates, especially in breast conservation therapy (BCT), due to the existence of dormant tumor cells in the breast parenchyma. Hypothetically, the transfer of adipose derived stem cells or adipose derived mesenchymal stem cells could induce silent tumor cells to reproduce and predispose to locoregional recurrence (LRR), especially after BCT. In vitro and animal studies are conflictive and show positive and also negative association with breast cancer cell proliferation. To date, no case series has clearly demonstrated or not demonstrated an association between fat grafting and breast cancer recurrence.

Petit and colleagues retrospectively studied the multicenter experience of Milan, Paris, and Lyon of 646 lipofilling procedures in 513 breast cancer patients treated with mastectomy or BCT [4]. There were 370 mastectomies and 143 breast conserving surgery cases. The average interval between the oncologic surgery and the lipofilling was 39.7 months and the lipofilling and follow-up was 19.2 months. The overall event rate was 5.6 % (3.6 % per year). The locoregional recurrence was 2.4 % (1.5 % per year) and the distant metastasis rate was 3.1 % (1.9 % per year). The authors concluded that lipofilling seems to be safe, but the higher incidence of recurrence found in patients with DCIS was determined to need further study. An important point about this study was that it included a large proportion of BCT patients that underwent partial breast irradiation with intraoperative radiation therapy (IORT) only. In addition, although this was a multicenter study, the data was collected in a retrospective manner which can be problematic. As opposed to a prospective multicenter study, retrospective collection of data points from multiple institutions tends to be inconsistent.

As a follow-up to the above-mentioned study, to address the concern of a higher incidence of recurrence in patients with DCIS who undergo subsequent fat grafting, Petit and colleagues performed a matched-cohort evaluation of fat grafting safety in patients with intraepithelial neoplasia [5]. In this retrospective follow-up, they studied only in-situ breast cancer and focused only on 59 patients with in-situ breast disease who had fat grafting and compared them with a matched cohort of 118 patients also with in-situ breast cancer but who did not have fat grafting. There were nine local events (defined as local relapse or locoregional relapse), six in lipofilling patients and three patients in the matched control group. The 5-year cumulative incidence of local events in the lipofilling and control patients was 18 and 3 %, respectively. They concluded a higher risk of local or locoregional recurrence in in-situ carcinoma patients following lipofilling. Again, it is important to realize that a large proportion of the patients included in this study had IORT only, and not whole breast radiation treatment as a component of BCT. Patients treated at the Milan Institute with IORT only (mobile linear accelerator using electron beam) have had a higher risk of local recurrence than radiation treatment using other modalities.

A more recent article published on the topic of fat grafting and oncological safety was a prospective study of BCT patients only, who hypothetically had a higher risk of local recurrence, because there is breast tissue remaining within the breast that may predispose dormant cancer cells to reactivation [6]. The study included 59 patients with prior BCT who underwent 75 fat grafting procedures (using Coleman technique, between 2005 and 2008). The mean follow-up was 34 months (longer than the above-mentioned studies). Another distinguishing feature from the Milan Institute studies was the use of external radiation in 95 % of patients. The average interval from the oncologic surgery and the lipofilling was 76 months. The average time from the lipofilling to follow-up was 34 months. Most patients were at stage 0 (11.8 %), I (33.8 %), or IIA (23.7 %). Only three cases of true locoregional recurrence (4 %) (observed during the follow-up of 34 months) were associated with the lipofilling procedure. This would produce a rate of 1.4 % per year. It is acceptable, based on the published literature, that locoregional recurrence occurs in the rate of 1–1.5 % per year. All three recurrences were invasive ductal, not DCIS and, recurred in the same quadrant of the breast as the primary tumor.

The most recent study was published by the author and colleagues [7]. Although, many plastic surgeons perform autologous fat grafting (lipofilling) for breast reconstruction after oncologic surgery, it has not been established whether lipofilling for breast reconstruction after oncologic surgery increases the risk of recurrence of breast cancer. This study assessed the risk of locoregional (LRR) and systemic recurrence in patients that underwent lipofilling for breast reconstruction. The authors identified all patients who underwent segmental or total mastectomy for breast cancer (719 breasts; cases) or breast cancer risk reduction or benign disease (305 cancer-free breasts) followed by breast reconstruction with lipofilling as an adjunct or primary procedure between June 1981 and February 2014. Kronowitz and colleagues also then identified matched patients with breast cancer treated with segmental or total mastectomy followed by reconstruction without lipofilling (670 breasts; controls). The probability of LRR was estimated by the Kaplan-Meier method. The mean follow-up times after mastectomy were 60 months for the cases, 44 months for the controls, and 73 months for the cancer-free breasts. LRR occurred in 1.3 % (9/719) of the cases and 2.4 % (16/670) of the controls. Breast cancer did not develop in any cancer-free breast. The cumulative 5-year LRR rates were 1.6 %, and 4.1 %, for cases and controls, respectively. Systemic recurrence occurred in 2.4 % of the cases and 3.6 % of the controls ($p = 0.514$). There was no primary breast cancer in healthy breasts reconstructed with lipofilling. The results of this controlled study showed no increase in LRR, systemic recurrence, or second breast cancer and supports the oncologic safety of lipofilling in breast reconstruction.

Summary of Fat Grafting (Lipofilling) Findings and Recommendations

Lipofilling does not appear to increase the risk for recurrence of breast cancer and appears safe for patients who have had breast cancer. In regards to accelerating or causing a primary breast cancer, lipofilling also does not appear to increase risk, even in those patients with the BRCA gene mutation and those without a history of breast cancer. These findings may have broad sweeping implication, not only for breast reconstruction, but also for cosmetic breast augmentation. In the future, the author envisions engineered breast reconstruction and cosmetic augmentation in which the fat is harvested from patients and the stem cells and vascularized stromal cells are extracted. The stem cells will be clonally expanded in-vitro and the vascularized stroma grown in a culture medium. The stem cells will be transferred along with vascularized stromal tissue back into the patient at varied time intervals, most likely every three months, until the optimal outcome is achieved.

The Science of ADM

Like with lipofilling, in order to understand the science of acellular dermal matrices (ADM), some important questions need to be answered. How much time does it take for ADM to neovascularize with tissue ingrowth? Does radiation affect cellularity (inflammation) and architecture of the ADM capsule? How does irradiated non-ADM reconstructions compare to irradiated ADM reconstructions? How does non-irradiated ADM reconstruction compare to irradiated ADM reconstructions? Does radiation decrease ADM thickness or gross incorporation?

So what does happen when we place a piece of ADM in our patients? Garcia and colleagues performed an analysis of ADM integration and revascularization following tissue expander breast reconstruction in a clinically relevant large-animal model [7]. The animal study was on 18 Yorkshire pigs who at the time of expander implantation were randomly assigned to either Allomax or Alloderm. The graft was sutured to the inframammary fold and the free inferior edge of the pectoralis major muscle. Microcirculatory analysis revealed early ADM angiogenesis at 4 weeks on the skin flap surface only, not the expander surface and well-formed vasculature on both surfaces at 8 weeks. Both surfaces were highly vascularized by 12 weeks. Gross necropsy at 4 weeks showed evidence of early tissue integration. Both ADMs showed complete remodeling and progressive increase in neovascularization over time. At gross necropsy, both types of ADMs had mature tissue integration at 12 weeks.

In 2014, Losken and colleagues at Emory studied the effect of radiation on ADM and capsule formation in breast reconstruction [8]. They evaluated clinical outcomes and performed a histologic analysis from the periprosthetic capsules of 6 patients. The irradiated native capsules had more elastin fibers and a two times increase in cellular infiltrate. There were no differences in cellular counts between the native capsule and the ADM capsule. Irradiating the ADM capsule did not alter the architecture or cellular components of the ADM capsules. Irradiated ADMs had the same cell counts as non-irradiated ADM. Cell counts were higher in irradiated native capsules than in irradiated ADM. Cellular counts in the peri-implant capsule are greatly increased by irradiation.

There was no difference in cell counts between native capsule and ADM capsule. However, architectural makeup showed a five times reduction in macrophages and 2.5 times increase in elastin in ADM capsules compared with native capsules. There was minimal histologic difference between irradiated and non-irradiated ADM. Irradiated ADM shows less peri-implant inflammation and nonvascular alpha smooth actin then irradiated capsules. Cell counts were significantly greater in irradiated native capsules than in irradiated ADM. The authors concluded that tissue expander breast reconstruction with radiation has a high rate of failure but it is not directly caused by ADM.

Dubin and colleagues applied radiation to rat hind limbs implanted with human ADM (HADM) [9]. They found that HADM thickness and neovascularization did not differ in irradiated HADM from nonirradiated HADM controls. However, fibroblast counts were diminished at 3 weeks but then were higher at 14 weeks. Using a similar rat model, Ibrahim reported that irradiated HADM did not differ in thickness from non-irradiated HADM controls; however, at early time points, cellularity and neovascularization were reduced [10]. Cellularity then returned to normal levels as controls by 12 weeks.

Komorowska-Timek and colleagues evaluated the effect of radiation on HADM in rat implant capsules [11]. This animal study evaluated radiation on HADM in rat implant capsules and found inflammatory infiltrates at 3 weeks and a steady decrease in mesh thickness over time in non-irradiated HADM. Within irradiated HADM, cellular invasion was decreased. They found invasion of inflammatory infiltrates into non-irradiated HADM at 3 weeks and a steady decrease in mesh thickness over time. Irradiation increased inflammation of non-mesh capsules at 12 weeks, but inflammation was significantly reduced in irradiated HADM. Irradiated capsules without mesh developed a pseudoepithelium, whereas HADM appeared to be protective from this transformation. Nahabedian found at the time of implant exchange, irradiated breasts had complete or nearly total gross incorporation of the HADM. He found irradiation did not significantly impact gross incorporation of HADM [12].

Some other important questions have been raised regarding the clinical use of ADM in reconstructive breast surgery. What are the clinical trends and complications that reconstructive breast surgeons are encountering in their patients? A survey of American Society of Plastic Surgeons members in 2010, revealed that in 82 % of patients undergoing implant-based breast reconstruction, 51 % included the use of an ADM [13]. In general, the use of ADM only, fat grafting only, and the combination of ADM and fat grafting continue to increase in breast reconstruction, while the use of latissimus dorsi flaps continues to remain stable or decrease. In non-irradiated patients, the increasing use of ADM in breast reconstruction has led to an increase in complications with ADMs, especially infection and seroma formation but not the overall complication rate because it decreases the incidence of other complications, like implant exposure and need for implant removal. The majority of infections that occur with ADMs, the author can treat successfully without requiring implant removal using image guided percutaneous drainage of seroma formation and an outpatient course of intravenous antibiotic therapy. In contrast, it appears that the increasing use of fat grafting has not led to increased complications. The addition of fat grafting to ADM implant-based breast reconstruction, also appears to have decreased the rate of complications associated with ADMs.

How does ADM affect complication rates in our patients that receive radiation therapy? The published literature reveals that ADM reconstructions receiving radiation have significantly higher complication rates than non-irradiated ADM reconstructions. Reports vary from a four times to 11 times increase in complications. In irradiated patients, the authors experience with 2-stage implant-based reconstruction between years 2004 and 2011 revealed that the use of ADM in irradiated patients had a higher rate of complications than in non-irradiated patients. The complication rate of fat grafting was not affected by the use of irradiation. In irradiated patients, fat grafting had a lower rate of complications than ADM. In irradiated and non-irradiated patients, the use of fat grafting or ADM had lower rates of complications than implant reconstructions performed without fat grafting or ADM. And the use of radiation more than doubled the rate of complications in implant-based reconstruction without ADM or fat grafting.

