Advances in Breast Conservation Therapy
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INTRODUCTION

Breast conservation therapy (BCT) is now well established as oncologically safe treatment for primary breast cancer, and in fact has been deemed the preferable surgical option in a 1991 National Cancer Institute (NCI) position statement on management of early-stage disease. This consensus was reached after the completion of several prospective, randomized clinical trials confirming survival equivalence in breast cancer patients randomly assigned to receive BCT versus mastectomy. Follow-up as long as 20 years has been reported (Table 1) as well as a meta-analysis of all trials, with stability of the outcome results.

TRENDS IN UTILIZATION OF BCT

Reports from the National Cancer Database and comparisons to practice patterns in England demonstrate that BCT tends to be underutilized in the United States, with rates ranging from less than 10% to 45%. Factors associated with increased likelihood of breast preservation include young age; treatment in the northeast compared to southern regions; affluent socioeconomic status; and treatment in metropolitan areas associated with a cancer center or teaching hospital. Recently, Lucci et al presented provocative data suggesting that the excessive mastectomy rates in the United States might also be related to the third party payers’ lower reimbursement scale for lumpectomy codes.

Eligibility and Exclusion Criteria for BCT

Established criteria for BCT eligibility are predicated on three issues that set the balance between optimal locoregional control of disease and minimal tissue resection: (1) delivery of breast irradiation; (2) breast cosmesis; and (3) ability to obtain a margin-negative lumpectomy. Radiation therapy may be influenced by access to a radiation facility or by medical conditions affecting toxicity and tolerance of treatment. Aesthetic results can be altered by the body habitus or primary tumor location, but acceptability of the final cosmetic result must be defined by the patient. Certain tumor features, such as an extensive intraductal component, may forecast difficulty in obtaining margin control, but occasionally a seemingly unifocal tumor will be found to have a surrounding field of microscopic disease that results in positive margins on multiple reexcision lumpectomies.

Radiation therapy is a necessary adjunct to lumpectomy as a means of treating microscopic foci of multifocal and multicentric cancer, thereby minimizing risk of local recurrence. As demonstrated by the 20-year follow-up results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study, local recurrence is decreased from 39% to 14% by the delivery of radiation after lumpectomy. The B-06 trial and other studies of lumpectomy with versus without radiation therapy have revealed comparable survival rates for these arms, leading to the widespread belief that adjuvant XRT does not contribute to
survival. This concept has recently been challenged, however, on the basis of established outcome benefits associated with postmastectomy XRT in high-risk patients; by extrapolation it can be argued that optimization of local control in the breast after lumpectomy by the addition of XRT will also improve survival. Support for this hypothesis is generated by findings from a meta-analysis conducted by Vinh-Hung and Verschraegen, where results were pooled from several randomized clinical trials of lumpectomy versus mastectomy with XRT. This study revealed a statistically significant 8.6% survival benefit associated with postlumpectomy XRT.

Guidelines from the American College of Radiology and the American College of Surgeons provide a general framework for identifying and managing BCT candidates: (1) unifocal disease is preferred; (2) diffuse, malignant-appearing microcalcifications on the preoperative mammogram contraindicate BCT. This frequently correlates with diffuse ductal carcinoma-in-situ, precluding the ability to achieve negative margins. If the volume of calcifications in comparison to the breast size is thought to be amenable to a successful lumpectomy, then mammographic guidance for the insertion of two or more localization bracketing wires may facilitate the effort. Postlumpectomy mammography must document absence of residual calcifications with XRT, even if the lumpectomy margins are negative. BCT in cases of indeterminate calcifications should be considered with caution; whenever possible the calcifications should be resected en bloc with the tumor. If the calcifications are remote from the primary tumor site, then breast preservation should only be undertaken if the radiologist is confident of benignity based on diagnostic views, and if mammographic follow-up appears safe; (3) prior therapeutic chest irradiation is a contraindication to BCT if the breast is within the prior treatment field.

This is relevant for Hodgkin’s disease patients treated with chest-wall XRT during adolescence/early adulthood because of the increased risk of radiation-induced breast cancers that appear two to three decades after treatment; (4) radiation therapy is contraindicated during pregnancy because of scatter exposure to the fetus; (5) positive lumpectomy margins. There is no predefined limit on the number of resections that should be attempted in seeking margin control, but multiple unsuccessful re-excisions may indicate an excessive breast tumor burden, delay administration of postoperative adjuvant therapy, and compromise cosmesis; (6) history of particular collagen vascular disease such as scleroderma (but not rheumatoid arthritis) is a relative contraindication to BCT because of radiation toxicity risks; (7) primary tumor size should be less than 5 cm, as the phase III BCT clinical trials were limited to T1 and T2 lesions. Larger tumors by definition require larger volume lumpectomies; this can make XRT planning more challenging and threatens the aesthetic result. The ratio of tumor-to-breast size should also be taken into account.

