Surgical Treatment of Breast Cancer

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INTRODUCTION

Surgery remains the bedrock of breast cancer treatment. During the past three decades, there has been a dramatic evolution in operative procedures that address both the primary tumor and the lymph nodes.

Prior to the 1970's the treatment of breast cancer was based on Halstead's concept that tumor cells spread along lymphatic pathways by direct extension. Regional lymph nodes were believed to be barriers to further tumor spread, and there was no understanding of the role of the bloodstream in disseminating tumor. Breast cancer was believed to be operable because it was a local/regional disease, and – prior to the advent of the CT Scan – outcomes were judged by the incidence of death and local regrowth of tumor on the chest wall. During the Halstead era, ever more radical procedures were carried out in the paradoxical belief that the radical mastectomy was insufficiently radical, but they did not improve outcome or survival, and radiation was added with increasing frequency.

In the 1960's, the Fisher hypothesis promoted a different concept of tumor biology: tumor cells do not disseminate directly in an orderly pattern, and they traverse lymphatics by embolization rather than by direct extension. The positive lymph node was no longer seen as the instigator of distant disease, but rather as an indicator that the host-tumor relationship permitted the development of metastases. The bloodstream was now understood to be the prime route of tumor dissemination, and many cancers were seen to be multicentric.

In 1971, NSABP (National Surgical Adjuvant Breast and Bowel Project) trial B-04 began to enroll patients. This landmark trial compared total mastectomy without axillary dissection with radical mastectomy in the treatment of patients who were clinically node-negative. One half of each group was randomized to receive regional radiation. At 5 and 10 years there was no statistically significant difference between the node-negative and the node-positive groups.[1] This pivotal study began to place in question the role of axillary dissection, and especially rebutted the arguments in favor of even more radical operations that included dissection of the internal mammary and supraclavicular lymph nodes. Lymph node dissection was now understood to be a staging procedure that provided prognostic information, rather than a therapeutic one.

The 1970's also ushered in the era of breast-conserving surgery as a result of NSABP trial B-06. Beginning in 1976, this trial randomly assigned patients to total mastectomy, segmental mastectomy, or segmental mastectomy followed by breast irradiation. Patients whose axillary nodes were clinically negative or positive were both eligible. There was no survival difference between any of the groups at 5 and 7 years, but in the group that received radiation, tumor recurrence in the operated breast was reduced by 25%.[2]

Thus, the NSABP B-04 and B-06 trials established the major principles that govern breast cancer treatment today.

ROLE OF LYMPH NODE ASSESSMENT

This discussion of state-of-the-art surgical care will begin with the recent evolution in lymph node staging. As noted, after NSABP trial B-04 it was already recognized that axillary dissection was not therapeutic, but nodal dissection remained an integral element of the breast cancer operation for its prognostic value. The landscape of breast cancer care was further transformed by the growing role of chemotherapy and screening mammography. Adjuvant chemotherapy, introduced 30 years ago, provides a statistically significant survival benefit that is much greater in patients with node-positive disease. In populations that participate in screening and routine mammography, it is currently estimated that 80% of newly detected breast cancers are in early stages, but clinicians are not very successful at predicting axillary lymph node involvement, and regardless of whether lymph nodes are predicted to be involved or uninvolved, about one third of patients are incorrectly staged clinically. Thus, pathologic assessment of lymph

nodes remains essential since the status of the axillary lymph nodes determines the need, extent, and type of adjuvant systemic therapy.

Sentinel Lymph Node Mapping

Sentinel lymph node (SLN) mapping was first established when clinicians, who were utilizing lymphatic mapping in patients with melanomas, discovered that if the first node of drainage did not contain tumor cells it was most rare to identify tumor in any of the subsequent regional lymph nodes. In 1995 Giuliano and colleagues reported using isosulfan blue dye to stage the axilla in breast cancer patients.[3] The sentinel lymph node accurately predicted the status of the axilla in 96% of the dissections. Careful analysis of the sentinel lymph node was more accurate in predicting a positive axilla than a standard level I and II dissection with routine histopathology of the identified nodes. Use of isosulfan blue dye (Lymphazurin™) can be complicated by anaphylaxis (1-2%), local skin necrosis, or permanent blue skin pigmentation at the injection site. Techniques for assessing the sentinel lymph node(s) have evolved rapidly. Other investigators introduced technetium-99m sulfur colloid, which further increased the rate of successful characterization of lymph nodes. The radioisotope is injected intravenously several hours before operation and is tracked intraoperatively using a Navigator probe that emits an auditory signal and helps the surgeon localize the "hot" node(s). Many surgeons combine these techniques and find significant benefit in having both auditory (technetium) and visual (blue dye) signals.