Although, the benefits of ADM for breast reconstruction have been well described, the clinical impact of ADM for breast reconstruction in the setting of radiation therapy had not been well reported. In 2012, the author and colleagues published an evidenced-based review article on the use of ADM in irradiated tissue expander and implant-based breast reconstruction [14]. The study reviewed the MEDLINE and EMBASE databases for articles on breast reconstruction using ADM in the setting of radiation therapy published between January 2005 and February 2012. The authors also reviewed their institutional experience (MD Anderson Cancer Center) of consecutive patients who underwent breast reconstruction using ADM in the setting of radiation therapy between January 2008 and October 2011. The database searches and review of identified articles yielded 13 articles for review: three on animal studies of ADM and ten providing level III evidence on use of ADM in humans. The ten clinical studies included 246 irradiated ADM patients. The MD Anderson experience included 30 irradiated ADM patients for a total of 276 irradiated patients evaluated in this review. These articles indicated that ADM use in implant-based breast reconstruction in the setting of radiation therapy does not predispose to higher infection or overall complication rates or prevent bioprosthetic mesh incorporation. However, the rate of mesh incorporation may be slowed. Use of ADM allows for increased intraoperative saline fill volumes, which improve aesthetic outcomes and allow patients to awake from surgery with a formed breast. The MD Anderson experience included 548 immediate breast reconstructions performed with ADM in 364 patients. In the 30 breasts irradiated after reconstruction, the overall complication rate was 43.3 % and the tissue expander loss rate was 13.3 %. In the 518 non-irradiated breasts, the overall complication rate was 15.6 % and the expander loss rate was 5.2 %. The author concluded that the use of ADM for implant-based breast reconstruction does not appear to increase or decrease the risk of complications but may provide psychological and aesthetic benefits. However, multicenter or single-center randomized controlled trials that provide high-quality, level I evidence are warranted.

Summary of ADM Findings and Recommendations

Breast implants can become severely contracted from radiation and require excision of the breast skin, losing the benefit of skin-sparing mastectomy. These reconstructions often require an extensive flap procedure for salvage usually with a suboptimal outcome. Consensus within the published literature is that irradiation increases the rate of reconstructive complications, including capsular contracture. The negative impact of irradiation is pronounced in implant-based reconstruction with complication rates upwards of 40 % or greater. Up to one-third of patients that receive radiation to breast implant reconstructions develop Baker Grade III or IV capsular contracture. Anecdotal and preliminary data suggest that ADM may contribute to decreased frequency of capsular contracture. However, much of the enthusiasm has been tempered by costs and complications.

ADM reconstructions receiving radiation have significantly higher complication rates than non-irradiated ADM reconstructions. Although reports vary for a 4–11 times increase in complications, these are most likely related to the radiation and not the ADM. Interesting scientific findings in animal studies include: no difference in ADM thickness between irradiated and non-irradiated ADM, diminished cellular invasion in irradiated implant reconstructions that had ADM compared to those did not have radiation, ADM decreases radiation related inflammation and delays or diminished pseudoepithelium formation in irradiated implant breast reconstruction. However, many of these changes have been in the short term without evidence of long term impact on the implant capsule.

If ADM provides a healing advantage and may reduce the occurrence or severity of capsular contracture, it seems logical that complete coverage of the implant with ADM should be provided, not limited to the lower pole of the breast reconstruction that is most commonly practiced. Over the last 7 years, the author has utilized a new technique, in which the entire expander or implant is covered with a large sheet of ADM. In some patients, especially with nipple-sparing mastectomy, a prepectoral position for the prosthesis is used, and in other patients, the pectoralis major muscle is sewn over the ADM in a vest-over-pants fashion (Fig. 20.1). The rationale is that if the ADM is decreasing capsular contracture, then complete coverage may help to decrease the incidence of severe capsular contracture.

ADM also provides less known advantages for implant-based breast reconstruction. ADM placed at stage 1 (tissue expander placement) of two-stage implant-based breast reconstruction creates a tissue plane for injection of fat grafts into the lower mastectomy skin flap during stage 2 (exchange for permanent implant), which without ADM, is not always possible. Fat grafting shows promise in potentially decreasing the morbidity and improving the outcomes of implant-based reconstruction in the setting of radiation.

ADM also allows for intraoperative saline filling of the expander allowing for a more ptotic-shaped breast after radiotherapy, which subsequently enables the surgeon to place the implant directly into the breast skin pocket. ADM-enabled intraoperative saline filling of the expander also avoids the need for postoperative expansion and delayed initiation of radiotherapy in patients who receive neoadjuvant chemotherapy. The ADM not only increases the thickness

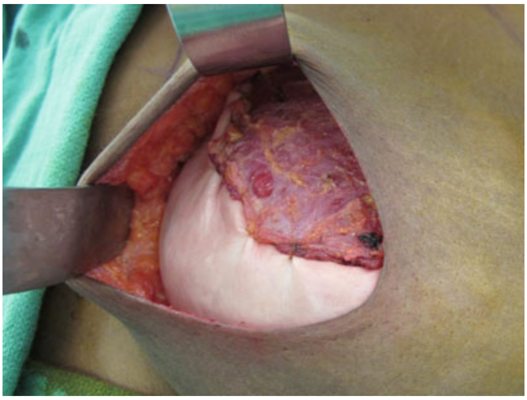

Fig. 20.1 The Kronowitz technique of utilizing complete coverage of an inflated tissue expander or breast implant with ADM. The pectoralis major muscle is then sewn to the ADM in a vest-over-pants fashion

of mastectomy skin flaps directly, but its use enables intraoperative saline filling and avoids thinning already thin mastectomy skin flaps, which can be treacherous in patients undergoing radiotherapy. At stage 2, during the exchange for the permanent implant, the thicker radiated mastectomy skin will provide better implant coverage than without ADM. The thicker mastectomy skin flaps that are being attained with ADM along with fat grafting have decreased the need for the addition of a flap, like a latissimus dorsi flap, for implant-based breast reconstruction. However, an equivalent safety profile has not yet been shown. The science indicates that ADM used along with fat grafting holds promise for improving the outcomes and safety of implant-based breast reconstruction, especially in the irradiated breast.

Conflicts of Interest Dr. Kronowitz has no conflicts of interest to report.

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21 The Team Approach to Nipple-Sparing Mastectomy and Reconstruction

Toni Storm-Dickerson, G. Patrick Maxwell, Pat Whitworth, and Allen Gabriel

Introduction

Plastic surgeons strive to achieve the aesthetic breast form following mastectomy. By selecting appropriate candidates and preserving the breast envelope while upholding oncologically sound treatment, surgeons can achieve better cosmetic outcomes following reconstruction. Clearly, good breast reconstruction starts with an excellent mastectomy and this begins with a breast surgeon and plastic surgeon team with excellent communication.

The development of breast reconstruction arose from the need created by mastectomy. William S. Halsted, made famous in the late 1800s for the development of the Halsted radical mastectomy, believed that breast cancer was a regional phenomenon. He theorized that cancer started at a single focus and moved out in an orderly fashion; therefore, the surgical removal of more breast tissue was better [1, 2].

So tightly held was this belief that it reigned supreme as the standard of care for nearly 100 years, until the 1970s when Bernie Fischer used the scientific method to perform the first randomized studies. While Dr. Fischer became the first chair of the NSABP (National Surgical Adjuvant Breast and Bowel Project) he was initially villainized for promoting BCT (breast conservative therapy) as a viable treatment option. Women who wanted something else, who demanded to feel better about themselves, lined up to enroll in the, now landmark, NASAP B04. Since then, several randomized studies (NSABP, B-04, B-06 and B-17), and now data from Oncoype Dx have demonstrated that the extent of local therapy is not paramount to patient survival [3–6].

Along the same lines, Halsted published an article directly stating his concern with closure of the mastectomy wound [7]. He urged surgeons to be aware of the man with the plastic operation as the plastic method is hazardous [7]. Times have changed and to uphold the Halstedian philosophy for both mastectomies and reconstruction is to deviate from the standard of care. During the last century breast reconstruction has evolved from a rarely performed surgical venture to a daily occurrence that has become an important part of

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the rehabilitation process following mastectomy or lumpectomy. The aesthetic quality of the reconstructions fostered by the desire to offer patients “more” and technical advances have emerged to allow the transformation of amorphous blobs, appearing as breast mounds, to nearly normal appearing breasts. Symmetry, which was hardly possible and seldom achieved and is now the standard. Along the same lines, the surgical management of breast cancer has undergone an evolution from radical mastectomies to less invasive breast conservation therapies and now to aesthetic mastectomies of which nipple-sparing mastectomies (NSM) are the ideal when appropriate. Nipple-sparing mastectomy is a procedure that combines skin-sparing mastectomy with preservation of the nipple-areolar complex (NAC). Several recent studies attest to the efficacy and safety of this procedure [8–21].

With the improvement in aesthetic mastectomies and reconstruction, more women are not only choosing mastectomy, but bilateral mastectomy and reconstruction. Many opponents feel that mastectomy and contralateral prophylactic mastectomies (CPM) should not be performed. unless strictly indicated [22, 23]. But similar to the 1970s, as we again see women lining up, requesting a certain procedure, we are seeing a trend towards CPM. There are multiple studies showing that women are choosing mastectomy and CPM in ever increasing numbers. Their reasons range from wanting to achieve a sense of well-being to overestimating their risk of recurrence and to avoiding future imaging [24, 25].

What we are learning is that by understanding the motivation driving women, we can work from a multidisciplinary approach to address their concerns and help them decide what is the right surgical approach for them. Physicians are most affective when there is collaboration among all members of the team, including the patient, to choose the best approach for that individual.

In the majority of women who have mastectomy, the devastating impact of the loss of physical self can be mitigated by breast reconstruction. The cosmetic outcome following immediate breast reconstruction is enhanced by preservation of the native skin envelope, inframammary fold, anterior axillary fold and when appropriate, the nipple areolar complex. Toth et al. described the importance of the plastic surgeon’s involvement in preoperative planning and decision making regarding the placement of the incision [26].

Several studies on skin-sparing mastectomy have now been published, showing that the incidence of local recurrence is similar to that following simple mastectomy [27–38]. No studies have investigated prospectively the comparative new primary cancer rate in simple versus skin-sparing mastectomy in the context of risk-reducing surgery. However, as the rate of new primary cancers following either simple or subcutaneous mastectomy is low, it is unlikely that simple mastectomy could show a statistically or oncologically significant advantage that outweighed major aesthetic disadvantages [39, 40].

Nipple-Areolar Anatomy

There is evidence to suggest that ductal and lobular breast cancer arises in the terminal duct/lobular unit (TDLU) [41]. Stolier et al. examined 32 nipples and concluded that all TDLUs were found at the base of the nipple, with none located near the tip. Others have also shown that the majority of breast tumors originate within the TDLU [42–44]. This information is useful when discussing nipple-sparing mastectomy for risk reduction surgery, including for those women with BRCA1/2 mutations.

There is variation in the number of ducts reported and little was known about the spatial location of ducts, their size, and their relationship to orifices on the surface until Rusby et al. reported the findings of nipple specimens from 129 consecutive mastectomies. The authors showed many ducts share a few common openings onto the surface of the nipple, explaining the observed discrepancy between the number of ducts and of orifices. Neither duct diameter nor position predicted whether a duct system will terminate close to the nipple or pass deeper into the breast [45]. There was also concern about the viability of the nipple tip following coring out the ducts. Rusby et al. once again presented their findings after exploring the precise anatomical relationship between ducts and vasculature within the nipple. Their study investigated nipple microvessels and their position relative to ducts and concluded that ducts can be excised leaving a rim of nipple tissue that contains a large proportion of microvessels [46]. Finally, the most important literature that was published by the same group concluded the detailed support and understanding that was needed for surgeons to perform these procedures. The authors built a predictive model using preoperative information to aid in the selection for NSM. This clinical tool included tumor size and distance from the nipple to help improve candidacy and appropriate patient selection for nipple-sparing mastectomy [47].