### Longstanding Issues Regarding BCT Eligibility

#### Family History

Family history has been investigated as a possible risk factor for BCT failure because of initial concerns that a genetic predisposition to breast cancer might increase the likelihood of subsequent neoplastic events in the treated breast. Several studies have investigated this question, and in each case, family history did not increase the risk of local recurrence following BCT for breast cancer. Patients with a strong family history, however, are often found to have a higher risk for developing new primary breast tumors.

#### Table 1. Randomized Trials Comparing Mastectomy and BCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Years</th>
<th>No. of Patients</th>
<th>Maximum Tumor size (cm)</th>
<th>Minimum Margin</th>
<th>OS (%)</th>
<th>LR/IBTR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06 (^2)</td>
<td>1976-1984</td>
<td>1851</td>
<td>4</td>
<td>Microscopically free at inked edge</td>
<td>20</td>
<td>47</td>
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<tr>
<td>Milan Cancer Institute (^3)</td>
<td>1973-1980</td>
<td>701</td>
<td>2</td>
<td>Grossly negative</td>
<td>20</td>
<td>58.8</td>
</tr>
<tr>
<td>NCI (^4)</td>
<td>1979-1987</td>
<td>237</td>
<td>5</td>
<td>Grossly negative</td>
<td>13.4</td>
<td>66</td>
</tr>
<tr>
<td>EORTC (^5,6)</td>
<td>1980-1986</td>
<td>868</td>
<td>5</td>
<td>Grossly negative</td>
<td>10.1</td>
<td>79</td>
</tr>
<tr>
<td>Institut Gustav Roussy (^7)</td>
<td>1970-1982</td>
<td>179</td>
<td>2</td>
<td>Grossly negative</td>
<td>6</td>
<td>82</td>
</tr>
<tr>
<td>DBCCG (^8)</td>
<td>1983-1989</td>
<td>905</td>
<td>5</td>
<td>Grossly negative</td>
<td>9.8</td>
<td>67</td>
</tr>
<tr>
<td>EORTC and DBCCG (pooled results) (^9)</td>
<td>1980-1989</td>
<td>1,772</td>
<td>5</td>
<td>Grossly negative</td>
<td>14.3</td>
<td>58.8</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCT, breast conservation therapy; OS, overall survival; LR, local recurrence; IBTR, in-breast tumor recurrence; NSABP, National Surgical Adjuvant Breast Project; Lump, lumpectomy; XRT, irradiation; NCI, National Cancer Institute; EORTC, European Organisation for the Research and Treatment of Cancer; NR, not reported; DBCCG, Danish Breast Cancer Cooperative Group.

\(^*\)There were no isolated chest wall events/recurrences in the mastectomy arm, but eight patients experienced a local failure with a regional and/or distant event; and three patients experienced a regional-only recurrence. In the BCT arm, 27 patients (22%) experienced an isolated local recurrence; there were four local with regional and/or distant failure, and there were no isolated regional recurrences.
Primary Lobular Histology and/or Coexisting LCIS

Invasive lobular cancers are notorious for their frequently insidious presentation, often symptomatic for only a vague area of thickened breast tissue, and lacking any specific findings on mammogram or ultrasound. Diffuse microscopic disease may underlie this nonspecific and misleading clinical picture. Not surprisingly, this pattern can make attempts at margin control particularly difficult. Moreover, invasive lobular cancers have been associated with a higher risk of contralateral new primary tumors compared with other histopathologic types of breast cancer. Several BCT outcome studies have therefore specifically addressed the possibility that invasive lobular cancer might indicate the presence of a field effect of microscopic disease that would increase the risk of local recurrence. Similarly, lobular carcinoma-in-situ (LCIS) is perceived as widespread, bilateral breast proliferative activity that might affect rates of local recurrence. Similarly, lobular carcinoma-in-situ (LCIS) is perceived as widespread, bilateral breast proliferative activity that might affect rates of local recurrence.

Retrospective, prospective, and case-control studies have now shown that invasive lobular cancers and cases of LCIS coexisting with an invasive cancer can be safely managed with breast preservation. The presence of LCIS at the lumpectomy margin is irrelevant. Some investigators have noted that invasive lobular lesions and infiltrating tumors coexisting with LCIS have an increased risk of in-breast events, but in both scenarios the excess breast events tend to occur over aproach in clinical practice is to resect the breast tumor with an approximately 1-cm-thick rim of surrounding tissue with the expectation that this will yield a microscopic margin of at least 1 to 5 mm on pathologic analysis. The oncologic priority of maximizing local control must be weighed against the desire to optimize the cosmetic result, which will depend on volume of resected breast tissue. As shown in Table 1, even the phase III BCT trials have varied substantially in defining a negative margin. The NSABP requires absence of tumor cells at the inked specimen edge; the NCI trial of BCT did not mandate microscopic margin negativity at all.

