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Current Surgical Innovations in the Treatment of Breast Cancer

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Abstract: Surgery is an essential component in the management of treatable breast cancer. With the use of standardized staging and data collection, evidence-based management of breast cancer has evolved to limit treatments to what is necessary but sufficient to allow tissue preservation and control of treatment-specific morbidity. As more tumors are discovered by pretreatment imaging and are not identifiable on physical exam, intraoperative tumor localization techniques have become increasingly sophisticated and reliable. Techniques for localization of "sentinel" nodes has become increasingly accurate and technically less complicated. Surgical treatment may occur after pretreatment with systemic agents (neoadjuvant) or a part of reconstruction (oncoplastic resection). Post-surgical morbidity has become an increasing focus of concern as more patients survive breast cancer with modern therapy. Cosmetic deformity is a significant cause of distress in many patients and attributed to causing delay in seeking treatment and contributing to postoperative depression. Reconstruction with

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autologous tissue or prosthetic implants is offered with increasingly improved results and patient satisfaction. This chapter provides an overview of the current surgical innovations in the treatment of breast cancer. Specialized techniques employed in the surgical management of breast cancer in our practice are also discussed.

Keywords: breast cancer localization; breast reconstruction after breast cancer; lymphadenectomy for breast cancer; mastectomy for breast cancer; oncoplastic surgery for breast cancer

INTRODUCTION

Surgery has been the essential component in the management of treatable breast cancer since the first reports of radical mastectomy by William Stewart Halstead (1) and Willy Myer (2) in 1894. With the use of standardized staging and data collection, evidence-based management of breast cancer has evolved to limit treatments to what is necessary, but sufficient to allow tissue preservation and control of treatment specific morbidity. An extreme example of this evolution might be the treatment of focal ductal carcinoma in situ which would have been treated with modified radical mastectomy in the 1960's and might now be treated with simple excision and hormone targeted oral therapy or in some cases observation alone. The specific treatment regimens for breast cancer are currently directed by multidisciplinary teams involving integration of surgical oncologists, radiation oncologists, medical oncologists, plastic surgeons, and rehabilitation specialists. This chapter focuses on specialized techniques employed in the surgical management of breast cancer reflecting practice employed by various members of our department.

In our current workflow, the patient's diagnosis is confirmed microscopically and characterized by histochemistry and biochemistry to identify the sub-type of breast cancer and allow for directed treatment. After staging, customized therapy is initiated that will depend on histology, molecular characterization (hormone receptors, Her-2, Ki-67, genomic profile), patient age, and performance status. For invasive breast cancer, surgical problems include localization of the tumor for removal and determination of nodal status. As more tumors are discovered by pretreatment imaging and are not identifiable on physical exam, intraoperative tumor localization techniques have become increasingly sophisticated and reliable. Currently, standard of care dictates localization of potentially involved lymph nodes eliminating the need for axillary dissection in many patients. Techniques for localization of "sentinel" nodes has become increasingly accurate and technically less complicated. Surgical treatment may occur after pretreatment with systemic agents (neoadjuvant) or a part of reconstruction (oncoplastic resection). Primary reconstruction of the breast is often performed at the time of mastectomy. For patients requiring lymph node dissection, lymphatic reconstruction procedures may be part of the initial operation (lymph-venous reconstruction, S-lympha). In some cases, devices are placed to direct radiation to the tumor bed at the time of initial surgery or intraoperative radiation is given for select patients.

Post-surgical morbidity has become an increasing focus of concern as more patients survive breast cancer with modern therapy. Two surgically addressable causes are arm lymphedema and physical deformity post treatment. In one recent study, long-term arm lymphedema occurred in 22.4% of patients after treatment for breast cancer (3). This can be challenging to manage and causes significant distress for the patient. Surgical correction of lymphedema offers a means of ameliorating this condition.

The cosmetic deformity is a significant cause of distress in many patients and attributed to causing delay in seeking treatment and contributing to postoperative depression (4, 5). Reconstruction techniques with autologous tissue or prosthetic implants is offered with increasingly improved results and patient satisfaction.

TUMOR LOCALIZATION

With the introduction and now ubiquitous use of image screening of the breast for early detection of breast cancer, more than 25% of breast cancers detected are non-palpable requiring physical localization for biopsy or removal of lesions, and in the case of breast malignancies, to achieve breast conservation (6). Wire localization was the earliest technique used, with positioning done with the aid of mammogram, but now performed with ultrasound and MRI as well. Wire localization most often requires placement in the radiology department by a radiologist with subsequent transport to the operating room. The surgeon must then mentally reconstruct a three-dimensional assessment of the location from the two-dimensional images provided and is dependent on the skill of the radiologist to position the wire correctly. Successful localizations can be limited by small lesions, multiple lesions, lesions containing multiple calcifications and small specimens. This two-step procedure on the day of surgery can wreak havoc with surgical schedules (6–8). It is surprising that only 2.5% of localizations are unsuccessful. In our experience, mispositioning or movement of the wire post placement are the most vexing problems.