Rusby's series of ex-vivo procedures provided information that can be used to modify surgical and pathologic techniques for nipple-sparing mastectomy [48]. The precise identification of the duct margin directly beneath the nipple proves to be difficult once the duct bundle has been divided. In their series, successful retro-areolar margin identification was achieved by grasping the duct bundle with atraumatic forceps as soon as it became exposed. A cut made below and above the forceps resulted in a full cross-section of the duct bundle. Modification of technique resulted in more complete excision of duct tissue [48].

This detailed information about NAC microanatomy is essential for understanding what we face when considering its preservation.

Nipple-Sparing Mastectomy

One may ask, why consider saving the nipple since we have advanced reconstructive techniques that can achieve similar goals? Nipple-areola reconstruction has always represented the final stage of breast reconstruction, whereby a reconstructed breast mound is transformed into a breast with maximal realism when compared with the patient's opposite breast. There are problems with reconstructed nipples, the greatest being loss of projection over time and the need for tattoos to provide pigmentation of both nipple and areola that fade over time [49]. There are also the issues of the patient's reconstructed breast appearing different or alien and the interval between surgery and nipple reconstruction where the patient may feel incomplete. Essentially all postmastectomy patients suffer distress brought on by the diagnosis of breast cancer and severe alteration of body image with resultant adverse psychological consequences [50]. As surgeons, we strive to reconstruct the most aesthetically pleasing breast form following mastectomy to reduce the psychological burden. Therefore, if a patient is a candidate for NAC preservation, preservation may further enhance our goal.

Nipple-sparing mastectomy was attempted in the 1980s but never gained popularity due to the controversies surrounding oncological safety [51]. Now better technologies for preoperative staging, assessment of lesion distance from the NAC, and increased understanding of the anatomy of the breast ducts with relation to the nipple are creating support for the return of this concept. One of the key publications that renewed and increased surgeon's enthusiasm for this technique was the multicenter publication of 192 patients undergoing NSM with 4 recurrences, all of which occurred distant from the NAC. Recurrences were seen in the upper outer quadrant, where nearly all recurrences occur with simple mastectomies, at the junction of the tail of the breast and axillary tissue [52].

In recent years, there has been a sudden increase in reports of NSM series for prophylaxis and cancer treatment, evidencing renewed interest in this technique. Of an approximate total of 1868 NSMs performed for breast cancer treatment published in recent literature [14–20, 27, 28, 52–65], only three local recurrences within the NAC have been reported [15, 27, 28, 55], representing a proportion of local events of 0.16 % attributed to patients with NAC preservation. However, it should be noted that most of these studies have a short follow-up, thus rendering definitive conclusions premature. In another study by Maxwell et al. 112 consecutive patients underwent nipple-sparing mastectomies with no recurrence at the time of publication. All patients underwent preoperative MRI (magnetic resonance imaging) to assess for the size of the tumor, its distance from the nipple, and to rule out multicentricity. Exclusion criteria included: tumors larger than 3 cm, clinical invasion of the NAC, tumors within 3 cm from the nipple, evidence of multicentric disease, positive intraoperative retro-areolar frozen section, and nodal disease, excluding isolated immunohistochemistery (IHC) positivity. All mastectomies were performed by a *plastic and breast surgeon team*. All incisions were pre-marked by plastic surgeons and the plastic surgeons were present during mastectomy. Nipple positions were marked on mastectomy specimens for pathological analysis for accurate distance calculation. Nipple-sparing mastectomies were performed for stage 0 (DCIS) in 26 patients, for stage 1A in 24 patients, and for stage 1B in three patients. Disease-free survival was calculated from date of surgery to any local, regional, or distant relapse, whichever occurred first, or to last visit date in case of no events [66]. This original series is now in its sixth year of follow-up with no recurrence to date. All patients are followed annually.

Nipple-Sparing Mastectomy for Risk Reduction

The management of women at high risk for breast cancer presents a clinical dilemma to the healthcare provider as well as to the woman herself. Current options include surveillance, prophylactic surgery (mastectomy and/or oophorectomy), and/or chemoprevention [67]. These patients can be divided into three groups; (1) Patients with BRCA1/BRCA2 mutation; (2) personal or family history of cancer following unilateral mastectomy for cancer; and (3) severe fibrocystic disease with strong family history of cancer. Hartmann et al. have shown that prophylactic mastectomy is associated with a substantial reduction in the incidence of subsequent breast cancer not only in women identified as being at high risk on the basis of a family history but also in known BRCA1 or BRCA2 mutation carriers [40]. McDonell et al. concluded that the incidence of contralateral breast cancer seems to be reduced significantly after contralateral prophylactic mastectomy in women with a personal and family history of breast cancer [68]. While mastectomy with or without immediate reconstruction has been established as the standard treatment for risk reduction with acceptable rates of local recurrence, NSM has evolved as an alternative technique to improve the overall quality of life for women. In the setting of prophylactic mastectomy, NSM can be considered virtually in all cases after ruling out malignancy and discussing with patients all risk-reducing strategies. Preoperative evaluation for NSM should include complete imaging studies, preferentially breast MRI, detailed family history, and physical exam.

There is no question that risk-reducing mastectomy provides the lowest rate of local recurrence [69]. In addition, NSM provides a natural appearing nipple with a better cosmetic outcome. With the current outcomes reported for NSM, it should not only be considered for risk reduction, but also as a treatment option for patients with breast cancer.

Nipple-Sparing Mastectomy for Treatment of Cancer

NSM for the treatment of cancer, however, is more controversial. It is imperative for the *plastic and breast surgeon team* to select good candidates for this operation. The goal as with any case of breast cancer is foremost to treat the breast cancer and perform the best oncological surgery followed by reconstruction. With recent literature support and our experience, the following criteria are used to evaluate the candidacy of NSM [47, 65]. It is recommended that tumors be 3 cm or less in size and have a distance of at least 3 cm from the center of the nipple. It is also important for the patient to have a clinically negative axilla and a negative sentinel node. In addition, a patient with any skin involvement, inflammatory breast cancer, or multicentric disease should not undergo NSM. Clearly, tumor characteristics should also be taken into account, as current evidence suggests that local failure is a manifestation of tumor biology rather than preservation of the NAC [64]. Therefore, this procedure should be discouraged in cases with extensive nodal involvement and in triple negative tumors (ER/PR negative and Her-2 neu negative). On the other hand, patients with an IHC positive sentinel node may be candidates for NSM. These patients do not require additional treatment of the axillae and each patient should be treated individually based on the personal/family history and tumor data available. Our goal is to achieve longevity with high quality of life; therefore, superior oncological management should always be the primary treatment. One can argue that these may be slightly more conservative than other published criteria [16–19].

NSM is an excellent alternative in patients who are poor candidates for breast conservation therapy (BCT). Nipple-sparing mastectomy is not meant to replace BCT; however, it serves as an option for informed patients who choose mastectomy over BCT or who need mastectomy because of anticipated poor result with BCT (i.e. small breasts, close lumpectomy margins) [70, 71]. As new data continues to accumulate on long term recurrence risk of BCT [70], it begs the question: should mastectomy be considered more strongly in younger women, especially those at high risk (i.e. ER/PR−). In addition, as we continue to improve our ability to preserve the aesthetic breast envelope including the NAC, NSM may serve as a viable alternative in this patient population.

Preoperative radiographic evaluation plays an important role whether it is with MRI or ultrasound guided mammotome biopsy of the duct and posterior nipple tissue. At our institutions most patients undergo MRI evaluation to assess the breast and the axilla to provide information for candidacy of NSM. The tumor size and the distance of the tumor from the NAC, and presence of other suspicious masses in the breast and axilla are evaluated. Of course, the final decision whether to keep the nipple will be made intraoperatively following results of the frozen section and finally the permanent pathology. At times, frozen section can be interpreted as benign and the permanent result may be found to be positive. In this case the nipple is removed and reconstructed with nipple sharing at the same time.

Selecting a Patient for NSM

In order to have a successful and oncologically safe NSM, the patient has to be both an oncological and reconstructive candidate for NSM (Fig. 21.1). Just because the patient is an oncological candidate (i.e. DCIS or BRCA), this does not mean that the patient can have a NSM. The patient has to be evaluated by the plastic surgeon and the reconstructive criteria then can be applied (Fig. 21.2). The patient who is a good oncological candidate, may have large breasts (D cup and larger) or have grade 3 ptosis. The critical measurement for a successful NSM is the nipple to inframammary fold measurement. This should be equal or less than 11 cm. Despite all of these factors, the bottom line is the patient's desire regarding the options that are available and what procedure will place her most at ease while not compromising oncological management.

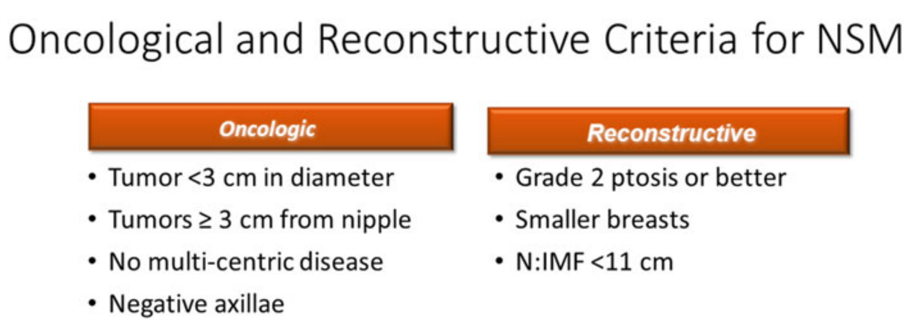

Fig. 21.1 Oncological and reconstructive criteria for NSM

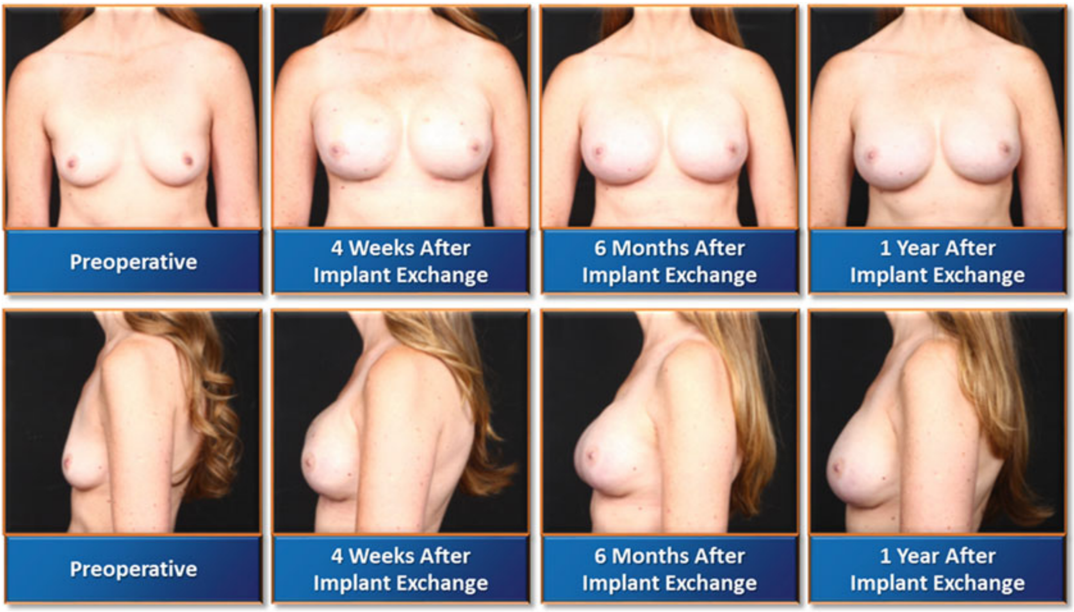

Fig. 21.2 Summary of her mastectomy and reconstruction with 410MF 470 cc silicone implants and fat grafting of the skin envelope with 150 cc of fat on each side

When choosing the incision, the size of the breast and degree of ptosis are the two most important factors. Regardless of the etiology of ptosis, a useful tool for the surgeon is to classify patients by the degree of ptosis present. It is important to clarify with the patient at this time what her goals are in terms of the final appearance of the breast. Regnault's classification system should be used to grade the extend of ptosis [72, 73]. The amount of preoperative ptosis can be used as a guide to selecting the operation necessary to achieve correction and symmetrization.

