The Changing Field of Locoregional Treatment for Breast Cancer

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Since 1990, death rates from breast cancer have decreased, mainly in women younger than 50 years of age (3.3% per year) vs women aged 50 years or older (2% per year), reflecting the benefit of widespread use of systemic treatment added to early detection. [1]

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Improved local control is also causally associated with improved breast cancer survival. An absolute reduction in local recurrence at 5 years is associated in a 4:1 ratio with an absolute survival advantage at 15 years in the overviews of clinical trials. [2] Guidelines for locoregional treatment of breast cancer were first published by the US National Institutes of Health in 1991. [3] Since then, new surgical and radiotherapeutic techniques have been developed, and revised guidelines for locoregional management were suggested in 2008 by the Biedenkopf Expert Panel Members. [4]

Over the past 50 years there have been major changes in the treatment of patients with breast cancer, with "less is more" being the theme. Treatment of breast cancer has evolved dramatically from the Halsted radical mastectomy, and many women now choose breast-conserving surgery and sentinel node biopsy. Breast-conserving surgery (BCS) is defined as the complete removal of the tumor with a concentric margin of surrounding healthy tissue and maintenance of acceptable cosmesis. BCS should be followed by radiation therapy to achieve an acceptably low rate of local recurrence.

Neoadjuvant Chemotherapy

In an effort to increase the number of patients eligible for breast conservation, neoadjuvant chemotherapy that shrinks the primary tumor before surgery has become an appealing option. [5] In a large randomized trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18, investigators randomized 1,523 women with Stage I–IIIa breast cancer to receive doxorubicin (Adriamycin, A) and cyclophosphamide (C) either preoperatively or postoperatively. [6] A reduction in tumor diameter of at least 50% was noted clinically in 80% of the patients, and in 37% no tumor was clinically apparent after chemotherapy. The initial findings of the study were reported at 5 years; in the 9-year follow-up publication, there continued to be no difference in overall survival or disease-free survival in patients receiving chemotherapy preoperatively vs postoperatively. The breast conservation rate was 68% for the neoadjuvant arm and 60% for the adjuvant arm. The reduction in tumor volume allows an improved cosmetic outcome in the majority of patients. Induction chemotherapy followed by BCS and radiation therapy is safe and increases the eligibility for breast preservation in approximately one-fourth of patients with large tumors relative to breast size. From a surgical standpoint, when the neoadjuvant approach is being considered, it is mandatory to insert a radioopaque marker into the tumor in order to localize the surgical site after partial or complete tumor regression.

Another important advantage of neoadjuvant chemotherapy is that it probes the chemosensitivity of the tumor, providing information of great importance in terms of development of systemic treatments for chemoresistant tumors. Tumors exhibiting the characteristics referred to as luminal A (strongly ER-positive, PR-positive, HER2-negative) exhibit less-dramatic reductions in volume with neoadjuvant chemotherapy but will often respond to neoadjuvant therapy with aromatase inhibitors or tamoxifen. Conversely, for HER2-positive tumors, adding trastuzumab (Herceptin) to a standard neoadjuvant regimen achieved a pathologic complete response (pCR) of 65.2%, compared with a 26% pCR in patients who did not receive trastuzumab. [8]

Margins

The first goal of breast-conservation surgery is to excise all apparent cancer. Adequate margins...
minimize the risk of local recurrence. Positive margin status correlates with local failure and is an important predictor of residual disease after BCS. The definition of what constitutes a clear margin represents one of the ongoing "great debates" in breast surgical oncology.

The NSABP defines a positive margin as the presence of tumor at the inked margin and a negative margin as the absence of tumor at the inked margin. Negative margins are associated with lower rates of local failure.

No uniform definition of surgical margin status has been established in the literature among institutions. In their survey of 702 institutions in North America, Taghian et al[9] found that definitions of negative margins vary from "no cells on the inked margin" to "no cells at 5 mm from the inked margin." About 50% of surveyed institutions are using "no cells at the inked margin" as a definition of a negative margin. The same variation exists for the definition of close margin. Schnitt et al have reported that 31% of institutions surveyed used a distance of less than 1 mm from the inked margin as a definition of close margin.[10] As reviews of contemporary series using multimodality therapy for early breast cancer fail to show an advantage for margins exceeding the "no tumor cells at inked margin" definition, a definition of "close margin" serves no purpose.[4] In a metaanalysis of 4,660 patients, Dunne et al[11] showed that for patients with ductal carcinoma in situ (DCIS), a 2-mm margin was superior to a margin of less than 2 mm for avoiding ipsilateral breast tumor recurrence (OR = 0.53; 95% CI, 0.26–0.96). Since that publication, our institution has adopted the 2-mm margin criterion in cases of DCIS.

It is still debated whether obtaining a wider margin will decrease the rate of local recurrence after breast-conserving surgery. What is clear is that it is absolutely unacceptable to have tumor cells at the cut edge of the excised specimen, regardless of the type of postsurgical adjuvant therapy.[12] For patients with positive margins who undergo reexcision, residual disease will be found in approximately 50% of the cases, with rates varying depending on histologic subtype.

Several clinical and morphological factors have been identified to predict a higher rate of positive margins.[13-15] These include smaller breast size, larger tumor size, previous surgical biopsy for diagnosis, use of neoadjuvant chemotherapy, lobular histology, mammographic density of the breast tissue, and an extensive intraductal component.[16]

Use of neoadjuvant chemotherapy can make evaluation of the primary tumor and margin status challenging. The scattered viable tumor cells are usually situated within the fibrosis and macrophage accumulation at the site of the tumor mass, so those areas are examined carefully if seen at the margin.