Radioactive seed localization (RSL) was an early alternative to wire localizations. This involved implant of an I^{125} titanium seed under image guidance at the tumor site within 5–7 days of operation. A technetium 99-based device was subsequently introduced. The seed is localized during surgery with a handheld gamma detection probe. Patient satisfaction and successful removal of target lesions was reported to be equivalent or better than wire localization, but regulatory restrictions for ordering, transport, storage, and recovery of radioactive devices along with the attendant infrastructure required to implement this program is considerable, especially in the face of other alternatives (9).

Currently, radiofrequency reflector devices (LOCalizer; SAVI scout) have offered an effective solution to the problem of localizing non-palpable breast lesions without the overhead of ionizing radiation devices (10, 11). The LOCalizer radiofrequency identification system (RFID) can be placed up to 30 days prior to surgery with image guidance. A dedicated portable unit is used to guide retrieval of the RFID tag. The first reported use documented 100% recovery of the tag. Comparison of the LOCalizer with the SAVI Scout showed similar efficacy with both devices comparing operative times, tissue volume removed, margin

involvement and re-excision rates (12, 13). The SAVI Scout has reported limitations including device inactivation by electrocautery, signal interference and nickel allergy (13). Our experience with the LOCalizer revealed problems with seed migration, mal-positioning, and probe calibration.

The latest device approved for use in the United States is the Magseed, a ferromagnetic 1 x 5 mm steel alloy implant introduced through an 18G needle in the preoperative period (generally 1–7 days prior to surgery). The seed is detected using a proprietary probe that detects the seed after activation to a magnetic state. Recovery of the seed has consistently been reported to be over 99% (14, 15). Localization requires non-ferrous instruments and requires some initial training with the probe. Pooled analysis of four studies showed the Magseed to be non-inferior to wire guided localization without the problems inherent in the wire technique. Personal experience (Weingrad) with over 150 Magseed guided localizations segmental resection of breast carcinomas and resection of other breast lesions is consistent with those reported findings.

LYMPH NODE LOCALIZATION AND PROCEDURES

The majority of breast cancers (65%) are confined to the breast and have excellent survival of 99% at 5 years (16). However, once the cancer has spread to the axillary lymph nodes, the survival drops significantly to 86% (17). As such, presence of axillary lymph node metastases is one of the most significant prognostic factors in breast cancer and a factor that is important to be addressed in the staging work-up (18). Since Halsted first described radical mastectomy, axillary lymph node dissection (ALND) has been accepted as a means to assess nodal burden while providing regional disease control (19–21). However, given the significant morbidity of this surgery including risk of lymphedema, which occurs in about 2–56% of patients (22), and injury to major neurovascular structures like the thoracodorsal and long thoracic nerves, efforts were made to adopt an approach that was as effective, but less morbid. In the mid-1990s, Giuliano and colleagues showed that the sentinel lymph node biopsy (SLNB) was effective at staging the clinically node negative axilla while limiting the morbidity of the more extensive axillary lymph node dissection. (23) Traditionally, this was performed by injecting 3 to 5 ml of 1% isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Inc., Richmond, VA) into the breast tumor and surrounding parenchyma or into the wall of the biopsy cavity and surrounding tissue if the malignancy was already removed. Then an additional incision was made in the axilla to identify the sentinel node which was colored blue and excised. Additional approaches to this technique include using radioactive colloid peritumoral injection and detection with an intraoperative gamma probe to remove the hottest lymph node and all lymph nodes with 10% or more of the ex vivo count of the hottest node. Using this technique along with isosulfan blue dye reduced the false negative rate to 5.8% (24). Additionally, if any suspicious palpable nodes are encountered, they should be removed regardless of whether they are radioactive or have blue dye, as it is felt that some nodes with a significant amount of tumor may not readily uptake the tracer. Alternative approaches have been explored to identify the sentinel lymph node, including injection of alternative tracer agents such as ICG, which is

injected in the breast and detected with a fluorescent imaging system. A meta-analysis of 12 studies has shown this method to be equally good if not better at detecting sentinel nodes (25). Additionally, magnetic tracer agents (e.g., super-paramagnetic iron oxide or SPIO) are oncologically safe and reliable technique to identify sentinel nodes. This is performed by injecting SPIO into the subareola or an intradermal location and detecting the uptake in the axilla with a handheld magnetometer (26).