The patient in Fig. 21.2 is a good example of an excellent candidate for NSM (Fig. 21.2). On the other hand the patient in Fig. 21.3 is an unclear example for NSM until the nipple to IMF is measured which in her case was 11 cm and therefore she was a reconstructive candidate for NSM (Fig. 21.3). Lastly, the patient in Fig. 21.4 with given asymmetry is an example of how a carefully selected patient who has asymmetry can achieve symmetry following mastectomy and reconstruction (Fig. 21.4). Her candidacy was determined by the measurement of the larger breast as this will play a major role in achieving symmetry postoperatively. Figure 21.5 demonstrates a patient with prior right BCT for medullary carcinoma and a newly diagnosed left triple negative infiltrating ductal carcinoma (Fig. 21.5) Given the nature of her triple negative disease and close proximity of the mass to the nipple, the left nipple will have to be removed and this is demonstrated in Fig. 21.5 with delayed removal of left nipple and simultaneous grafting from the right nipple. In addition, this patient is an example of whether an implant-based reconstruction should be attempted in a patient with prior radiation following lumpectomy. This discussion is beyond the scope of this chapter but the criteria for successful reconstruction depends on where the lumpectomy scar is located. If her lumpectomy scar is in the upper pole of the breast, as seen in Fig. 21.5, and her skin is not scarred down, then an attempt for implant-based reconstruction can be made. However, if the scar is in the lower pole, where the maximum expansion is going to take place, then an autologous vs. latissimus flap and expander should be considered.

For patients with small and medium sized non-ptotic breasts, an inframammary (IMF) incision can be chosen safely. Lateral mastectomy incisions can also be chosen for NSM, but the

Fig. 21.3 Summary of her mastectomy and reconstruction with 410MF 525 cc silicone implants and fat grafting of the skin envelope with 100 cc of fat on each side

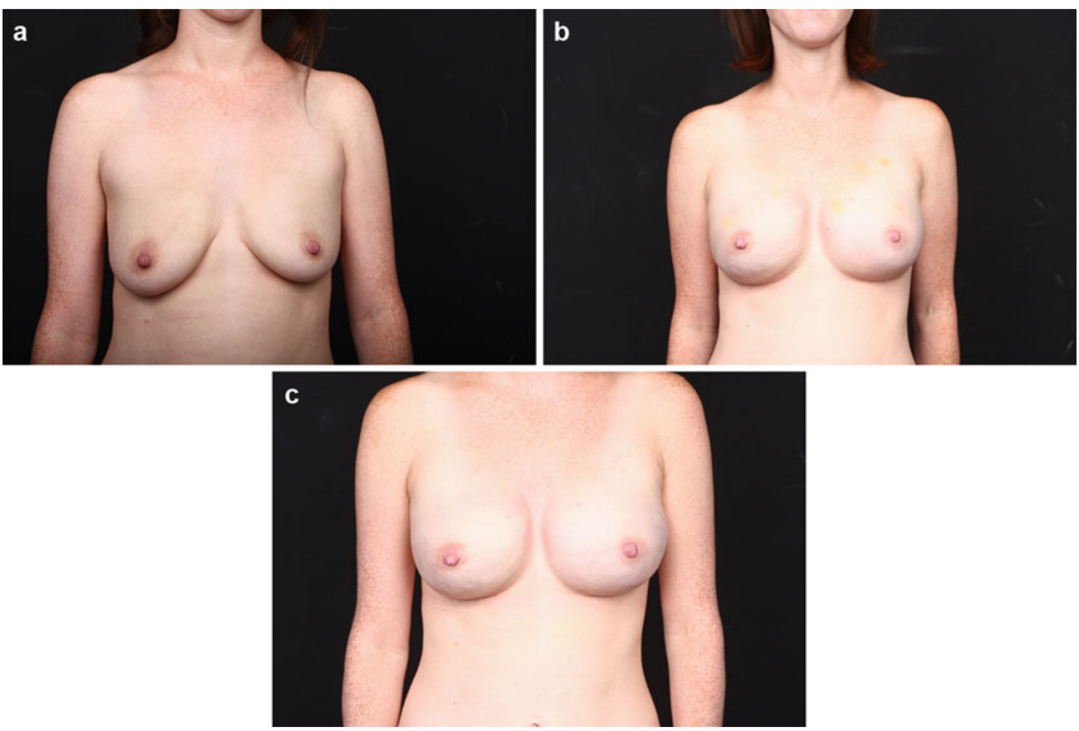

Fig. 21.4 (**a**) Preoperative patient history patient characteristics: 32 years, 5′4″, 118 lb, BMI: 20.3. Patient history: no prior breast surgery; BRCA+. (**b**) Three weeks following bilateral breast reconstruction with 410Mx 550 cc silicone implants and fat grafting of the skin envelope with 80 cc of fat on each side. (**c**) Year following bilateral breast reconstruction with 410Mx 550 cc silicone implants and fat grafting of the skin envelope with 80 cc of fat on each side

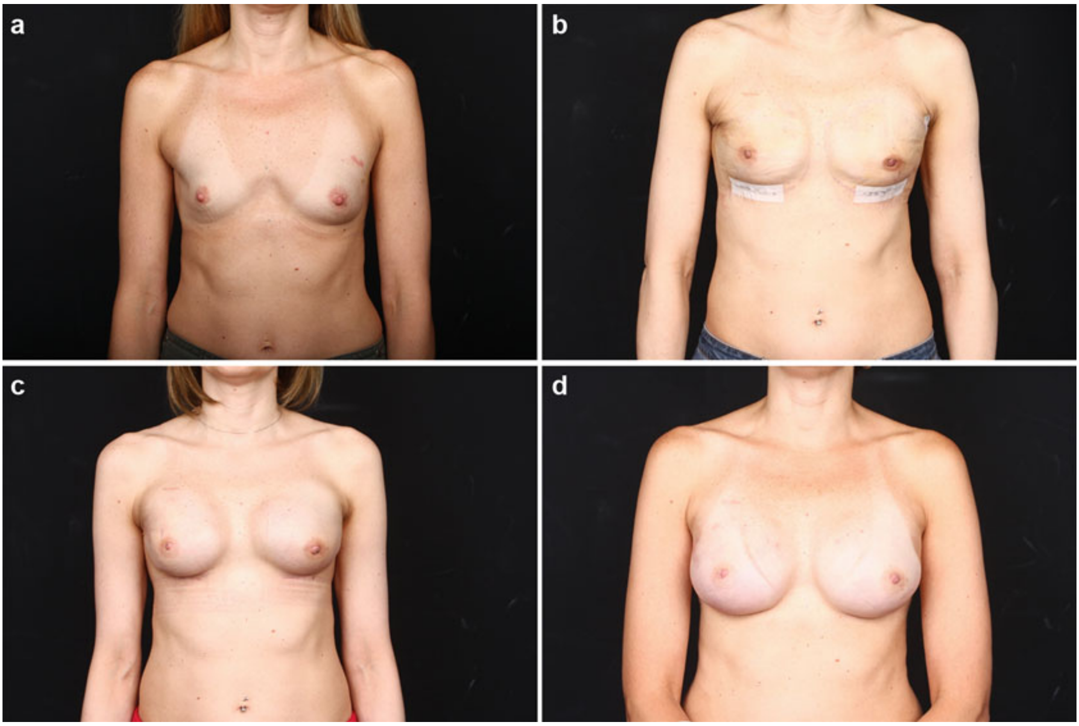

Fig. 21.5 (**a**) Preoperative patient history. Patient characteristics: 48 years, 5′8″, 130 lb, BMI: 20.0. Patient history: preoperative chemotherapy and port placement; prior right BCT for medullary ca of UOQ in 2005; new diagnosis of left invasive ductal carcinoma, stage1A. (**b**) Two weeks following bilateral nipple sparing mastectomy through IMF incision, with immediate reconstruction with tissue expanders/AlloDerm and injection of Botox. With plan of left nipple removal given the patient has triple negative disease. (**c**) Four weeks following left nipple removal and nipple grafting from the right side. (**d**) Year following bilateral breast reconstruction with 410Mx 410 cc silicone implants and fat grafting of the skin envelope with 90 cc of fat on each side

risk is that the NAC can be pulled laterally when the scar heals. Surgeons have also used the central vertical incision.

Conclusion

Nipple-sparing mastectomy is evolving and serves as an important option in carefully selected patients. The guidelines stated in this chapter are not intended to replace good clinical judgment but rather to serve as another avenue worth considering. The conscientious preoperative patient selection, multidisciplinary collaboration, pathological analysis of the NAC core, and attention to NSM incision placement is unique for each patient and should be considered carefully.

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The Intraoperative Team Approach to Nipple-Sparing Mastectomy

22

Arthur H. Salibian and Jay K. Harness

Team Approach to Nipple-Sparing Mastectomy

For the past two decades nipple-sparing mastectomy has given the oncologic and plastic surgeons the opportunity to restore the shape and surface anatomy of the breast for women undergoing therapeutic mastectomy [1–3]. Oncologic and plastic surgeons have worked together through joint seminars and publications to strengthen their communication for a better understanding of the problems related to nipple-sparing mastectomy [4, 5]. The one area where oncologic/plastic collaboration has been weakest is in the operating room. This chapter discusses the importance of the oncologic and plastic surgeons' side-by-side surgical collaboration and the advantages of their teamwork in enhancing inframammary nipple-sparing mastectomy outcomes.

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The team approach to a surgical procedure refers to the participation of two or more surgeons, from the same or different specialties, performing an operation in different anatomic areas or in tandem in the same area. In a broader sense the term "team approach" may point to the collaboration of surgical and nonsurgical specialties in the overall management of cancer patients. Nipple-sparing mastectomy with immediate expander/implant reconstruction is a unique operation with closely interrelated oncologic, aesthetic, and functional elements. The plastic surgeon's participation in a therapeutic nipple-sparing mastectomy gives the term "team approach" a new meaning denoting the *intraoperative collaboration* of two different surgical specialties to perform an oncologic procedure [6].

The plastic surgeon's involvement in a therapeutic mastectomy has been marginal. In skin-sparing mastectomy, it is customary for the plastic surgeon to follow the oncologic surgeon after the mastectomy has been completed. The same may be said for nipple-sparing mastectomy, this in spite of greater concerns about nipple/areola viability, skin loss, and related implant exposure. As a nonparticipant in nipple-sparing mastectomy, and before starting the reconstruction, the plastic surgeon is unaware of the extent of flap thinning, the degree to which the circulation to the nipple areola has been compromised, and whether intraoperative measures are to be taken to "protect" the implant from exposure.