The concept that wider margins reduce LR risk was shown by the Milan Cancer Institute where quadrantectomy (involving removal of 2- to 3-cm tissue surrounding the breast tumor en bloc with overlying skin and underlying fascia) was compared to tumorectomy (lumpectomy aimed at removal of gross tumor mass only, with no effort made to clear surrounding microscopic disease) for 705 patients with cancers up to 2.5 cm in size. Both arms received 45-Gy breast XRT and a 15-Gy boost dose. Although actuarial survival curves were identical for the two arms of the study at 7 years, there were fewer local recurrences in the quadrantectomy arm (5.3%) compared with the tumorectomy arm (13.3%). Pathologic margin assessment revealed positivity in eight of 178 assessable quadrantectomy cases (4.5%), and in 46 (16%) of 289 assessable tumorectomy cases. The LR rates were similarly elevated in these two groups of margin-positive patients (12.5% vs. 17.4%).

It is clear that tumors should not be transected, leaving gross residual disease. However a single microscopically close or involved margin focus may not necessarily increase the local recurrence risk substantially, especially if followed by a radiation boost dose. In general, a microscopic margin of at least 2 mm seems to insures reasonable likelihood that that local failure rates will be less than 5% at 5 years. To some extent, the margin issue is a sampling one, since technical limitations preclude the feasibility of complete microscopic analysis of the entire lumpectomy specimen surface area. If the margin sampling catches a single focus where a tumor abuts the edge of an otherwise widely negative lumpectomy specimen, this probably identifies a breast with a lower microscopic tumor burden compared to a lumpectomy specimen where multiple foci of cancer cells approach several aspects of the lumpectomy surface. As summarized by Gould and Robinson, variation between pathologists in the processing, interpretation, and reporting of margins may also influence results.

Extensive Intraductal Component

The extent of DCIS involved with an invasive breast cancer was initially analyzed as a predictor of local...
recurrence by Schnitt et al\textsuperscript{62} from the Joint Center for Radiation Therapy (JCRT) in 1984. For 231 patients treated with BCT between 1968 and 1978, the overall 5-year LR rate was 11%; for 19 patients found on pathology review to have had a less-than-complete excisional resection, LR occurred in 64%. The investigators excluded these incompletely resected patients and analyzed local recurrence as a function of DCIS within the primary tumor and in adjacent tissue. DCIS within the primary tumor was stratified as absent, slight (less than 25% of tumor area), moderate (25% to 50%), and marked (more than 50%). Five-year LR was 15% for the combined moderate and marked subset, and 1% for the combined absent and slight subset ($P = .004$). For patients with DCIS present in adjacent tissue, the LR rate was 17% and there were no recurrences if adjacent tissue was DCIS-free ($P = .002$). Nearly one third of evaluated cases had the combination of moderate/marked DCIS within the primary tumor as well as DCIS present in adjacent tissue; this subset had a 5-year LR rate of 23% compared to 1% for all other cases ($P = .001$).

The extensive intraductal component (EIC) has since come to be accepted as a significant risk factor for local recurrence and is commonly defined as tumors having at least 25% DCIS within the primary lesion, as well as DCIS present in adjacent breast tissue. As demonstrated by Holland et al,\textsuperscript{63} EIC is a marker for patients with a diffuse microscopic cancer burden within the breast, a feature that hinders efforts to obtain margin control, and limits the likelihood of successful breast XRT. Several investigators have confirmed the increased local failure rates (averaging 25% at 5 years) in BCT cases characterized by the presence of EIC.\textsuperscript{36,42,43,47,58,64-66}

Aggressive attempts to optimize margin control may compensate for the elevated risk expressed by an EIC-positive tumor. Schnitt et al\textsuperscript{67} reported outcome for 181 BCT cases from the JCRT where rigorous margin resection was possible; median follow-up was 86 months. The 5-year LR was 20% for EIC-positive tumors compared to 7% for EIC-negative lesions. However, subset analysis of the EIC-positive cases revealed that when the final microscopic margins were clear there were no recurrences, compared to 50% of the EIC-positive cases experiencing LR if the margins were more than focally positive. Similarly, Anscher et al\textsuperscript{68} and Smitt et al\textsuperscript{69} both found that EIC failed to be a significant predictor of local failure after controlling for margin status in multivariate analysis. The prevailing opinion, therefore, is that EIC-positive disease can be managed safely with breast preservation as long as margin control is achieved.