At present, SLNB is the standard of care for axillary staging in clinically node-negative patients. When SLNB is performed, and axillary lymph nodes are found to be negative, multiple studies have shown that no further surgery is needed (27). If SLNB is positive, standard of care was to proceed with axillary lymph node dissection (ALND). However, several studies show that ALND can be safely omitted (27). This included the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (28). This study showed that patients with T1-T2 invasive primary breast cancer with clinically negative axilla, 1 or 2 sentinel lymph nodes containing metastases, and who had breast-conserving surgery followed by whole-breast irradiation, had noninferior overall survival outcomes if ALND was omitted (28). If a mastectomy is performed, and occult metastases, or tumor cells in the lymph node are not seen on initial hematoxylin and eosin examination, but found on further examination of the node, ALND may also be omitted based upon the NSABP B-32 trial which showed that there was a nonsignificant, lower overall survival (0.6%) in patients with occult metastases (29). Likewise, studies have shown no benefit of ALND over its omission for patients with primary tumors <5 cm in size and clinically nonpalpable axillary nodes who had SLNB with micrometastases (≤2 mm) according to The International Breast Cancer Study Group (IBCSG) 23-01 trial (30). Of note, this trial included patients who received Breast Conserving Surgery in addition to patients who underwent mastectomy (30). As for clinically T1-2 node-negative breast cancer patients who undergo mastectomy and SLNB and are found to have 1-2 SLN+ and receive axillary radiation therapy, ALND can be omitted based upon the findings in AMAROS trial (31). This trial showed no difference in overall and disease-free survival and a lower rate of lymphedema in patients receiving axillary radiation instead of the ALND (11% vs 23%) (31). All of the aforementioned studies were in patients who did not receive neoadjuvant systemic therapy. In patients who did receive neoadjuvant chemotherapy, ACOSOG Z1071 showed that SLNB can be safely performed in cN1 patients, as long as two or more SLNs are examined, as this practice keeps the false negative rate to <10% (32). Of note, further analysis of this trial showed that there was improved sentinel node identification when using both blue dye and radioactive colloid (93.8%), compared to either blue dye alone (78.6%) or radioactive colloid alone (91.4%) (33).

Follow-up studies showed that when the clipped node is identified and retrieved, the false negative rate is further reduced (34). In the setting of surgery after neoadjuvant systemic therapy, if any sentinel lymph nodes, clipped nodes, wire-localized nodes, or palpable nodes have tumor in them, an axillary lymph node dissection is indicated. In the event patients have more extensive axillary nodal burden on imaging following neoadjuvant therapy, one should forgo axillary SLNB and proceed with ALND instead. Our practice is to still wire localize clipped lymph nodes in this situation to guarantee its removal.

ONCOPLASTIC SURGERY

While the primary focus of breast surgery is providing maximal control of malignancy, we recognize the importance of simultaneously optimizing aesthetic outcomes, and in turn improving quality of life, body image, and self-esteem of the patient. As such, oncoplastic surgery, which was first termed as such in 1993, has been developed to try to achieve this goal. Some of the approaches to achieve this in the setting of breast conserving surgery include aesthetic placement of incisions, using either tissue remodeling or volume replacement with distant tissue to reconstruct volume defects, de-epithelialization, and donut mastopexy (35, 36). Additionally, oncoplastic surgery attempts to create symmetry between the two breasts. Attempts to do this include mastopexy or a breast reduction technique at the time of breast conserving surgery. Fortunately, studies have shown this to be safe in regard to not causing significant complications or delays to adjuvant therapy (37). As for mastectomies, attempts to achieve these goals include nipple-sparing mastectomies, in which the whole breast and major ducts from within the nipple lumen are removed, while saving the nipple areola complex dermis and epidermis (38). This is felt to be oncologically safe for patients, as shown in a 2018 systematic review comparing nipple sparing to skin sparing mastectomies and finding no statistically significant difference in 5-year disease-free survival and mortality, and similar local recurrence rates (39). Of note, many of the initial studies on this were performed on breasts with tumors that were greater than 2 cm from the nipple areola complex; however, in our practice, we do not find this to be a hard rule. We do make sure to remove a small periareolar biopsy to confirm that the residual retroareolar tissue is free of cancer or DCIS. Nipple-sparing mastectomy has also been found to be safe and effective at preventing breast cancer in high-risk populations, including patients with pathogenic BRCA mutations (40). Most surgeons will only offer nipple sparing mastectomy to women with small to moderate sized breasts with minimal ptosis to reduce the risks of flap and nipple necrosis and prevent nipple malposition (41), and to avoid this in patients with advanced disease, in whom a complication associated with nipple necrosis would delay much needed adjuvant therapy. Novel approaches to prevent this have been developed, including the surgical delay procedure in which the skin flap is created extending beyond the nipple–areolar complex and surrounding mastectomy skin by about 4–5 cm between 7–21 days prior to surgery. Of note, the tissue at the nipple is sampled and sent for permanent section pathology, and if negative, the patient returns for the completion of the nipple-sparing mastectomy (42). In the event the nipple cannot be saved, areolar-sparing mastectomy can be performed safely as well (43). If the cancer involves the nipple areola complex, or the cancer is too locally advanced, or the patient's breast size and ptosis are not amenable to nipple-sparing approach, a skin-sparing approach is performed. A skin-sparing mastectomy conserves more of the skin flaps than the traditional mastectomy to allow for enough skin to be saved to perform reconstruction after. Following surgery, various approaches can be used to recreate the nipple areola complex.