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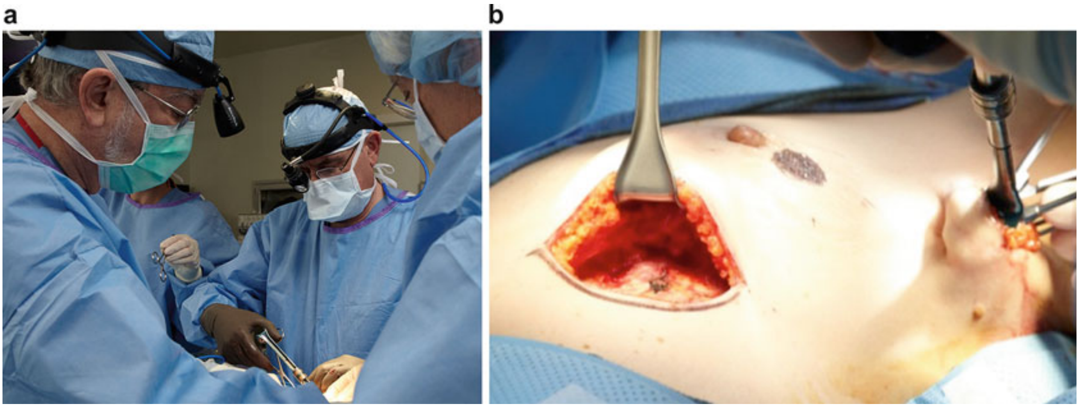

Fig. 22.1 Team approach to inframammary nipple-sparing mastectomy. (**a**) Both oncologic surgeon and plastic surgeon work simultaneously on opposite sides of the table to start the axillary dissection and mastectomy. (**b**) The tail of the breast is released from the axillary incision while the breast is lifted off the pectoralis major muscle. The superficial inframammary dissection may be started while the sentinel lymph node biopsy is being obtained

In addition, the plastic surgeon has limited input in choosing the mastectomy incision that leaves the least perceptible scar, yet does not jeopardize the nipple-areola. As an example, the oncologic surgeon may be reluctant to choose the inframammary approach to nipple-sparing mastectomy because of technical difficulties and concerns related to nipple-areola loss, preferring instead a lateral approach through a radial incision or a vertical lower pole incision that leaves readily visible scars. With the participation of the plastic surgeon in the mastectomy, issues related to skin loss that are largely dependent on the management of the subareolar breast tissue, the thickness of the adjacent breast flaps, and selective flap thinning for tumor clearance, are better understood, analyzed, and resolved for an improved aesthetic result. Because inframammary nipple-sparing mastectomy is a more difficult operation than other nipple-sparing mastectomy methods the involvement of the plastic surgeon is more advantageous.

Intraoperative Team Approach to Inframammary Nipple-Sparing Mastectomy

The interaction between the oncologic surgeon and the plastic surgeon in the operating room starts with the review of pertinent mammograms, ultrasound, and magnetic resonance images to determine the location of the tumor/tumors and potential areas of flap thinning. The use of ultrasound prior to or during surgery is helpful in determining the location of the tumor with respect to the skin and whether the flap is to be thinned at the subcutaneous or subdermal level.

In our practice, a unilateral therapeutic nipple-sparing mastectomy is performed using two separate incisions, one in the axilla and the other in the inframammary fold. This approach allows the oncologic surgeon and the plastic surgeon to work simultaneously on opposite sides of the operating table to start the mastectomy (Fig. 22.1a). First, the oncologic surgeon releases the deep portion of the tail of the breast from the underlying pectoralis major muscle through the axilla while the plastic surgeon lifts the breast off the pectoralis muscle through the inframammary incision (Fig. 22.1b). Both planes of dissection are connected to elevate the entire breast off the muscle. This maneuver allows the breast to be retracted more efficiently and facilitates the more difficult subcutaneous dissection of the axillary tail and upper pole of the breast. In the next step the superficial dissection of the tail of the breast is carried out through the axilla followed by the sentinel lymph node biopsy and/or lymph node dissection. If the tumor is in the upper hemisphere of the breast, the plastic surgeon may start the subcutaneous lower breast dissection while the sentinel lymph node biopsy and/or lymph node dissection are being performed.

After the completion of the sentinel lymph node biopsy the plastic surgeon assists the oncologic surgeon in the mastectomy to perform the following:

1. Preserve the subcutaneous fat by pushing the fat up against the skin with the back of a DeBakey forceps to expose the anterior mammary fascia and Cooper's ligaments.
2. Provide the appropriate counter traction of the breast, particularly in the axillary tail and upper pole of the breast. The subcutaneous dissection in the upper pole is the most difficult part of the inframammary nipple-sparing mastectomy, more so in women with long chests, because of limited visibility and less effective counter traction. The plastic surgeon's assistance is important here not only to provide exposure and counter traction but, if need be, to also surgically release the breast from a more suitable visual angle.
3. Ensure that subdermal areola dissection does not exceed 16 cm^2. Subcutaneous fat thinning up to 25 cm^2 may be performed in the breast flap provided the thinned area is not contiguous to the areola as this may jeopardize the circulation to the areola skin. The surface area of flap thinning may vary depending on the overall thickness of the flap because thicker flaps tolerate larger areas of thinning.
4. Protect the skin by minimizing the use of metallic retractors and avoiding excessive skin traction.

In bilateral nipple-sparing mastectomy, we perform the prophylactic side first with the plastic surgeon assisting the oncologic surgeon (Fig. 22.2). After the prophylactic mastectomy is completed, the oncologic surgeon starts the sentinel lymph node biopsy and/or the lymph node dissection on the opposite side while the plastic surgeon reconstructs the preventive mastectomy side with tissue expander. The therapeutic mastectomy and reconstruction are performed last.

With both surgeons working together, operative time for a bilateral nipple-sparing mastectomy and reconstruction may be cut down to less than 3 h. The same is said for a more complex

Fig. 22.2 The plastic surgeon assisting the oncologic surgeon on the nipple-sparing mastectomy. Dissection of the axillary tail of the breast and the upper pole of the breast is facilitated by the onco-plastic surgical collaboration

primary mastopexy and nipple-sparing mastectomy [7]. The combined mastopexy-mastectomy procedure should in theory take longer to complete than a nipple-sparing mastectomy because of the deepithelialization of the large inferior flap and closure of the extensive inframammary and periareolar wounds. In actuality, it takes the same amount of time to perform a mastopexy-nipple-sparing mastectomy as it does to complete an inframammary nipple-sparing mastectomy if both surgeons work together.

Intraoperative Decision-Making

Intraoperative decisions regarding the thinning of the breast flaps to clear the tumor are best made by both the oncologic and plastic surgeon. Tumors in the vicinity of the areola require special consideration because of the potential for excessive thinning and resultant nipple/areola loss. If a superficial tumor close to the areola requires thinning of the subcutaneous fat, a decision has to be made whether to remove the entire subareolar breast tissue subdermally, or retain a thin breast layer for removal at the time of the second-stage reconstruction. If both the areola and the adjacent flaps are thinned down to the dermis the likelihood of nipple/areola loss is high.

Another example of intraoperative decision-making has to do with the management of large areolae having a surface area greater than 16 cm^2 (diameter greater than 4 cm). Here the extent of subareolar flap thinning depends on the thickness of the remaining breast flap, and whether other localized areas of the flap have been thinned. For a large areola having a 5 cm diameter, subareolar breast tissue may have to be left in place and removed later at the time of second-stage reconstruction to avoid nipple/areola loss.

Buttonhole mastopexy (see Chap. 7), when combined with nipple-sparing mastectomy also exemplifies the importance of joint intraoperative oncologic and plastic surgery decision-making. Issues related to flap design, reduced circulation to the nipple/areola, and tumor location have to be considered in this complex dual operation. In a buttonhole mastopexy-nipple-sparing mastectomy, the large inferiorly based random pattern flap supports the tenuous circulation to the nipple-areola placed at the apex of the flap. The viability of the nipple-areola is affected by the design of the flap, the volume of breast tissue retained beneath the areola, and the location of the tumor with respect to the skin. At the time of the nipple-sparing mastectomy a thin layer of subareolar breast tissue is left in place to prevent nipple/areola loss, removing it later during the second-stage reconstruction. For tumors in the lower hemisphere of the breast, the decision to thin the inferior flap is made by both surgeons. Deep lower hemisphere tumors may be cleared without affecting the circulation to the nipple-areola. Superficial tumors, on the other hand, that require thinning of the inferior dermal-fat flap will result in nipple-areola loss.

Intraoperative Collaboration Enhances Perioperative Communication and Patient Management

The intraoperative collaboration of the oncologic and plastic surgeons positively influences the perioperative communication between the oncologic and plastic surgery specialties. Preoperatively, the specifics of the operative planning can be discussed in more detail, and candidates for mastopexy-nipple-sparing mastectomy can be screened more easily based on mutual intraoperative experiences. Postoperative complications related to flap ischemia are better understood and discussed objectively to make the necessary technical changes to prevent similar problems in the future. Seromas after drain removal are managed in a timely fashion by the insertion of a seroma evacuation catheter with ultrasound guidance, a procedure that may be readily performed in the oncologic surgeon's office. During the second-stage implant exchange, excision of the retained subareolar breast tissue by the oncologic surgeon is made easier with the plastic surgeon's assistance. Finally, as a team both surgeons evaluate the outcome of each individual patient to determine whether the mastectomy technique and the method of reconstruction contributed to an untoward result.

Onco-plastic Inframammary Nipple-Sparing Mastectomy

Therapeutic nipple-sparing mastectomy/reconstruction is both an oncologic and aesthetic procedure because sparing the nipple/areola, in spite of attendant risks, is meant to enhance the final aesthetic result. Unfortunately, the preservation of the nipple-areola carries the risk of skin loss that may result in significant complications. The surgical collaboration of the oncologic surgeon and the plastic surgeon should be encouraged to minimize skin complications without adversely affecting the oncologic safety of the procedure. We refer to this type of surgical collaboration as an *onco-plastic* inframammary nipple-sparing mastectomy.

The term "oncoplastic" was coined by Werner Audretsch [8] in the 1990s to denote the rearrangement of breast tissue after a partial mastectomy in order to fill in the dead space and preserve the shape of the breast. In oncologic breast surgery, the term oncoplastic has come to refer to the oncologic surgeon's use of various plastic surgery techniques to reshape the breast after breast conserving surgery. Onco-plastic therapeutic inframammary nipple-sparing mastectomy, in contrast, refers to the oncologic and plastic surgeons' collaboration to perform the mastectomy while sharing equal responsibility for clearing the tumor and preserving the circulation to the nipple-areola.

Conclusion

The performance of therapeutic inframammary nipple-sparing mastectomy challenges oncologic and plastic surgeons to work together across the operating table to better preserve thick mastectomy flaps and carry out targeted flap thinning for tumor clearance while preserving the circulation to the nipple-areola. This shared intraoperative experience can be used to an advantage in making the necessary technical changes to lessen skin complications. Mastopexy-nipple-sparing mastectomy is a prime example of the importance of onco-plastic surgical collaboration to perform a complex operation efficiently and safely without compromising the oncologic or aesthetic result.

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The American Society of Breast Surgeons Nipple-Sparing Mastectomy Registry

23

Sunny D. Mitchell and Peter D. Beitsch

Introduction/Background

Scientific Advisory Committee ASBrS NSMR: Sunny Mitchell MD, Peter Beitsch MD, Sheldon Feldman MD, Shawna Willey MD.