Young Age

Young breast cancer patients are frequently highly motivated to avoid the disfigurement of mastectomy by pursuing breast-sparing surgery. Unfortunately, several investigators have demonstrated that young age at diagnosis is associated with an increased risk of local recurrence following BCT.\textsuperscript{42,46,49,57,58,70,71} The definition of young age varies between studies, but the evidence for higher risk is most compelling in studies of breast cancer patients younger than 40 years at time of diagnosis.\textsuperscript{9,30,46,49,51,57,58,72,73} Since overall survival is not compromised by choice of breast preservation, young women should not be denied the option of BCT. They should, however, be informed of the potential for higher local failure rates, and efforts to optimize margin control should be aggressive.

### INTEGRATING MEDICAL ADVANCES INTO BCT PROGRAMS

#### Advanced Breast Imaging and BCT

Breast magnetic resonance imaging (MRI) is increasingly being used, and has been reported to have sensitivity approaching 100% in detecting breast cancer.\textsuperscript{74} It is therefore potentially valuable in ruling out multicentric lesions, defining the extent of a primary breast tumor, and it is now standard-of-care management in screening patients with axillary metastases from an occult primary for breast preservation.\textsuperscript{75-79} Tan et al,\textsuperscript{80} Fischer et al,\textsuperscript{81} and Lee et al\textsuperscript{82} reported that breast MRI findings altered breast cancer management in 18%, 14%, and 30% of cases, respectively. MRI has also been reported to be particularly useful in defining extent of invasive lobular cancers, and determining eligibility of these cases for breast-conserving surgery. Rodenko et al\textsuperscript{83} found that MRI-assessment of invasive lobular tumor size correlated with pathology findings in 85% of 20 cases, compared to mammography correlation in only 32%; Schelfout et al\textsuperscript{84} reported similar success with MRI guidance in cases of invasive lobular carcinoma.

Specialized forms of computed tomography (CT) scanning have been developed for breast imaging and are being used for distinguishing patients with unicentric disease from those with multicentric lesions in hopes of optimizing the selection of BCT candidates. Uematsu et al\textsuperscript{85} reported that use of three-dimensional helical CT images to plan lumpectomy volumes resulted in an approximate halving of the positive margin rate. This technique has also been reported to improve success with lumpectomies performed for invasive lobular cancer.

Breast ultrasonography has become a routine adjunct in preoperative breast cancer imaging, and its applications have been expanded to the intraoperative setting. Henry-Tillman et al\textsuperscript{86} reported that of 25 breast cancers excised with intraoperative ultrasound guidance, negative margins were obtained in 92%. Rahusen et al\textsuperscript{87} reported similar success with intraoperative ultrasound facilitating lumpectomy performance, and demonstrated its superiority over standard wire localization for achieving margin control in a prospective, randomized study of 49 breast cancer patients requiring image-guidance for lumpectomy. A major

disadvantage of intraoperative ultrasound is the requirement for either specialized surgical training or the availability and flexibility of a committed radiologist.

Sonographic imaging of the breast has typically been implemented as a targeted study of a breast segment, directed by some clinical or mammographic finding. Whole-breast ultrasound, however, is now being utilized for breast cancer screening in high-risk women because of its advantages in imaging dense tissue. A natural progression was therefore to evaluate the known cancer-containing breast for multicentric disease. Similar to studies of MRI to detect multicentric disease, whole-breast ultrasound has been used to evaluate breast cancer patients prior to definitive surgery, and reported findings have influenced therapy in approximately 15% of cases.88,89

Choosing between these imaging modalities can be a dilemma, but this will largely be resolved by availability of institutional resources. Comparative analyses of these various tests in newly diagnosed breast cancer patients suggest that ultrasound and breast MRI contribute similar added-value to a high-quality mammographic evaluation.88,90 Hata et al91 found that in a series of 183 breast cancers, MRI and breast ultrasound were equivalent diagnostic modalities for detecting breast tumors, but MRI was superior to ultrasound in detecting microscopic extent of disease and intraductal spread.

Integrating any of these specialized imaging modalities into the work-up of lumpectomy candidates can increase treatment costs, and expertise with the various technologies is not widely available. Furthermore, we are obligated to define the implications associated with whatever findings are generated. The latter issue, in particular, has not been completely addressed.92 As noted previously, postlumpectomy adjuvant radiation therapy is quite effective in controlling microscopic foci of multifocal/multicentric disease. Some of the tumor foci that are being identified through sophisticated breast imaging may represent sites of disease that would have been effectively treated with radiation. A clinical trial of BCT patients, designed to study this question prospectively with blinding from imaging results, would be a valuable but challenging contribution.