INTRAOPERATIVE RADIATION

Over the last 30 to 50 years, with the validation of breast conservation therapy for breast cancer (44, 45), radiotherapy has been established as part of the primary treatment for resectable breast carcinoma, although there are reports documenting local radiotherapy for treatment of breast cancer dating back to 1937 (46). Radiation therapy to all or the affected part of the breast is essential to minimize local recurrence. Recently, in select cases, patients with low risk, hormone receptor-positive, node-negative tumors over the age of 70 have been found to not benefit from treatment (47). With subsequent refinement of radiation delivery protocols, select patients are eligible for accelerated partial breast irradiation (APBI), which involves the delivery of radiation to limited volume of breast tissue with shorter treatment protocols, resulting in fewer side effects and equivalent treatment results (48). Intraoperative radiotherapy (IORT) and an implant targeting device (BioZorb) are recent techniques that require surgical participation to allow radiation delivery to restricted volumes.

Intraoperative radiotherapy (IORT)

While there are currently multiple trials with various entry requirements comparing various methods of delivering APBI, single fraction IORT has already generated level-1 results from randomized trials comparing IORT to external beam whole breast radiotherapy (49–52). The TARGIT-A trial demonstrated noninferiority of IORT compared to conventional whole breast radiotherapy (WBRT) for patients who met the specific criteria for post pathology single dose therapy. The ELIOT Trial had a similar design to TARGIT-A, but used mobile electron technology to deliver a single dose of 21 Gy. The ELIOT Trial had an unselected population for inclusion with no difference in overall survival. Risk factors associated with a higher incidence of breast recurrence were identified. At our center, a low energy ZEISS Intrabeam unit is used to deliver therapy. Patients are selected with low-risk tumors and favorable demographics (Table 1). The surgeon fits an appropriately sized applicator in the tumor cavity after tumor excision. Confirmation of clear margins of resection, negative sentinel nodes, and adequate depth is determined by ultrasound. Tumor control, excellent cosmetic outcomes and low risk of complications are the norm with a high degree of patient acceptance and satisfaction (53).

TABLE 1 Inclusion criteria for IORT

1.	Small tumors (T1 for IDC or below 2.5cm for DCIS)
2.	Low or intermediate grade
3.	ER positive
4.	HER-2 negative
5.	Age 50 or older

BioZorb

The BioZorb is an implantable, bioabsorbable device in a spiral configuration fitted with titanium clips that serves as a radiotherapy target. It is secured in the tumor cavity providing precise identification of the tumor site and offers partial reconstitution of the excised volume of tissue. It is offered in multiple sizes and two different shapes to fit nicely into various cavities. This allows for reduction in planned target volumes for treatment. Some centers are using this for patients who are receiving radiation boost to the tumor bed. Cosmetic outcomes over two years are reported by Kaufman in his study of 818 patients (54) to be good to excellent in over 87% of patients with adverse effects in 3.8% of patients (n = 31). Our experience largely confirms what is reported (unpublished). There is a "learning curve" for effective use of this device. The re-absorption can take up to two years with persistence of a palpable presence of the device at the tumor site, but with careful sizing of the implant this has rarely been an issue (55). Most of our patients have been treated with APBI as opposed to targeted boost of the tumor bed. Re-excision for involved margins is simplified because of the orientation of the device in the excision cavity. A retrospective review by Rashad et al. discusses the issue of cost effectiveness of a BioZorb implant versus marking the cavity with clips (56). Kaufman counters pointing the benefit of the BioZorb to precisely target the tumor bed and decrease treatment volumes. He cites the known inaccuracy in defining the tumor site with clips because of tissue distortion, rearrangement and clip movement. In some cases, we found the partial restoration in lost tissue volume to markedly improve the cosmetic outcome (e.g., upper inner and medial breast). Long term results are anticipated for this new device.