Anatomic studies demonstrated that lymphatic drainage in the breast occurs in a nonrandom fashion to the axillary SLN. Subareolar injection has replaced peritumoral injection because it is more sensitive, i.e. more successful in localizing sentinel lymph nodes, even though it is not more accurate, i.e. it does not actually change the percentage of false positives. The already low false negative rate of 2% - 3% can be reduced even further by careful intraoperative palpation of the axillary contents. If the surgeon fails to identify the SLN with confidence, standard axillary dissection should be performed. In a review of our own results at Lancaster General Hospital, the SLN was the only site of tumor extension in over 25% of patients. A recent multi-institutional prospective study found that of the 1253 patients who had at least one positive node, the SLN was the only disease in the axilla in 791 (63%).[4] It is not uncommon to find two or more nodes that qualify as a SLN. SLN mapping is utilized with both lumpectomy and mastectomy. SLN mapping is also recommended for patients with extensive or high grade DCIS (ductal carcinoma in situ), and for those DCIS patients treated by mastectomy, in case occult invasive disease is discovered in the original operative specimen. SLN mapping should also be performed in patients who are clinically node-negative, before they undergo neoadjuvant chemotherapy. The results of NSABP B-27 trial indicate SLN biopsy (SLNB) may be an adequate staging procedure after chemotherapy in patients who present with advanced disease and receive chemotherapy before surgery.[5]

At LGH, mapping of sentinel lymph nodes utilizes technetium-99m sulfur colloid in all cases, and isosulfan blue dye at the discretion of the surgeon. Obesity and poor signal localization during intraoperative scanning increase the chances of unsuccessful localization. Immediate pathologic assessment, generally by touch prep, is performed with 95% accuracy. If the sentinel lymph node contains tumor a standard level I and II dissection is performed. If sentinel-lymph node metastases are only found subsequently on permanent pathology, the risk of additional metastases ranges from 12% to 34%, so we recommend a return to the operating room for completion of the axillary dissection (ALND). In a recent multi-center study, patients who had sentinel-lymph node metastases up to 0.02cm in diameter had the same disease free and overall survival as those whose sentinel lymph nodes were negative.[6] Post-operative morbidity is significantly decreased in patients undergoing SLNB compared with ALND.[7] Sequelae that are reduced by SLNB include pain (8% vs. 39%), numbness or paresthesia (1% vs. 68%), decreased mobility (0% vs. 31%, and lymphedema (7% vs. 75%).[8] Though lymphedema rates are far lower in our practice, the benefits of SLNB are still clear.

SURGICAL TREATMENT OF THE BREAST

The 1990 National Cancer Institute Consensus Conference on the treatment of early-stage breast cancer[9] concluded that "breast conservation treatment is an appropriate method of primary therapy for most women with stage I and II breast cancer and is preferable because it provides survival rates equivalent to those of total mastectomy and axillary dissection while preserving the breast." This statement brought to an official and welcome close to the long era during which women went to the operating room for an excisional breast biopsy, only to learn their fate when they awakened to find their breast had been removed. Now, there are

many factors that govern the choice of surgery, and the majority of patients who undergo mastectomy will not require radiation. Table I outlines absolute and relative contraindications to breast conservation.