Genetic Testing for Hereditary Breast Cancer Susceptibility

Approximately 5% to 10% of newly diagnosed breast cancers in the United States are related to an inherited germline mutation, most frequently in the BRCA1 and BRCA2 genes. When the BRCA genes were first identified and sequenced nearly 10 years ago, it was commonly assumed that women harboring mutations in these genes who developed breast cancer would be ineligible for BCT. This perception was based on fears that the mutation would excessively increase the risk of local recurrence. Also, our limited understanding of the exact function of the normal BRCA protein in DNA damage response led to concerns that breast irradiation in mutation carriers would be associated with increased toxicity and risk of radiation-related second cancers. Available (albeit limited) data thus far have yielded somewhat inconsistent results, but suggest that BCT can safely be considered in selected BRCA mutation carriers, as long as the patient is counseled regarding the increased risk of new primary tumors bilaterally.

In one of the earliest studies, Robson et al93 evaluated 305 Ashkenazi breast cancer patients treated with BCT and identified 28 with BRCA mutations. A slightly increased relative risk of 1.79 was found for local recurrence in the BRCA carriers, although this difference was not statistically significant. More recently, Haffty et al94 reported long-term results (median follow-up, 12.7 years) of BCT in 105 patients with sporadic breast cancer compared to 22 patients with BRCA mutation–related breast cancers. Rate of ipsilateral breast cancer events was higher in the mutation carriers (49% v 21%; \( P = .001 \)). However, the majority of these events were probably second primaries, based on the prolonged time to detection (median time, 8 years), location remote from the original primary tumor, and different histology from the primary tumor in the majority of cases. It is also notable that the incidence and locations of ipsilateral lesions were not consistent with neoplastic transformations related to scatter radiation.

In a series reported by Pierce et al,95 73 BRCA mutation carriers undergoing lumpectomy and radiation therapy for early-stage breast cancer were matched to 219 women with presumed sporadic breast cancer who were also treated with BCT. With a median follow-up of approximately 5 years, there were no differences in the rates of local failure-free survival (96% for sporadic cancers v 99% for BRCA-associated cancers) or overall survival (91% for sporadic cancers v 86% for BRCA-associated cancers). No significant differences were seen in radiation toxicity either. An update of these findings with 10-year outcome was reported by Pierce et al96 at the 2003 San Antonio Breast Cancer Symposium.

All of these studies (summarized in Table 2) have demonstrated similarly high rates of new contralateral breast cancers in patients with BRCA mutations, averaging four- to five-fold higher than the rates of new contralateral breast cancer seen in sporadic breast cancer cases. This increased incidence of contralateral disease represents further support for the impression that the high rates of developing new ipsilateral breast tumors after BCT are related to inherent risk in the breast tissue as opposed to radiation-induced transformations.

Expanded BCT Eligibility

Neoadjuvant CTX and lumpectomy. Preoperative chemotherapy (CTX) is standard management for patients...
with locally advanced breast cancer, resulting in primary tumor response rates of approximately 80%, and progression of disease in only 2% to 3%,52,103,104 This sequence allows complete response overestimates the pathologic findings by approximately three-fold, and local recurrence rates tend to be higher when radiation therapy is the only local therapy delivered after the neoadjuvant CTX.120

The NSABP B-18 trial114-116 randomly assigned more than 1,500 women with stages I to IIIA breast cancer to receive preoperative versus postoperative chemotheraphy. This study demonstrated a statistically significant increase in BCT utilization for the preoperative CTX arm (68% v 60%). With a median follow-up of 72 months, the LR rates were 7.9% and 5.8% (no statistically significant difference) following BCT in the preoperative and postoperative chemotherapy arms, respectively. The conversion rate to BCT eligibility was greatest in the patients with T3 tumors at diagnosis. The NSABP also reported that local recurrence was somewhat higher in the subset of lumpectomy patients that were downstaged to become BCT-eligible in comparison to the BCT patients who were BCT candidates at presentation.115 However, this subset of downstaged BCT cases was predominantly made up of T3 tumors, and since LR is one manifestation of underlying tumor biology, it is not surprising that the more advanced-stage lesions would