BREAST RECONSTRUCTION

Treating breast cancer with a mastectomy resulting in the loss of a breast disrupts the harmony of the feminine body structure which has the potential to cause dramatic effects on a woman's self-identity affecting body image, psychosocial well-being, and sexual well-being (57–60). In 1998, The Women's Health and Cancer Rights Act (WHCRA), a federal law mandating all payer coverage with the opportunity to undergo breast reconstruction following mastectomy, was passed (60). Since then, breast reconstruction has seen an increase by 75% between 2000 and 2020, with 137,808 breast reconstruction procedures performed in 2020 (61). The goal of breast reconstruction is to recreate a breast mound to restore form and psychosocial function (60). Considerable advances have been made in breast reconstruction where the principles of both reconstructive and cosmetic surgery have merged with the goal of optimizing patient outcomes and minimizing the effects of a mastectomy.

Improved knowledge of breast anatomy and its circulation as well as advances in mastectomy and reconstruction techniques have enhanced our ability to preserve the entire breast skin envelope and all of the breast subunits including the nipple areola complex without sacrificing oncologic principles. In doing so, our ability to restore the appearance of the native breast has improved considerably.

As previously mentioned, a nipple sparing mastectomy preserves the breast skin envelope including the nipple areola complex. An appropriate candidate for a nipple-sparing mastectomy is a patient with grade 1 or 2 ptosis and favorable tumor findings (62–65). Incision locations are decided together between the breast and reconstructive surgeons. Various factors, such as, cosmesis (inferolateral inframammary fold incision), optimal preservation of blood supply to the nipple areola complex, surgeon's experience on the technique (horizontal radial incision), and breast ptosis and repositioning of the nipple areola complex (vertical incision), will determine the optimal placement of incisions (63, 65, 66). Patients with breast hypertrophy or grade 3 ptosis may be considered for nipple areola complex preservation if the mastectomy is risk reducing in the setting of a genetic predisposition for breast cancer. This is best accomplished in a staged fashion beginning with a Wise pattern breast reduction or mastopexy with a superomedial pedicle followed by a mastectomy three months later. From an oncologic perspective, predictors of nipple involvement include tumor-nipple distance ≤ 1 cm, tumors > 3 cm in dimension, extensive DCIS component and multicentricity; therefore, patients with these findings should not be considered for a nipple sparing mastectomy (67).

Accounting for up to 75% of breast reconstruction following mastectomy in the United States, prosthetic based reconstruction has several advantages compared to other reconstructive options including reduced operative time, rapid recovery, avoiding surgical donor site morbidity, and ease of technique (68). Prosthetic based breast reconstruction has seen substantial advancements in technology and technique over the last fifty years. When silicone breast implants were first marketed in the 1960s, breast reconstruction was performed in the subcutaneous plane following a mastectomy. This technique was fraught with complications including capsular contracture, infection, and high explant rates (69, 70). As a result, the approach to breast reconstruction shifted to placing the breast prosthesis in the submuscular pocket, deep to the pectoralis major and serratus anterior muscles, after studies demonstrated that breast augmentation with silicone implants in a subpectoral pocket experience less capsular contracture. Unfortunately, placement in this plane also contributed to increased discomfort and a less natural appearing breast associated with animation deformity and implant displacement. After acellular dermal matrix (ADM), a biologic mesh, was introduced to the market in 2006, a dual plane strategy was incorporated into breast reconstruction where the pectoralis major was detached from its origin along the fifth and sixth ribs and the ADM is used as an inferior sling along the inframammary fold and lateral breast footprint or merely serves as an extension to the pectoralis muscle. ADM has been shown to decrease capsular contracture rates and preferentially allows for lower pole fullness while allowing for more control of the mastectomy pocket (70). While this technique is used today, the pendulum appears to be swinging back to the pre-pectoral pocket. The development of highly cohesive silicone gel implants has reduced implant rippling while providing a more ideal breast appearance with favorable soft contours when ADM is utilized for soft tissue support. ADMs now come in multiple sizes, shape, and thicknesses allowing for more options depending on the reconstructive strategy. Alternative to ADMs include synthetic meshes including absorbable and permanent varieties (70–72). More studies are needed to evaluate the two types of mesh in breast reconstruction.