Options for intraoperative evaluation for margin status include gross examination of the specimen, frozen section, and touch preparation cytology of the margins.[17] Owing to high false-negative rates, technical complexity, and the duration of such intraoperative procedures, none of these methods has been accepted as standard for margin assessment.[18,19] In retrospective studies,[20] taking multiple additional margins of tissue from each aspect of the biopsy cavity during the initial operation reduced the rate of reoperation with adequate cosmetic results.

### Evaluation of the Axilla

Sentinel lymph node biopsy (SNB) has become the standard approach to axillary evaluation in clinically node-negative patients.

SNB accurately stages the axillary nodes and carries significantly lower rates of complications such as seroma, infection, arm stiffness, pain, paresthesia, and lymphedema,[21,22] compared with axillary node dissection. Use of isosulfan blue 1% dye (Lymphazurin), radioisotopes, or both has proved to be less important than expertise in identifying the sentinel lymph nodes. Obtaining a second node reduces the risk of false-negative staging. Removing more and more "sentinel lymph nodes" can approach the number of nodes in an axillary dissection with the attendant risks that the sentinel approach was designed to avoid.[23] SNB has changed the way breast cancer is treated, and is contraindicated only in cases of inflammatory breast cancer. In breast oncology it was not clear until very recently whether a positive SNB required a full axillary dissection. NSABP's B-04 study failed to show a survival benefit to axillary dissection, but axillary dissection has remained the standard of care for local control. The greatly improved survival rates associated with modern systemic therapy have raised the question anew.

The American College of Surgeons Oncology Group Z0011 trial,[24] conducted at 115 sites, tried to determine the impact of SLB alone vs complete axillary node dissection on survival in clinically node-negative breast cancer patients undergoing partial mastectomy and whole breast irradiation (WBI). Results of the Z0011 trial showed no survival advantage for complete axillary node dissection.
in patients with one or two positive SLNs. Those patients can be treated safely without axillary node dissection.

**Radiation Therapy**

BCS followed by radiation therapy has been shown in multiple trials to yield survival and recurrence rates equivalent to those seen with total mastectomy for patients with early-stage breast cancer.[25] Although the benefit of whole-breast irradiation (WBI) in terms of reducing local recurrences is well documented, this technique is associated with many burdens for patients, including daily treatment for 6 weeks and permanent skin changes. The paradigm "less is more" has certainly applied to the surgical technique used in the breast and axilla, and the same concept of greater benefit with conservative management may also apply to radiation therapy. Instead of irradiating the entire breast, a new concept of partial irradiation has emerged. The rationale of accelerated partial breast irradiation (APBI) is that 90% of breast recurrences occur at or adjacent to the original tumor bed.[26] This suggests that irradiating the whole breast may be unnecessary. The first device for breast APBI was approved by the US Food and Drug Administration (FDA) in 2002. APBI is delivered via insertion of a brachytherapy catheter in the tumor cavity at the time of the original surgery. The shorter duration of APBI, 5 days (vs 6 weeks with WBI), is very convenient for many patients.

**REFERENCE GUIDE**

**Therapeutic Agents**

- **Capecitabine (Xeloda)**
- **Cyclophosphamide**
- **Doxorubicin (Adriamycin)**
- **Tamoxifen**
- **Trastuzumab (Herceptin)**

Multiple multicenter randomized clinical trials (including the NSABP B-39/ Radiation Therapy Oncology Group 0413 phase III trial) have been initiated or completed to compare the effectiveness and safety of APBI vs WBI.[27] Shaitelman et al reported on outcomes of APBI in patients treated in the NSABP B-39 trial according to the American Society for Radiation Oncology (ASTRO) consensus statement on APBI use. Patients were classified as “suitable,” "cautionary," and "unsuitable." At a median follow-up of 53.5 months, the 5-year actuarial rates of ipsilateral breast tumor recurrence (IBTR) were 2.59%, 5.43%, and 5.28%, respectively, for the three groups.[28] Vicini et al[29] recently reported long-term data (median follow-up, 11.1 years) demonstrating equivalent rates of IBTR among matched pairs of 199 patients who received APBI vs WBI. The efficacy of APBI has yet to be validated in prospective comparative trials, and limited long-term data exist for the more than 50,000 women in the US who have been treated with various forms of APBI. At present, APBI has been associated with better quality of life, patient satisfaction, and body image than WBI.[30,31] Some concerns remain, however, that longer follow-up may reveal complications of the less fractionated delivery of irradiation to the surrounding normal tissue. Only the late results of randomized trials will address this issue. Selection of patients able to avoid breast irradiation was addressed in a National Cancer Institute...
Breast Intergroup study led by Dr. Kevin Hughes. Patients in the study were women over 70 years of age with estrogen receptor–positive breast cancers that had been completely excised. They were free of axillary nodal metastases based on either clinical or pathological criteria and were receiving 5 years of tamoxifen therapy. The investigators previously reported 5-year data from the trial,[32] and an updated report with a median follow-up exceeding 10 years was presented at the 2010 meeting of the American Society of Clinical Oncology.[33] The 5-year and 10-year trial results showed that women randomized to lumpectomy plus WBI vs lumpectomy alone had no advantage in either survival or breast preservation rates compared with those receiving lumpectomy without irradiation. Although local recurrence rates were higher in the group treated with lumpectomy alone, they remained acceptably low and there was no difference in risk of distant metastasis or death from any cause.

Sophisticated techniques of breast irradiation can now avoid "hot spots" and consequently allow hypofractionation compared with the number of fractions previously used. The work of Whelan and colleagues has shortened the duration of whole-breast treatment from 6 weeks to 3 weeks. This was initially demonstrated in older women but is now being evaluated in younger women as well, and would appear to provide some of the benefit of APBI with whole breast treatment.[34]

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