<table>
<thead>
<tr>
<th>Study</th>
<th>Breast Cancer Patient Subsets</th>
<th>Median Follow-Up (years)</th>
<th>Local Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BCT</td>
</tr>
<tr>
<td>Verhoog, 199857</td>
<td>BRCA1: n=47 (18 BCT; 29 Mast)</td>
<td>NR</td>
<td>10% at 2 years</td>
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<td></td>
<td>Sporadic: n=186 (90 BCT; 96 Mast)</td>
<td>NR</td>
<td>14% at 5 years</td>
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<td></td>
<td>Robson, 199953</td>
<td>BRCA 1/2: n=35 (all BCT)</td>
<td>10</td>
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<tr>
<td></td>
<td>Sporadic: n=294 (all BCT)</td>
<td>7% at 10 years</td>
<td>NA 87% at 10 years</td>
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<td>Pierce, 200059</td>
<td>BRCA 1/2: n=71 (all BCT)</td>
<td>5</td>
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<tr>
<td></td>
<td>Sporadic: n=213 (all BCT)</td>
<td>4% at 5 years</td>
<td>NA 91% at 5 years</td>
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<td></td>
<td>Eccles, 200160</td>
<td>BRCA 1: n=75 (36 BCT; 39 Mast)</td>
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<td></td>
<td>Sporadic: n=436 (32 BCT; 31 Mast)</td>
<td>9</td>
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<td>Sporadic: n=162 (83 BCT; 79 Mast)</td>
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<td>Haffty, 200261</td>
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<td>14</td>
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<td>BRCA2: n=16 (all BCT)</td>
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<td>FH positive, BRCA negative:</td>
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<td>El-Tamer, 200464</td>
<td>BRCA1: n=30 (13 BCT; 17 Mast)</td>
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<td>BRCA2: n=218 (13 Mast)</td>
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<td></td>
<td>Sporadic: n=436 (220 BCT; 216 Mast)</td>
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<td>Seynaeve, 200465</td>
<td>BRCA 1/2: n= 26 (all BCT)</td>
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<td>Unspecified hereditary breast cancer: n=61 (all BCT)</td>
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<td>Sporadic: n=174 (all BCT)</td>
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<td>Rosbon, 200466</td>
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<tr>
<td></td>
<td>BRCA2: n=14 (all BCT)</td>
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Abbreviations: BCT, breast conservation therapy; Mast, mastectomy; OS, overall survival; NR, not reported; NA, not applicable; FH, family history.
*Survival rates reported for mastectomy and BCT cases combined.
†Overall survival rate estimated from survival graph; difference not significant.
‡In multivariate analysis, only age < 40 years was predictive of local failure, not BRCA status.

Several randomized, prospective studies have now been completed (Table 3) which prove the oncologic safety of neoadjuvant CTX in early-stage as well as locally advanced breast cancer, with the concurrent demonstration that tumor downstaging does indeed improve eligibility for BCT without increasing local recurrence rates.106-116 A surgical component in the multidisciplinary care of these patients is essential, as the clinical assessment of...
have higher local failure rates regardless of surgery type and treatment sequence. Also, radiation boost doses were not consistently used in the lumpectomy patients, and tamoxifen therapy was restricted to patients older than 50 years. Both of these interventions might have influenced local control in downstaged tumors. Lastly, the NSABP requires that only margin-negative lumpectomies be free of any tumor cells at the inked edge; a more aggressive approach to margin control might be necessary for lumpectomies in tumors that have been downsized by preoperative CTX.

Induction CTX is a reasonable and safe treatment approach for patients with breast cancer of any stage if the clinician is certain that chemotherapy would be recommended in the postoperative setting. The risk of overtreatment can be minimized by obtaining multiple diagnostic core biopsy specimens to confirm that a lesion is predominantly invasive, as CTX is clearly inappropriate therapy for large-volume/palpable DCIS tumors or DCIS with microinvasion. Patients presenting with multiple tumors or extensive calcifications on initial mammogram should be counseled that preoperative CTX will not convert them to BCT eligibility, regardless of the extent of primary tumor shrinkage. Estimation of treatment response tends to be more challenging with invasive lobular cancers as well.121,122 If the tumor is not associated with any microcalcifications, then a radio-opaque clip should be inserted (preferably under ultrasound guidance) either prior to delivery of the neoadjuvant CTX or within the first couple of cycles. In the event that the patient has a complete clinical response to the preoperative CTX, this clip will serve as the target for subsequent mammography-assisted wire localization lumpectomy. Lesions associated with microcalcifications have an inherent localization target.

Imaging with ultrasound and/or mammogram can be repeated after a couple of CTX cycles to evaluate tumor response. A decision may be made to switch the patient over to a non–cross-resistant chemotherapy regimen at this point if the tumor is failing to respond adequately. Alternative imaging modalities, such as CT,123,124 MRI,125-128 and PET129,130 scanning have also been proposed for monitoring CTX response. Inconsistent results have left physical examination, mammography, and ultrasound as the mainstay modalities for monitoring tumor response.

Complete breast imaging should be repeated after all preoperative CTX cycles have been delivered, to facilitate final surgical planning. The mammogram should be studied for interval appearance of diffuse calcifications that may accumulate during treatment, or that may be unmasked as the primary tumor density responds to treatment. Plans for breast-preserving surgery may proceed if there was no evidence of multicentric disease at presentation and if the tumor is resectable by lumpectomy after the neoadjuvant treatment.

**BCT for subareolar tumors and Paget’s disease.** Tumors involving the subareolar tissue and/or nipple (eg, Paget’s disease of the nipple) have previously been considered relative contraindications to BCT because of the need for nipple removal. However, if disease appears to be confined to a central unifocal area, without diffuse microcalcifications, and if margin negativity can be achieved, then performing a central segmentectomy is a reasonable approach. The patient can undergo elective nipple-areolar reconstruction following completion of breast irradiation, if she so desires. The safety of the breast-sparing approach in Paget’s disease has been reported by Pierce et al31 in a multicenter series of 30 patients revealing an 8-year disease-free survival of 95%.