Several factors are taken into consideration whether to perform breast reconstruction in one stage or two stages. This is a decision that is made with the breast surgeon and the patient. Factors that may influence this decision include breast volume and degree of ptosis, expectation for a larger or smaller reconstructed breast, and desire for limiting the number of operations. Furthermore, the quality of a mastectomy flap may also contribute to the decision-making process. The skin envelope should be evaluated intra-operatively assessing for thickness and perfusion. If there is any concern about viability, intraoperative fluorescent angiography with indocyanine green may be utilized to assess for vascular inflow and washout. While a single stage direct to implant reconstruction is becoming more popular, two-stage prosthetic-based reconstruction remains the more common strategy in the United States, beginning with placement of a tissue expander with ADM followed by exchange for a permanent implant once adequately expanding. The benefit of a two-stage approach is that a second operation provides another opportunity to improve the aesthetic outcome whereas a one stage operation may allow a patient to return to their life more quickly without the need for serial expansion or a second operation.

While implant-based reconstruction is the more common approach to breast reconstruction in the United States, patients tend to have higher satisfaction following autologous tissue reconstruction. Traditionally, autologous breast reconstruction was performed using pedicled flaps including the transverse rectus abdominis myocutaneous (TRAM) and latissimus dorsi myocutaneous flaps. There were limitations with these options including flap volume, high rate of partial flap loss, and donor site morbidity. With improvements in technology including microsurgery instruments, operating microscopes, expertise with perforator flaps as well as comfort with microsurgery technique, autologous tissue breast reconstruction takes advantage of transplanting one's own soft tissue from a distant site in the form of a free flap to reconstruct the breast. The most common donor site for breast reconstruction is the abdomen whereby a muscle sparing TRAM or deep inferior epigastric perforator (DIEP) flap is harvested. This donor site is ideal as most women have excess lipodystrophy and skin laxity along the abdominal wall. Venous microanastomoses are performed to the internal mammary vessels to restore flap circulation. The major complication is total flap loss which has been reported to have a 2–5% risk (73, 74). Moreover, Chang (74) and Baumann (75) et al. demonstrated that the risk of fat necrosis can be decreased as the number of flap perforators are preserved in abdominally based autologous tissue breast reconstruction. Alternative flaps can be used when the abdomen cannot be used as a donor site due to a history of an abdominoplasty or if the patient is thin and additional soft tissue is needed to supplement the volume of the abdominal flap. These donor sites include the thigh (gracillis myocutaneous flap, profunda artery perforator flap), gluteal region (superior or inferior gluteal artery perforator flap), and the lumbar region (lumbar artery perforator flap) (76–79). Furthermore, for the patient who has previously undergone a mastectomy and has an acquired absence of the breast associated with lymphedema, a DIEP flap may be harvested with the superficial inguinal lymph nodes as a composite flap to reconstruct both the breast and the lymphatic system. Approximately 3-4 lymph nodes may be transferred with this adipofascial flap when it is harvested with the superficial circumflex iliac artery and vein with the goal of restoring lymphatic physiology (80). Lymph nodes are positioned in the axilla during flap inset.

These lymph nodes are dissected with great care, and it is recommended that they be harvested with reverse mapping to avoid iatrogenic injury resulting in lower extremity lymphedema (81, 82).

Secondary procedures to improve the final aesthetic outcome of the reconstructed breast may be offered. Fat grafting has become a common tool to treat and correct a variety of defects that may not have been addressed during the initial breast reconstruction procedure (83). These defects may be intrinsic to the reconstructed breast mound such as fat necrosis in an autologous breast flap or rippling of an implant with an overlying thin mastectomy flap. Extrinsic defects may be observed following radiation therapy or in the presence of scarring that may cause a contour irregularity. Fat grafting may also be used to soften a sharp transition between the reconstructed breast mound and the native chest wall, referred to as a step off deformity. Alternatively, large volume and mega volume fat grafting, defined as 100–300 cc and >300 cc/breast respectively, can be performed to augment the volume of an already reconstructed breast (83). Complications of fat grafting include cyst formation and fat necrosis both of which can be treated easily. While it was once considered that fat grafting reduced the ability to detect cancer on imaging, and increased cancer risk, more recent research has distinguished the evolutionary change of fat grafting from suspicious findings on mammographic imaging (84, 85). Moreover, Spear et al. has demonstrated the safety and efficacy of fat grafting the reconstructed breast (86). Nipple reconstruction and/or three-dimensional nipple areola complex tattooing can be offered to complete reconstruction of the aesthetic subunits of the breast.