Definition of Nipple Sparing Mastectomy

Nipple-sparing mastectomy (NSM) entails removing all breast tissue while sparing the overlying skin envelope including the nipple–areola complex (NAC). This type of mastectomy combined with immediate reconstruction leads to a postoperative breast appearing nearly identical to a preoperative breast. Benefits include preserved nipple–areola complex and improved cosmesis. This is in direct contrast to the more traditional mastectomy: modified radical mastectomy, total mastectomy, or skin-sparing mastectomy; all of which entail removing the NAC. The subcutaneous mastectomy entails leaving a variable amount of breast tissue immediately below the NAC; this is NOT a nipple-sparing mastectomy. Historically, concerns have included oncologic concerns with possible NAC involvement and risk of recurrence, technical difficulty, aesthetic (final nipple position), viability of the nipple, and postoperative surveillance to detect recurrence.

Rationale

The rationale behind this type of mastectomy is simple. The ability to perform a mastectomy for an individual while leaving the NAC in place allows us to accomplish two goals: continued optimal oncologic surgical treatment as well as markedly improved aesthetic outcome. Psychological benefits of retaining the nipple and immediate reconstruction can only aid in facilitating the healing/recovery process as incidence rates of depression and anxiety can be markedly elevated at the time of a breast cancer diagnosis. Sparing the NAC leads to greater patient satisfaction, body image, and psychological adjustment [1–5].

Previously the nipple and areola were removed routinely. This was based on a presumption of possible NAC involvement, concern for NAC viability, as well as concern regarding detecting recurrence and risk of recurrence. Currently, as a

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result of basic science studies evaluating breast anatomy, the ductal system, and terminal ductal lobular units (TDLU's) as well as clinical reports, much more about the nipple is understood. Although the NSM is not a new concept, this information has resulted in more cases in which the nipple–areola complex is routinely being spared during mastectomy in appropriately selected patients.

ASBrS NSM Registry Purpose

The American Society of Breast Surgeons (ASBrS) Nipple Sparing Mastectomy Registry (NSMR) was designed to compile information on metrics utilized, techniques utilized, aesthetic outcomes, as well as oncologic outcomes of the nipple sparing mastectomy. We aim to provide a large prospective collection of data points specifically gathered to provide evidence based medicine on outcome measures and metrics utilized for the nipple sparing mastectomy.

Registry Design and Duration

Feasibility of this registry was demonstrated in a pilot conducted at Stamford Hospital, CT; Columbia University College of Physicians & Surgeons, N.Y.; and Georgetown, Washington D.C. This is an IRB approved, non-randomized, multicenter, prospective Nipple Sparing Mastectomy Registry based within the Mastery of Breast Surgery Program of the ASBrS. The NSMR is open to members of the ASBrS, enrolled in the Mastery of Breast Surgery Program, who are facile at performing NSM's, up to date on appropriate patient selection, and routinely offer nipple-sparing mastectomies within their armamentarium of breast surgery options. Participating surgeons must also have successfully completed the equivalent of at least three previous cases prior to participation. After consent is obtained, participating surgeons enter data from patients undergoing an NSM for either a cancer diagnosis or as risk-reducing surgery into the NSMR in a prospective manner. Specific data points assessing metrics utilized, surgical technique, aesthetic outcomes, as well as oncologic outcomes are collected. Primary and secondary endpoints (outlined below) are assessed on a yearly basis. The Registry is ongoing for ten years with expected entry of 2000 patients. This registry is conducted in concordance with the following documents: IRB approval; ASBrS Nipple Sparing Mastectomy Protocol; Consent to Act as a Participant in the Nipple Sparing Mastectomy Registry; Investigator Agreement.

ASBrS NSM Registry Objectives

The objectives of the ASBrS NSMR are as follows:

- Evaluate metrics utilized for patient selection when performing a nipple-sparing mastectomy.
- Evaluate techniques utilized when performing a nipple-sparing mastectomy.
- Compile aesthetic outcomes (i.e., epidermolysis, infection rate, sensation, breast size/shape) of a nipple-sparing mastectomy.
- Evaluate patient characteristics (i.e., demographics, medical comorbidities, previous breast surgery or treatment) in outcomes/patient selection of a nipple-sparing mastectomy.
- Evaluate long-term outcomes of a nipple-sparing mastectomy (i.e., LRR, DFS, OS).
- Evaluate utilization of a nipple-sparing mastectomy as a prophylactic procedure.

ASBrS NSM Registry Endpoints Include

Primary Endpoints

- Primary outcome measures will be assessed via local regional recurrence, disease free survival, and overall survival.

Secondary Endpoints

- Metrics utilized for successful patient selection when performing a nipple-sparing mastectomy.

- Surgical techniques utilized when performing an NSM.
- Aesthetic outcomes of an NSM (i.e., epidermolysis, sensation, infection rate, breast size/shape).
- Patient characteristics (i.e., demographics, medical co-morbidities, previous breast surgery or treatment) which may/may not influence patient selection and/or outcome.

Justification of the Registry

The ASBrS is an organization that does research to learn about the causes of cancer and how to prevent and treat cancer. The purpose of this registry is to provide a large, prospective, non-randomized database of patient characteristics, tumor characteristics, medical comorbidities, and surgical technique utilized in nipple sparing mastectomies. Outcome measures including recurrence rates and overall survival will be assessed. The ASBrS is an ideal conduit for the implementation of the Nipple Sparing Mastectomy Registry secondary to the size and nature of its membership. These data will aid in direct comparisons of outcome results to other types of surgical treatment of breast cancer.

Table 23.1 Nipple/NAC ischemia

Nipple/NAC	# of mastectomies	
No Ischemia	232 (88 %)	
Ischemia (any degree)	33 (12 %)	
Surgical debridement	3 (1 %)	
Excision	1 (0.3 %)	
Epidermolysis w/ full recovery	29 (11 %)	Topical treatment: 17 No treatment: 12

No correlation was found between the incidence of nipple/NAC ischemia and incision type, method of flap or sub-areolar dissection (sharp +/− tumescent injection, electrocautery, PlasmaBlade) separate axillary incision, size or location of tumor, type of reconstruction, previous breast surgery, history of radiation therapy, chemotherapy, smoking history, initial fill of tissue expander (TE) utilized, cup size, degree of ptosis, or indication for surgery. Neither patients nor surgeons perceived a difference in cosmetic outcome with either epidermolysis or full thickness ischemia.

Nipple–Areolar Complex Ischemia/ Epidermolysis

The first preliminary analysis of the ASBrS NSMR assessed the incidence of nipple–areolar complex ischemia after an NSM [6]. The analysis included 265 NSMs performed by 35 surgeons on 173 patients. Ischemia was defined as epidermolysis (partial thickness necrosis) or full thickness necrosis. Median follow up at this time was 5 months, reflecting a range of 1–11 months from the time of surgery.

We reported a 12 % incidence of nipple or nipple–areolar complex ischemia ranging from epidermolysis to full thickness necrosis (Table 23.1):

- 3 (1 %) of NACs required surgical debridement.
- 1 (0.3 %) of NACs required excision.
- 29 (11 %) exhibited epidermolysis with full recovery.

Sub-areolar Tissue Specimen Assessment

The utilization of intraoperative vs final pathology assessment of the sub-areolar tissue specimen as well as management of pathology results was assessed [7]. This analysis was done after 320 NSMs had been performed on 207 patients by 37 investigators at 35 institutions. Indications included: invasive carcinoma 83 (26 %), DCIS 46 (14 %), and prophylactic 191 (60 %). An intraoperative sub-areolar (SA) pathology assessment was requested on 104 (33 %) of NSMs at the surgeon's preference. Tumor size ranged from 1 to 7 cm. Distance from tumor to NAC ranged from 1.6 to 4.1 cm (measured by physical exam, ultrasound (US), mammogram (MMG), or breast MRI).

Two NACs were unnecessarily excised secondary to intraoperative pathology results (one indeterminant and one suspicious)

Table 23.2 Sub-areolar tissue assessment

Intraoperative SA assessment (*n* 104)	Final SA Pathology Results	Final NAC status	Excised NAC pathology
No evidence of disease (NED) (98)	NED (97) DCIS (1)	(98) Not excised	
Indeterminate (2)	NED (2)	*(1) Excised intra-op secondary to prelim path assessment* (1) Not excised	*NED*
Cancer (1)	DCIS (1)	(1) Not excised	
Suspicious for cancer (1)	NED (1)	*(1) Excised intra-op secondary to prelim path assessment*	*NED*
Other (2)	NED (2)	(2) Not excised	
NO intraoperative SA assessment (216)	NED (215) DCIS (1)	(1) Excised secondary to final path results	*+ DCIS*

(Table 23.2). Of the 216 NSMs that did not undergo an intraoperative SA path assessment, one positive SA final pathology (DCIS) resulted in NAC resection. None of the final SA pathology specimens yielded invasive carcinoma. The risk of obtaining an intraoperative SA pathology appears to outweigh the benefit of finding a positive intraoperative SA pathology and avoiding an unnecessary NAC excision.

Compatibility of Breast Size, Degree of Ptosis, Type of Reconstruction, and Incision Placement

Breast characteristics (cup size and degree of ptosis), type of reconstruction, and incision placement in NSMs were assessed [8] after 386 NSMs performed by 39 surgeons from 36 sites for cancer (163) or prophylaxis (223) on 225 patients had been entered in the registry. All patients underwent immediate reconstruction with tissue expander, direct to implant (DTI), DIEP flap, TRAM flap, or latissimus dorsi flap. Breast size included cup sizes A, B, C, D, or ≥E. Degree of ptosis was; grade 1, 2, 3, none, or pseudoptosis. Incisions utilized included inframammary, peri-areolar, ellipse/hemibatwing, radial, radial with peri-areolar extension, previous lumpectomy scar, previous mastopexy scar, or Weiss pattern.

Cup size, degree of ptosis, incision placement, and type of reconstruction were assessed (Table 23.3). Free nipple transfer was performed on seven mastectomies.

One (0.2 %) NAC was excised secondary to full thickness necrosis. Four NACs (1 %) required debridement. Five (1 %) tissue expanders/implants were removed/exchanged secondary to flap infection. Cosmetic outcome as evaluated by 169 patients was excellent (58 %), good (36 %), or fair (7 %).

Patients undergoing an NSM had a wide variety of reconstruction techniques. The technique was not dependent on breast size or the degree of ptosis. The complication rate was low and there were too few complications to differentiate any differences based on size, ptosis, technique, or incision placement.

Postoperative Infection Complication Risk

The incidence of postoperative infections in nipple sparing mastectomies was analyzed [9]. At the time of this analysis, 52 investigators from 41 institutions had performed 631 mastectomies. Indications included risk-reduction (365), cancer (248), and unknown (18) on 373 patients. A sub group of 449 mastectomies, with indications of risk-reduction (253) and cancer (196) that had all data sets completed was assessed.

An analysis of infection rates in the entire group as well as by indication (cancer vs. prophylaxis) was completed. Factors analyzed were smoking

Table 23.3 Cup size, degree of ptosis, incision placement, and type of reconstruction

	Tissue expander, $n=219$	Direct to implant $n=104$	DIEP flap $n=22$	TRAM flap $n=1$	Latissimus dorsi flap n 2
Cup size					
Cup A	36	7	3		
Cup B	93	48	8	1	
Cup C	66	36	9		
Cup D	8	7			2
Cup ≥ E	2				
Unknown	3	6	2		
Degree of ptosis					
Ptosis: none	100	45	3		
Pseudoptosis	5				
Grade 1 ptosis	70	41	10	1	
Grade 2 ptosis	25	10	4		2
Grade 3 ptosis	9	6	5		
Unknown	10	2			
Incision type					
Inframammary incision	50	77	2	1	
Periareolar ellipse/ hemibatwing	4	4	2		
Previous lumpectomy scar	3	2	1		
Previous mastopexy scar	4	1	1		
Radial	46	2	15		
Radial w/periareolar extension	55	15	1		
Weiss pattern	2				
Unknown	55	3			
Unk reconst. type: 38					

history, previous radiation therapy, previous surgery, incision type, reconstruction technique, and flap dissection technique were analyzed.