### Table 3. Randomized Studies of Neoadjuvant Versus Adjuvant Chemotherapy for Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Accrual Years</th>
<th>No. of Patients</th>
<th>Stages</th>
<th>Median Follow-Up (months)</th>
<th>BCT Rate (%)</th>
<th>Local Recurrence After BCT (%)</th>
<th>Overall Survival at Median Follow-Up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instut Bergonie106,107</td>
<td>1985-1989</td>
<td>272</td>
<td>II-IIA</td>
<td>124</td>
<td>63.1</td>
<td>0</td>
<td>55*</td>
</tr>
<tr>
<td>Institut Curie106,107</td>
<td>1983-1990</td>
<td>414</td>
<td>I-IIIA</td>
<td>66</td>
<td>82</td>
<td>77</td>
<td>55*</td>
</tr>
<tr>
<td>Royal Marsden111-113</td>
<td>1990-1995</td>
<td>309</td>
<td>I-IIIB</td>
<td>48</td>
<td>89</td>
<td>78</td>
<td>60*</td>
</tr>
<tr>
<td>NSABP114,116</td>
<td>1988-1993</td>
<td>1,523</td>
<td>II-III</td>
<td>108</td>
<td>60</td>
<td>68</td>
<td>69*</td>
</tr>
<tr>
<td>EORTC117</td>
<td>1991-1999</td>
<td>698</td>
<td>II-III</td>
<td>56</td>
<td>37</td>
<td>21</td>
<td>69*</td>
</tr>
<tr>
<td>ECTO118</td>
<td>2001</td>
<td>892</td>
<td>II-III</td>
<td>23</td>
<td>71</td>
<td>35</td>
<td>80*</td>
</tr>
<tr>
<td>ABCSG119</td>
<td>1991-1996</td>
<td>423</td>
<td>IIIB</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: BCT, breast conservation therapy; PreOp, preoperative; PostOp, postoperative; CTX, chemotherapy; XRT, radiation; L, lumpectomy; ALND, axillary lymph node dissection; NA, not applicable; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organisation for Research and Treatment of Cancer; ECTO, European Cooperative Trial in Operable Breast Cancer; ABCSG, Austrian Breast and Colorectal Cancer Study Group.

*Rate estimated from graph.
†Local recurrence rates reported for lumpectomy and mastectomy patients combined.
‡Overall survival rate at 9 years.
§Recurrence and survival rates not reported, but relapse-free survival noted to be lower in neoadjuvant CTX arm, while overall survival similar for the two study arms.
Lumpectomy for multiple breast tumors. Early studies of lumpectomy for patients with multiple tumors revealed rates of local failure in excess of 20%, leading to this feature being widely considered to represent a contraindication to BCT.132-134 More recent studies, however, with closer attention to margin control, have demonstrated markedly improved outcome, as shown in Table 4. The generally accepted approach is that BCT can be attempted in these cases as long as the tumors can be encompassed within a single margin-negative lumpectomy specimen, and with a cosmetically acceptable volume of residual breast tissue.

Lumpectomy for LR after BCT. A true local recurrence of breast cancer following prior lumpectomy and breast XRT would be characterized by location in the vicinity of the lumpectomy bed, and histology similar to the initial tumor. Second primary lesions are more likely to occur at peripheral sites remote from the initial cancer, frequently have a different microscopic pattern, and develop after a more prolonged interval. Numerous studies have shown that the true LR is a poor prognostic feature, especially if it is invasive rather than in situ, large, associated with skin involvement, or is detected after a short disease-free interval.

Salvage mastectomy is currently standard-of-care for both in-breast recurrences and new ipsilateral primary breast cancers. The rationale for this approach is related to concerns regarding the biologic implications of a breast that continues to demonstrate tumorigenic potential, and to uncertainties about local management with minimal toxicity in a breast that has already received therapeutic chest wall irradiation. On the other hand, it can be reasonably argued that a repeat attempt at breast conservation may not necessarily threaten overall survival. Local recurrence is frequently viewed as an indicator of underlying tumor biology and not a source of metastatic disease. Improvements in breast imaging capable of detecting recurrence earlier, as well as more effective systemic therapies and innovative radiation delivery systems, may obviate the need for completion mastectomy if the breast can accommodate another lumpectomy.

One of the earliest experiences with repeat lumpectomy in the setting of LR following prior lumpectomy and XRT was reported by Recht et al in 1989. In this study of 90 LR patients from the JCRT, one patient refused salvage mastectomy and was therefore managed with wide local excision followed by iridium implantation; she died disease free 6 years later. Since that time, several other investigators have reported their experiences with breast-sparing procedures (either with or without additional radiation therapy) in the management of recurrent cancer (Table 5). Advances in radiation delivery systems (intra-cavitary, brachytherapy, intensity-modulated radiation therapy, etc) have motivated Kuerer et al to propose a pilot multicenter clinical trial of BCT in women who experience an LR after prior lumpectomy and standard breast XRT.