A remaining challenge in breast reconstruction has been the ability to restore sensation to the reconstructed breast. While evidence of neurotization in the breast dates back to the early 1990s, it has only been recently that consistent and reproducible results have been achieved. Peled et al. presented a new technique, whereby coapting a nerve allograft (Avance Nerve Graft, Axogen, Jacksonville, FL) using 8-0 or 9-0 nylon between the transected T4 or T5 lateral intercostal nerve to the sub-areolar nerves, demonstrated light touch sensibility to the breast and a two point discrimination of the nipple areola complex was preserved in immediate implant-based reconstruction without the associated morbidity of harvesting an autologous nerve (87). Autologous flap neurotization has also demonstrated that restoring sensation in autologous tissue-based reconstruction can be achieved and provide patients with a positive impact on the quality of life according to the BREAST-Q (88, 89).

Halsted wrote “Beware the man with the plastic operation” when he introduced the radical mastectomy for treatment of breast cancer in 1907 (19, 90). It is because of advances in knowledge, technique, and technology that plastic and reconstructive surgeons now have the ability to provide superior outcomes with high patient satisfaction to those who have not only been diagnosed with cancer, but also sustained the loss of a breast and perhaps a sense of self.

LYMPHATIC RECONSTRUCTION PROCEDURES

A common yet feared consequence of an ALND for metastatic breast cancer is lymphedema. Secondary lymphedema is a pathologic condition characterized by

insufficient drainage of interstitial fluid caused by a disruption in the lymphatic vasculature involving the affected extremity. This condition may contribute to a decrease in quality of life and results in symptoms of upper extremity pain, heaviness, swelling, skin tightness, and reduced range of motion. It raises psychosocial concerns about one's own body image and studies have shown that patients with lymphedema also demonstrate higher levels of anxiety, depression, and fatigue (91). Moreover, the development of lymphedema increases susceptibility to upper extremity infections. Not only does lymphedema impose a considerable cost on patients, but it also impacts our healthcare system with conservative management accounting for $498 million annually ranking 13th among all treatments by the Center for Medicare and Medicaid Services reimbursement (92).

The incidence of lymphedema has been shown to be 0–13% following sentinel lymph node biopsy, 30% following an axillary lymph node dissection with even higher rates following adjuvant radiation (91, 93–96). Traditionally, treatment has consisted of physiotherapy and lifelong compression garments (97). More recently, efforts have been made intraoperatively to reduce injury to the lymphatic system draining the upper extremity and thus minimize the development of lymphedema. Axillary reverse mapping, introduced in 2007, is a technique whereby blue dye is injected along the subcutaneous tissue in the ipsilateral upper extremity prior to performing an axillary lymph node dissection (98). Performing this technique aids in identifying the upper extremity lymphatic anatomy with the potential of preserving it during an axillary lymph node dissection and subsequently reducing lymphedema risk. Unfortunately, this technique does not eliminate the risk of lymphatic system injury. Nor should oncologic resection be compromised to reduce the risk of lymphedema (91).

In 2009, Boccardo et al. described the first efforts in performing immediate lymphatic reconstruction following an axillary lymph node dissection (99). Using a technique referred to as Lymphatic Microsurgical Preventive Healing Approach (LYMPHA), lymphovenous bypasses were performed between divided lymphatic channels draining the upper extremity to tributaries from the axillary vein, in essence re-routing lymphatic drainage and restoring physiologic lymphatic flow. A follow-up study at four years following axillary surgery demonstrated a 4% incidence of lymphedema with immediate lymphatic reconstruction that increased to 10% if patients who experienced transient lymphedema were included (100). Feldman et al. attempted immediate lymphatic reconstruction in 37 women with successful completion in 27 patients (101). They reported 8% risk of lymphedema in patients 24 months after immediate lymphatic reconstruction and 12.5% risk of transient lymphedema. They were unable to perform LYMPHA in 10 patients due to lack of a suitable recipient vein, inability to identify a lymphatic channel, and extensive axillary disease. More recently, Johnson et al. also demonstrated promising results in a cohort of 97 women who underwent immediate lymphatic reconstruction at the time of axillary surgery with an incidence of 3.1% after a median follow up time of 11.4 months (102).