Mastectomy

The original Halsted mastectomy consisted of en bloc removal of the entire breast and wide excision of the overlying skin, full dissection of the axilla, and resection of the pectoralis major muscle. In his 1894 paper, Halsted was able to report a local recurrence rate of only 6% compared to the rates reported by European surgeons who performed the von Volkmann mastectomy, which ranged from 51% to 82%.[10] In Halsted's era, breast cancer was almost exclusively a locally advanced disease. In 1948, a report by David H. Patey and W. H. Dyson of the Middlesex Hospital in London questioned the practice of routinely removing the pectoralis major muscle, particularly when the muscle is not involved by tumor, and proposed a modified procedure that preserved the pectoralis major muscle.[11] Today, the Patey modified radical mastectomy has been replaced by total mastectomy with SLN mapping in patients who do not have axillary metastases proven by biopsy. Mastectomy is often combined with either immediate or delayed reconstruction. Reconstructive techniques and options will be discussed in a subsequent article in this series. There are several recent modifications of mastectomy that are applicable in select patients.

TABLE I. CONTRAINDICATIONS TO BREAST-CONSERVING THERAPY

Absolute Contraindications

- Prior therapeutic radiation to the involved breast
- First or second trimester of pregnancy
- Two or more distinct cancers involving different quadrants of the breast
- Suspicious microcalcifications involving more than one quadrant
- MRI documentation of cancer involving more than one quadrant

Relative Contraindications

- Large tumor-to-breast volume ratio precluding a good cosmetic result
- Very large breast
- History of collagen-vascular disease
- Severe primary lung disease
- Severe coronary artery disease

Skin-sparing mastectomy

In a skin-sparing mastectomy, the incision is made around the nipple-areola complex (NAC) so as to eliminate the mammary ducts within it, as they often harbor cancer cells. Small extensions may be added extending medially and laterally to facilitate dissection of the remaining breast. This technique leaves less mismatched skin in the case of tissue reconstruction, and leaves generous skin flaps that often allow one stage prosthetic reconstruction without need for the standard temporary expander that is used in most prosthetic breast reconstructions.

Areola-sparing mastectomy

Although the lining of the mammary ducts is a primary source of breast cancer, malignancy rates in the entire NAC fall within a very broad range - 5% to 58%. When Simmons and colleagues examined the nipple and areolar complex independently, however, they saw a malignancy rate of less than 1% in the areola and 10.6% in the nipple. The areola-sparing mastectomy resects the nipple and any preexisting biopsy scars, then removes all of the breast parenchyma through an incision around the areola This technique may enhance the cosmetic effects of breast reconstruction by permitting a natural looking postoperative restoration of the nipple.[12]

Prophylactic Mastectomy

Prophylactic mastectomy of the contralateral uninvolved breast is recommended to or requested by patients in various circumstances, including a strong family history of cancer or large breasts. The procedure provides the patient with an end to screening mammography, reassurance that she will never need treatment for a second denovo breast cancer, and freedom from any need to consider long-term prophylaxis with Tamoxifen, Evista, or the aromatase inhibitors, which have demonstrated they provide substantial (50%) reduction of cancer incidence in the contralateral breast. In addition, simultaneous reconstruction avoids the trauma of seeing the post-mastectomy amputation in stark contrast with the intact remaining breast, and it enhances the likelihood of symmetrical reconstruction – a particularly appealing solution for women with large breasts, since it is very unlikely that unilateral reconstruction after mastectomy will be able to match a large natural breast. Women who carry the genetic mutation (BRCA1/2) or have a strong family history of breast cancer may request bilateral prophylactic mastectomies even if no cancer is clinically apparent. In a study of 745 women with a history of breast cancer, prophylactic mastectomy reduced the

risk of cancer in the contralateral breast from 27.4% to 1.5% in premenopausal women and from 14.1% to 4.0% in postmenopausal women. [www.breastcancer.org]

Breast Conserving Surgery

Two major trials which accrued patients in the 1970's (NSABP trial B-06, and Umberto Veronesi at the National Cancer Institute of Milan) established breast conserving procedures as equal to mastectomy with the same relapse-free and overall survivals.[13] The Veronesi group limited patients to tumors 2 cm or less and utilized a very wide resection of the tumor, designated a quadrantectomy. NSABP B-06 included patients with up to 4cm tumors. In the following decades progressively less normal tissue has been removed by surgeons with equivalent survival.