Infections were characterized as: treatment with oral antibiotics alone, treatment with I.V. antibiotics alone, IV antibiotics with washout or debridement, or antibiotics and implant/tissue expander removal.

Postoperative infections were reported in 4.9 % ($n=22$) of patients: 3.6 % (7) of NSMs with an indication of cancer and 5.9 % (15) of prophylactic NSMs (p-value 0.3140). No correlation was found with infection and: smoking status (p-value 1.000); previous breast surgery (p-value 0.1277); previous radiation therapy (p-value 0.6024); reconstruction technique, incision placement, or dissection technique (Table 23.4).

The rate of postoperative infections in nipple-sparing mastectomies is comparable if not lower than non-nipple sparing mastectomies. No statistically significant difference in infection rate was found between mastectomies completed for risk-reduction or cancer. Improved aesthetics with a nipple-sparing approach (technically more demanding and typically through a smaller incision) does not come at the cost of a higher rate of infectious complications.

Ptosis

A preliminary data analysis of the ASBS NSMR 32 months into accrual was performed to specifically look at the degree of preoperative ptosis in patients undergoing a nipple-sparing mastectomy and its effect on outcomes [10]. A comparison was made of incision type, reconstruction type, infection rate, cup size, patient satisfaction, and cosmetic outcome as they related to degree of preoperative ptosis. This assessment comprised a total of 471 patients who

Table 23.4 Post-op infection

	Post-op infection	No post-op infection	All subjects	*p*-Value
Surgical indication				
Cancer, *N* (%)	7 (3.6)	189 (96.4)	196	
Prophylaxis, *N* (%)	15 (5.9)	238 (94.1)	253	
Total, *N* (%)	22 (4.9)	427 (95.1)	449	0.3140
Smoking history				
Current smoker, *N* (%)	1 (5.3)	18 (94.7)	19	
Never/quit, *N* (%)	21 (4.9)	408 (95.1)	429	
Total, *N* (%)	22 (4.9)	426 (95.1)	448	1.0000
Smoking history				
Current smoker, *N* (%)	5 (9.3)	49 (90.7)	54	
Never/quit, *N* (%)	17 (4.3)	377 (95.7)	394	
Total, *N* (%)	22 (4.9)	426 (95.1)	448	0.1667
Previous breast surgery				
Prior surgery, *N* (%)	13 (6.8)	177 (93.2)	190	
None, *N* (%)	9 (3.5)	250 (96.5)	259	
Total, *N* (%)	22 (4.9)	427 (95.1)	449	0.1227
Previous breast radiation				
Yes, *N* (%)	1 (5.6)	17 (94.4)	18	
No, *N* (%)	21 (4.9)	410 (95.1)	431	
Total, *N* (%)	22 (4.9)	427 (95.1)	449	0.6024

underwent 780 mastectomies with indications of cancer (339), risk-reduction (440), and unknown (10) by 55 surgeons at 44 institutions.

Degree of ptosis was defined as: none ($n=301$), pseudoptosis ($n=9$), Grade I ($n=261$), Grade 2 ($n=105$), or Grade 3 ($n=44$). Types of reconstruction included: DIEP Flap ($n=49$), latissimus dorsi Flap ($n=2$), DTI ($n=253$), TRAM flap ($n=5$), and tissue expander ($n=451$).

Incision types utilized included: inframammary ($n=301$), peri-areolar or hemibatwing ($n=17$), previous lumpectomy scar ($n=9$), previous mastopexy scar ($n=5$), radial ($n=133$), radial with periareolar extension ($n=172$), Wise mastopexy incision ($n=7$), other ($n=64$), and unknown ($n=72$) (Table 23.5).

Patient satisfaction was reported on 60 % of the total and 93 % reported excellent/good satisfaction. Similarly, surgeon-reported cosmetic outcome for 60 % of the total rated 95 % excellent/good.

Ptosis is not a contraindication to a nipple sparing mastectomy. Nipple sparing mastectomy with immediate reconstruction may be successfully performed on a breast with or without ptosis utilizing a variety of reconstruction techniques via a variety of incisions. Rate of infection does not vary by presence of or degree of ptosis. Although patient satisfaction and cosmetic outcome (assessed by surgeon) was available on only 60 % of patients, ptosis appears to have no bearing on patient satisfaction or cosmetic outcome.

Cup Size

The analysis of preoperative breast size as measured by cup size and feasibility of a nipple-sparing mastectomy was performed at 30 months [11]. Fifty-five surgeons from 44 institutions performed 780 NSMs on 471 patients, with indications of cancer (339), prophylaxis (440), and unknown (10). Preoperative cup size, identified as A, B, C, or D/D+ of individuals who underwent a nipple-sparing mastectomy was recorded. The group of D/D+ includes two mastectomies with cup size E.

Nipple-sparing mastectomies were performed on individuals with cup sizes A, B, C, D/D+ via a variety of incisions utilizing multiple reconstruction techniques. Incisions utilized included: inframammary, peri-areolar ellipse or hemi batwing, previous lumpectomy scar previous mastopexy scar, radial incision, radial with peri-areolar extension, or Wise mastopexy incision. Reconstruction techniques included DIEP, latissimus dosi flap, permanent implant, TRAM, or tissue expander. Infection rates were low (4.7 %) and not correlated to cup size. Patient satisfaction ratings were available on 457 NSMs: Excellent (271), Good (149), Fair (37). Cosmetic outcome evaluations by the surgeon were available on 492 of the NSMs: Excellent (309), good (157) and Fair (26). Conclusions: A nipple-sparing mastectomy with immediate reconstruction may be successfully performed on breasts with cup sizes of A, B, C, D/D+, via a variety of incisions utilizing multiple reconstruction techniques. Rates of postoperative infection are low in each cup size. Patient satisfaction as well as cosmetic outcome was most consistently rated as excellent or good.

Device-Based Reconstruction in Nipple-Sparing Mastectomy

The utilization of non-autologous reconstruction in nipple-sparing mastectomy, specifically DTI (direct to implant) and tissue expander on 1314 NSMs performed by 61 surgeons was assessed. Fifty-three NSMs were excluded secondary to unlisted type of reconstruction [12]. We compared patient characteristics, preoperative breast characteristics, surgical techniques, adverse events, and cosmesis between the two device-based reconstruction options.

DTI was utilized in 416 NSMs and a tissue expander (TE) in 826 NSMs. No significant variation was noted in preoperative characteristics.

The most common incision used for DTI was inframammary (66 %) and radial or radial with periareolar extension (58 %) in TEs. Infection rates were similar between DTI (3 %) and TE (5 %). Epidermolysis with full recovery was similar between DTI (9.2 %) and TE (10.7 %). Nipple/NAC necrosis was slightly higher in the TE group (5.1 %) vs. DTI reconstruction (0.3 %). Patient reported satisfaction regarding cosmesis was comparable between the two groups. Surgeon assessment of cosmesis varied slightly between DTI (62 % excellent, 36 % good) vs TE (48 % excellent, 47 % good). Preoperative characteristics of patients such as smoking history and previous radiation therapy did not vary significantly in patients receiving DTI or tissue expander. Preoperative breast characteristics such as degree of ptosis or cup size were also equivalent between groups (Table 23.6). Infection and epidermolysis rates were equivalent as was cosmesis between DTI and tissue expander. DTI reconstruction is an excellent option for NSMs.

Association of Incision Type and Infection Rate

An analysis comparing incision technique and presence or absence of infection in an NSM was presented in May, 2015 [13]. Sixty-one surgeons from 67 institutions performed 1367 mastectomies on 817 patients (550 bilateral and 267 unilateral) with indications of invasive carcinoma, DCIS, and prophylaxis. Analysis of incision technique and presence or absence of infection was performed on a subset of 925 mastectomies with recorded incision technique and infection status (Table 23.7).

Infection was noted in 2.3 % of mastectomies performed via an inframammary line incision, 0 % of periareolar/periareolar ellipse or hemibatwing incisions, 6.3 % of radial/radial with peri-areolar extension, (radial: 7.4 %, radial w/ peri-areolar extension: 5.3 %), 0 % previous lumpectomy scar, 0 % previous mastopexy scar (*p*-value 0.0467).

Among all above listed incision types, an overall rate of infection of 4.3 % was noted. Excluded from the above analysis is trans-areolar incision (one of six demonstrated infection), other (represents multiple incision types), and unknown incision type. NAC complication rates included: epidermolysis resulting in full recovery (11 %), ischemia/necrosis resulting in debridement (1.5 %), ischemia/necrosis resulting in NAC

Table 23.5 Ptosis

Characteristic	All subjects	None	Pseudo ptosis	Grade 1	Grade 2	Grade 3	Unknown
Enrolled cases (breasts)	780	301	9	261	105	44	60
Number subjects with bilateral mastectomy	309	130	3	99	42	20	15
Number of subjects	471	171	6	162	63	24	45
Indication							
Cancer indication, *N* (%)	330 (42.9)	118 (39.5)	6 (66.7)	105 (40.7)	42 (41.2)	20 (45.5)	39 (67.2)
Prophylaxis indication, *N* (%)	440 (57.1)	181 (60.5)	3 (33.3)	153 (59.3)	60 (58.8)	24 (54.5)	19 (32.8)
Unknown, *N* (%)	10	2	0	3	3	0	2
Incision technique							
Inframammary, *N* (%)	301 (38.6)	141 (46.8)	5 (55.6)	102 (39.1)	30 (28.6)	4 (9.1)	19 (31.7)
Peri-areolar ellipse, or hemibatwing, *N* (%)	17 (2.2)	6 (2.0)	0 (0.0)	3 (1.1)	0 (0.0)	6 (13.6)	2 (3.3)
Previous lumpectomy scar, *N* (%)	9 (1.2)	2 (0.7)	0 (0.0)	3 (1.1)	2 (1.9)	2 (4.5)	0 (0.0)
Previous mastopexy scar, *N* (%)	5 (0.6)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Radial, *N* (%)	133 (17.1)	32 (10.6)	2 (22.2)	51 (19.5)	26 (24.8)	4 (9.1)	18 (30.0)
Radial w/peri-areolar extension, *N* (%)	172 (22.1)	90 (29.9)	1 (11.1)	50 (19.2)	22 (21.0)	4 (9.1)	5 (8.3)
Wise mastopexy incision, *N* (%)	7 (0.9)	0 (0.0)	0 (0.0)	2 (0.8)	1 (1.0)	4 (9.1)	0 (0.0)
Other, *N* (%)	64 (8.2)	8 (2.7)	0 (0.0)	21 (8.0)	17 (16.2)	14 (31.8)	4 (6.7)
Unknown, *N* (%)	72	18	1	29	7	5	12
Cup size							
A, *N* (%)	113 (15.7)	73 (24.9)	0 (0.0)	33 (13.1)	3 (2.9)	0 (0.0)	4 (19.0)
B, *N* (%)	282 (39.3)	147 (50.2)	5 (62.5)	81 (32.3)	27 (26.2)	10 (23.8)	12 (57.1)
C, *N* (%)	243 (33.8)	64 (21.8)	1 (12.5)	114 (45.4)	50 (48.5)	9 (21.4)	5 (23.8)
D+, *N* (%)	80 (11.1)	9 (3.1)	2 (25.0)	23 (9.2)	23 (22.3)	23 (54.8)	0 (0.0)
Unknown, *N* (%)	62 (8.6)	8 (2.7)	1 (12.5)	10 (4.0)	2 (1.9)	2 (4.8)	39 (185.7)