Techniques for Optimizing Success With Lumpectomy and Margin Control

Percutaneous diagnostic needle biopsy. Approximately 50% of open, surgical diagnostic biopsies that reveal cancer have positive margins necessitating re-excision if the patient wishes BCT. The re-excision lumpectomy is likely to worsen the ultimate cosmetic result because of the larger volume of breast tissue resected. Percutaneous needle biopsies are increasingly being used to establish a diagnosis of breast cancer, and several studies have demonstrated that lumpectomies are more likely to be margin-negative when the breast cancer diagnosis has been established via percutaneous needle biopsy as opposed to open surgical diagnostic biopsy. Core needle biopsies are more accurate than fine needle aspirates, and have the advantage of providing adequate tissue for determining whether or not the lesion has an invasive histology. Core needle biopsies can be done freehand for palpable lesions, or they can be performed with stereotactic mammography or ultrasound guidance for non-palpable lesions.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Median Follow-Up (months)</th>
<th>Margin Status</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leopold, 1989</td>
<td>10</td>
<td>64</td>
<td>Unclear; all lesions completely excised grossly</td>
<td>4</td>
</tr>
<tr>
<td>Kurtz, 1990</td>
<td>61</td>
<td>71</td>
<td>Positive/unknown: 39 cases; negative: 22 cases</td>
<td>Overall: 15</td>
</tr>
<tr>
<td>Wilson, 1993</td>
<td>13</td>
<td>71</td>
<td>Unclear; all lesions completely excised grossly</td>
<td>Negative margin cases: 1</td>
</tr>
<tr>
<td>Hartsell, 1994</td>
<td>27</td>
<td>53</td>
<td>Grossly negative in all cases; microscopically</td>
<td>1</td>
</tr>
<tr>
<td>Cho, 2002</td>
<td>15</td>
<td>77</td>
<td>Microscopically negative in all cases</td>
<td>0</td>
</tr>
<tr>
<td>Kaplan, 2003</td>
<td>36</td>
<td>98</td>
<td>Microscopically negative in all cases</td>
<td>1</td>
</tr>
<tr>
<td>Okumura, 2004</td>
<td>34</td>
<td>45</td>
<td>&gt; 2 mm in 21 cases; positive/close: 13 cases</td>
<td>1</td>
</tr>
</tbody>
</table>
Specimen handling and intraoperative margin assessment. Direct communication between the surgeon and pathologist is the first step in optimizing margin control. At a minimum, the lumpectomy specimen should be oriented by the surgeon (when logistically feasible, this should be done in the presence of the pathologist), and the tissue margins should be inked (multiple-color inks may facilitate the orientation of the specimen margins). While frozen-section analysis of multiple margins is notoriously time consuming and inefficient, touch-prep evaluations are being increasingly advocated as a rapid and reliable alternative.86,163-166

The touch-prep method (also called imprint cytology) is relatively straightforward, and is based on the premise that cancer cells are more adherent to a glass surface than benign cells. The pathologist touches a microscope slide against the lumpectomy surface, fixes, and then stains the slide with hematoxylin and eosin. Several surfaces can be evaluated fairly quickly in this fashion, and reported results have been very favorable. Cox et al163 found an accuracy of 97.3% in use of touch-preps for margin analysis, and Klimberg et al164 estimated an accuracy of 97.3% in use of touch-preps for margin analysis, revealing a false positive rate of 2.3%

for touch preps and 0% frozen sections; false negatives occurred in 1.2% of touch preps compared to 5.5% of frozen sections.

Other techniques that have been promoted in the effort to improve margin control with the initial lumpectomy have included recommendations to obtain shavings of the cavity margins for extended margin assessment,167 and performing mammograms of the lumpectomy specimens, as has been reported by Rubio et al168 for mastectomy specimens in cases of diffuse DCIS. For the latter strategy, the pathologist essentially sections the lumpectomy specimen "breadloaf"-style, and the specimens are aligned sequentially along the mammogram plate. The surgeon is then guided intraoperatively to cavity margins requiring wider excision by the demonstration of calcifications or tumor mass abutting any focal edge by mammography.

CONCLUSION

BCT is established as a safe oncologic treatment for breast cancer. A thorough understanding of risk factors for local recurrence and innovative maneuvers to achieve lumpectomy margin control is necessary for optimal application. Neoadjuvant CTX, as well as advances in breast imaging, cytopathology, and radiotherapy, have successfully expanded the number of lumpectomy-eligible cases.

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.
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