Patients with breast cancer and metastasis to the axillary lymph nodes requiring axillary lymph node dissection and potentially adjuvant radiation may be identified as high risk for developing lymphedema and are referred from the surgical oncologist to a plastic and reconstructive surgeon with microsurgical training for preoperative evaluation for immediate lymphatic reconstruction. Evaluation will include obtaining both subjective and objective set of measurements to

establish a baseline preoperatively. A validated lymphedema-specific patient reported outcome using the 18-question Lymphedema Life Impact scale version 2 that answers questions across four domains including physical, psychosocial, and functional concerns is completed by the patient. Bioimpedance spectroscopy (L-Dex; ImpediMed, Carlsbad, CA) provides objective information regarding the amount of fluid and fat distribution and the ability to detect early changes in extracellular fluid compartments in the affected extremity. Volume distribution using a perometer (optoelectric volumetry) is yet another instrument used to evaluate lymphedema (103).

Intra-operatively, the surgical oncologist and reconstructive surgeon will work together to determine the optimal incision location, which generally tends to be high along the axilla. However, in certain circumstances, the axilla can also be approached through a mastectomy incision. The surgical oncologist will perform reverse axillary mapping with the injection of lymphazurin blue dye intradermally into the upper medial arm before proceeding with the axillary lymph node dissection. Attention is paid to identifying and preserving lymphatic channels draining the arm with as much length as possible. It is also critical to preserve axillary vein branches with a suitable length (6–7 cm) found within level one and level two of the axilla, specifically targeting the thoracoepigastric vein, lateral thoracic vein, medial pectoral vein, and branches emanating from the thoracodorsal vein, if possible, from an oncologic perspective (104). If neither of these veins have been preserved, an unnamed vein could be used if it is found within proximity to the lymphatic vessel or alternatively a vein graft could be used. Ideally, the recipient vein should have a competent valve to prevent back bleeding.

Once the ablative component has been performed, the reconstructive microsurgeon will inject indocyanine green intradermally in the medial upper arm and use near infrared fluorescence imaging including SPY Elite and Phi (Stryker Inc., USA) to aid in locating lymphatic channels draining the upper extremity that have been transected in the axilla. Others have advocated the use of fluorescein isothiocyanate to map the extremity lymphatic system (91, 105). After the vein and lymphatic channel have been dissected free, a surgical microscope will be introduced into the field and used to prepare the vessels for microanastomosis by stripping them free of adventitia and trimming the edges. Specialized microsurgery instruments are used to handle the delicate tissues. In general, due to a size mismatch between lymphatic vessel and recipient vein, most lymphovenous bypasses in the axilla will be performed in an end-to-end fashion using an intussusception technique whereby the lymphatic vessel is telescoped into the vein and temporarily secured using 9-0 nylon with a U-stitch (99, 104). Interrupted sutures are then placed from the vein edge to the lymphatic adventitia circumferentially until a good seal is achieved. The temporary U-stich is then removed, and patency of the anastomosis is assessed using a strip test, confirmation of blue dye in the vein, or use of SPY to evaluate ICG across the anastomosis. A 15F drain is usually placed in the axilla and removed when output is sufficiently low.

An alternative has been proposed for patients that do not have access to microsurgeons who perform LYMPHA. Simplified LYMPHA (S-LYMPHA) is another approach to immediate lymphatic reconstruction and should be considered when use of a microsurgical technique is not available (106, 107). Following immediate lymphatic reconstruction, the patient is referred to a certified lymphedema

therapist for education and range of motion exercises. They are also monitored closely for the development of lymphedema. LLISv2 is completed, LDEX and/or perometry values are obtained every three months for the first 3 years, every 6 months for years 4 and 5, and annually thereafter (108). These measures are compared to the patient's baseline measurements. In the event that immediate lymphatic reconstruction cannot be performed or with the development of lymphedema, other procedures to restore lymphatic physiology such as distal lymphovenous bypasses or vascularized lymph node transplant can be offered. Johnson and colleagues performed a cost utility analysis that demonstrate that the addition of LYMPHA to patients undergoing axillary lymph node dissection with or without adjuvant radiation is cost effective (109). Moving forward, further investigation is warranted that standardizes technique and outcome measures.

CONCLUSION

Over the past hundred plus years, treatment for breast malignancy has progressed from physical ablations to evidence-based multidisciplinary care directed at the systemic nature of the disease and the effect of treatment. As discussed here, the current focus is towards tissue preservation, restoration of physical function and appearance achieved through de-escalation of treatment or reconstruction of lost function. We have discussed some of the innovations that are part of our current practice that have altered the treatment of breast cancer. These are surgical procedures using imaging modalities to localize and define the extent of tumors, positioning of therapeutic devices for novel delivery of radiotherapy, reconstruct breast lost to disease and physically restore lymphatic drainage.

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