The definition of a negative margin differs among institutions. Extensive intraductal component (EIC) around the primary increases the risk of recurrence. In the Joint Center of Radiation Therapy (JCRT) study, patients with EIC-negative tumors had a 5-year local recurrence rate of 1% if margins were negative and 2% if margins were negative but the carcinoma was within 1mm of the ink. If there was focal involvement of the margin, recurrence rose to 9%. For patients with EIC-positive tumors, risk for recurrence was 8% with negative margins and 27% when margins were histologically positive.[14] Re-excision rates after lumpectomy average 35% – 40% if later returns to the O.R. after the final pathology report are counted. Re-lumpectomy specimens often contain no residual tumor, and it is now time for surgeons to tackle the relumpectomy issue as one of the next frontiers for improvement.

Cryo-assisted Lumpectomy Study

Most surgeons would state that a lumpectomy is one of the most imprecise procedures they perform. Determining an accurate margin even around a palpable lesion is often limited by tissue composition; dense fibrocystic tissue in young women, and fatty tissues that all too readily separate from the tumor in older women. The latter tendency may mislead the pathologist into thinking that surgical margins were inadequate when in fact an adequate margin was excised. Based on a promising pilot study, we participated in a prospective multi-institutional trial that compared cryo-assisted and needle-wire localization of ultrasound-visible breast cancers.[15] The cryoprobe was placed with ultrasound guidance through the center of the tumor. The Visca Treatment System (Sanarus Medical) was set to Hi freeze and Argon gas flowed through the probe, bringing it to temperatures of −60.C. The Hi freeze setting was maintained until ultrasound revealed that a predetermined ice margin of at least 8mm had developed around the lesion. At that point the Visica system was set to Lo freeze, which maintained the iceball shape without further growth while it was excised. Specimens were marked for orientation and x-rayed, and their mass was determined by water displacement. In the patients enrolled at LGH, re-excision rates were significantly lower with this technique than with needle-wire excision, though both groups were significantly lower than historical controls, which suggested that techniques were improved in study patients, a common phenomenon in trials of all kinds. The use of cryo-assisted lumpectomy (CAL) added about 12 minutes to operative times, but resulted in removal of significantly less tissue and better cosmesis.[16] We continue to use this modality in select patients with small and deep tumors. The CAL cavity is ideally conformed for those patients who will undergo partial breast irradiation with Mammosite®. (Mammosite®, the only FDA-approved catheter device for delivery of cavity brachytherapy, will be discussed further in a coming article on radiation therapy.)

Intraoperative Ultrasound Localization

For nonpalpable tumors, the most frequently used method of localization has been a hookwire (Kopan's wire, Homer wire) inserted under mammographic or ultrasound guidance. Patients are not sedated for these procedures and often point to this as the most difficult and uncomfortable portion of their surgical treatment. Surgeons practicing breast surgery have gained proficiency with ultrasound to identify, characterize and biopsy breast tumors. Some surgeons who have demonstrated additional skills in ultrasound are now utilizing it in the operating room to localize tumors and assess margins. After SLN biopsy is completed, the patient is scanned to localize the tumor which is then excised through an incision placed directly over the lesion. After excision, the ultrasound probe is placed over the specimen at various axes to determine the adequacy of margins of excision in each plane. In a recent report by Bennett from Australia, adequate margins of excision were achieved in 93% of cases.[17] This approach promises to decrease patient anxiety and discomfort; provide potential cost savings by reducing operative time (especially the wait for results of the specimen radiograph); potentially reduce infection rates; and potentially reduce the volume of tissue removed and improve cosmesis. It may also prevent having lesions

missed due to wire retraction or displacement while awaiting surgery, and avoid the substantial organizational difficulty of arranging for a skilled radiologist to place the hook wire on the day of surgery.

Table II outlines the circumstances where postmastectomy chest wall irradiation is indicated.

FUTURE DIRECTIONS

The era is rapidly approaching when small breast cancers may be treated by radiofrequency ablation, cryoablation, or even microwave therapy via probes placed with ultrasound guidance. It may even be possible to eliminate the need for any excision. As diagnostic and screening methods improve, it is possible that surgeons will be able to treat breast cancer without removing tissue and without disfigurement.

TABLE 2: INDICATIONS FOR POST-MASTECTOMY CHEST WALL IRRADIATION

Indicated

- Positive or close margins
- T3 tumors (especially T3, N1)
- All T4 tumors
- Extracapsular nodal disease

Considered

- >3 lymph nodes

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