Reconstruction technique							
DIEP, *N* (%)	49 (6.4)	11 (3.7)	0 (0.0)	24 (9.2)	8 (7.7)	6 (13.6)	0 (0.0)
Latissimus dorsi flap, *N* (%)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	0 (0.0)
Permanent implant, *N* (%)	253 (33.2)	107 (36.1)	0 (0.0)	83 (31.9)	34 (32.7)	23 (52.3)	6 (12.0)
TRAM, *N* (%)	5 (0.7)	0 (0.0)	0 (0.0)	3 (1.2)	2 (1.9)	0 (0.0)	0 (0.0)
Tissue expander, *N* (%)	451 (59.2)	176 (59.5)	8 (100.0)	150 (57.7)	58 (34.1)	5 (34.1)	44 (88.0)
Other, *N* (%)	2 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown, *N* (%)	18	5	1	1	1	0	10
Infection							
Yes, *N* (%)	29 (4.7)	13 (5.3)	0 (0.0)	3 (15)	6 (7.4)	3 (7.5)	4 (8.3)
No, *N* (%)	583 (95.3)	232 (94.7)	4 (100.0)	11 (98.5)	75 (92.6)	37 (92.5)	44 (91.7)
Unknown, *N* (%)	168	56	5	67	24	4	12

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Table 23.6 Device based reconstruction 6

Characteristic	Permanent implant	Tissue expander
Enrolled cases (mastectomies)	416	826
Previous breast surgery		
None, *N* (%)	228 (56.2)	455 (57.3)
Yes, *N* (%)	178	339
Unknown, *N* (%)	10	32
Prior XRT		
Yes, *N* (%)	16 (4.0)	24 (3.1)
No, *N* (%)	388 (96.0)	754 (96.9)
Unknown, *N* (%)	12	48
Cup size		
A, *N* (%)	34 (9.1)	146 (21.8)
B, *N* (%)	142 (37.9)	264 (3 9.3)
C, *N* (%)	146 (38.9)	204 (30.4)
D+, *N* (%)	53 (14.1)	57 (8.5)
Unknown, *N* (%)	41	155
Ptosis		
None, *N* (%)	175 (45.9)	251 (38.6)
Pseudo ptosis, *N* (%)	2 (0.5)	20 (3.1)
Grade 1, *N* (%)	120 (31.5)	240 (36.9)
Grade 2, *N* (%)	56 (14.7)	114 (17.5)
Grade 3, *N* (%)	28 (7.3)	25 (3.8)
Unknown, *N* (%)	35	176
Smoking history		
Current smoker, *N* (%)	12 (2.9)	46 (5.6)
Quit 1–12 months ago, *N* (%)	16 (3.9)	46 (5.6)
Quit 1–3 years ago, *N* (%)	5 (1.2)	11 (1.3)
Quit >3 years ago, *N* (%)	66 (16.1)	99 (12.1)
Unknown, *N* (%)	5	6

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excision (1.8 %) (Table 23.8). Mastectomies performed via radial and radial with peri-areolar extension incisions with infections had the highest rate of NAC complications requiring intervention/treatment (Table 23.8). No correlation was noted between history of previous surgery, history of radiation therapy, cup size, degree of ptosis, or indication for surgery.

This analysis provides important information regarding expectations and feasibility of incision placement when performing a nipple sparing mastectomy. The variation of infection rates between the most commonly utilized incisions: inframammary (2.3 %), radial (7.4 %), and radial with peri-areolar extension (5.3 %) is within range of the overall infection rate of 4.3 %. There appears to be no significant association between NAC complications to incision placement and infection status.

Preliminary Oncologic Outcome of ASBS NSMR

Recurrence rates in therapeutic NSMs and occurrence rate in risk-reducing mastectomies were assessed [14].

Recurrence was delineated as: distant, local/ipsilateral breast outside the NAC and local nipple/NAC. Occurrence was defined as a primary breast cancer diagnosis after risk-reducing NSM.

This analysis, performed at 58.6 months into accrual, represents a total of 2129 NSMs performed on 1291 patients performed by 87 Investigators at 65 sites. Mean follow-up is 24.4 months, median follow-up 23.3 months, range of 0.2–58.6 months. Indications for the 2129 NSMs performed include cancer $n=852$ (invasive carcinoma 567 and DCIS 285) and risk-reduction ($n=1262$). Unilateral NSMs were performed on 453 patients (cancer indication: $n=302$ and risk-reduction $n=144$). Bilateral NSMs were performed on 838 patients (1676 total NSMs, 550 indication of cancer, 1118 for risk-reduction).

Of the 852 NSMs performed for cancer there were nine recurrences (eight invasive, one DCIS). Tumor size measured by exam or imaging ranged from 0.1 to 9 cm.

There was a 1 % incidence of breast cancer recurrence (Table 23.9) after 852 NSMs performed for an indication of cancer. In the 1252 NSMs performed for risk-reduction, there was a 0.2 % incidence of breast cancer occurrence noted.

No recurrences or occurrences were noted at the nipple and/or nipple–areola complex.

Table 23.7 Incision technique and infection status

Incision technique	Inframammary	Peri-areolar and periareolar ellipse or hemibatwing	Radial and radial w/ peri-areolar extension[a]	Previous lumpectomy scar	Previous mastopexy scar	Total
Infection						
Yes, *N* (%)	9 (2.3 %)	0 (0.0)	31 (6.3)	0 (0.0)	0 (0.0)	40 (4.3 %0
No, *N* (%)	375 (97.7)	29 (100.0)	485 (93.7)	15 (100.0)	8 (100.0)	885
Total	384	29	489	15	8	925
p-Value	0.0467					

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[a]Radial 7.4 %, radial w/peri-areolar extension 5.3 %
[*]This chart excludes analysis of Trans areolar incision: one of six demonstrated infection

Table 23.8 Incision technique and incidence of NAC complications

Incision technique	Inframammary	Peri-areolar and periareolar ellipse or hemibatwing	Radial and radial w/ peri-areolar extension	Previous lumpectomy scar	Previous mastopexy scar	Total
NAC post-op complications						
Epidermolysis-full recovery, *N* (%)	47 (77 %)	1 (20.0)	58 (57.4)	1 (100.0)	2 (66.7)	109
Epidermolysis-required surgery, *N* (%)	0 (0 %)	0 (0)	5 (5.0)	0 (0.0)	0 (0.0)	5
Necrosis, *N* (%)	7 (11.5 %)	2 (40.0)	20 (19.8)	0 (0.0)	1 (33.3)	30
Other, *N* (%)	7 (11.5 %)	2 (40.0)	18 (17.8)	0 (0.0)	0 (0.0)	27
Total	61	5	101	1	3	171
p-Value	0.0924					

Table 23.9 Incidence of recurrence, mean follow-up 24.4 months

Indication	Total NSMs performed	Recurrence	Recurrence site
Cancer Invasive carcinoma DCIS	852 567 285	9 (1 %) 8 1	Distant: 7 Ipsilateral breast: 1 Ipsilateral breast: 1
		Occurrence	
Risk-reducing	1252	2 (0.2 %)	Distant: 2

[a]No recurrences noted at the nipple or NAC

Discussion

Advances in basic science research [15, 16] outcome data, surgical technique and technology have resulted in more candidates for nipple sparing mastectomy. The NSM has been associated with increased patient satisfaction and enhanced cosmetic outcome [1, 2, 17, 18].

Proposed preoperative metrics to delineate patient candidacy for an NSM have evolved from specific tumor size and distance from the NAC [19] to definitive decision making resulting from final path [7] of the retroareolar margin [3, 20] excised at surgery. Nipple-sparing mastectomies are safely performed for risk-reduction [21] as well as advanced disease [22]. A variety of recommendations of limitations regarding tumor size and location [19], breast characteristics, and patient characteristics [3–5, 18, 20, 23–26] have been proposed and continue to evolve to delineate acceptable NSM candidates.

As a direct result of maintaining the native skin envelope, a wide variety of incisions and reconstruction types are feasible, allowing for the option of hiding the scar in the inframammary fold and challenging the era and necessity [26] of automatically placing a tissue expander. The rationale for offering DTI [27, 28] or autologous tissue reconstruction rather than utilizing a tissue expander is motivated by reducing the need for additional procedures.

Although still an option, the tissue expander is no longer the only option for immediate reconstruction in the setting of an NSM. An additional option for large/ptotic breasts undergoing bilateral prophylactic mastectomy is a staged approach involving mastopexy or reduction followed by prophylactic NSM [29, 30]. The ASBrS NSMR sheds light on the feasibility of performing NSMs with immediate reconstruction on individuals with a wide range of cup size and degree of ptosis via numerous incisions and utilizing different reconstruction options performed by multiple surgeons.

Conclusion

- The ASBrS NSMR demonstrates an overall epidermolysis with full recovery rate of 11 %. Neither patients nor surgeons noted a difference in perceived cosmetic outcome with either epidermolysis or full thickness ischemia.
- No correlation was noted between incidence of nipple/NAC ischemia and incision type, method of flap or sub-areolar dissection, separate axillary incision, size or location of tumor, type of reconstruction, previous breast surgery, history of radiation therapy, chemotherapy, smoking history/status, initial fill of tissue expander utilized, cup size, degree of ptosis, or indication of surgery.
- The risk of obtaining an intraoperative SA pathologic assessment appears to outweigh the benefit of finding positive intraoperative SA pathology and avoids an unnecessary NAC excision.
- Patients with varying degrees of ptosis and cup size may successfully undergo an NSM with a wide variety of reconstruction techniques. The complication rate is low and there are too few complications to differentiate any differences based on size, ptosis, technique, or incision placement.
- There appears to be no significant association between NAC complications and incision placement.
- Postoperative flap infections were reported in 4.9 % of patients.

No correlation was found with infection and smoking status; previous breast surgery, previous radiation therapy, reconstruction technique, incision placement, or dissection technique. The rate of postoperative infections in nipple-sparing mastectomies is comparable if not lower than non-nipple sparing mastectomies. No statistically significant difference in infection rate was found between mastectomies completed for risk-reduction or cancer.

- Improved aesthetics with a nipple sparing approach (technically more demanding and typically through a smaller incision) does not come at the cost of a higher rate of infectious complications.
- Ptosis is not a contraindication to a nipple-sparing mastectomy. Nipple-sparing mastectomy with immediate reconstruction may be successfully performed on a breast with or without ptosis utilizing a variety of reconstruction techniques via a variety of incisions. Rate of infection does not vary by presence of or degree of ptosis. It appears that cosmetic/aesthetic outcome expectations may be maintained with no increase in rate of infection.
- A nipple-sparing mastectomy with immediate reconstruction may be successfully performed on breasts with cup sizes of A, B, C, D/D+, via a variety of incisions utilizing multiple reconstruction techniques. Rates of postoperative infection are low in each cup size. Patient satisfaction as well as cosmetic outcome is most consistently rated as excellent or good.

- The ability to perform DTI enhances the patient experience, decreases the number of operations a patient needs, and decreases the financial burden of breast surgery. DTI is successfully utilized in a large group of patients with varying cup size and degree of ptosis that may have previously been offered tissue expander as the only non-autologous immediate reconstruction option.
- Mastectomies performed via radial and radial with peri-areolar extension incisions with infections have the highest rate of NAC complications requiring intervention/treatment. No correlation was noted between complications and a history of previous surgery, history of radiation therapy, cup size, degree of ptosis, or indication for surgery. The variation of infection rates between the most commonly utilized incisions are all within the range of the overall rate of infection (4.3 %): inframammary (2.3 %); radial (7.4 %); radial with peri-areolar extension (5.3 %).

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