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REVIEW ARTICLE

Advances in Breast Conservation Therapy

Lisa A. Newman and Henry M. Kuerer

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From the Department of Surgery, University of Michigan, Ann Arbor, MI; and Department of Surgical Oncology, University of Texas, M. D. Anderson Cancer Center, Houston, TX.

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Address reprint requests to Lisa A. Newman, MD, MPH, FACS, Breast Care Center, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109; e-mail: lanewman@umich.edu.

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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[1] 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,[10] 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,[11,12] with rates ranging from less than 10% to 45%. Factors associated with increased likelihood of breast preservation include young age[13-16]; treatment in the northeast compared to southern regions[14,16,17]; affluent socioeconomic status[14]; and treatment in metropolitan areas associated with a cancer center[14] or teaching hospital.[15,17] Recently, Lucci et al[18] presented provocative data suggesting that the excessive mastectomy rates in the United States might also be related to the third party payors' 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,[2] 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[2,19-23] have revealed comparable survival rates for these arms, leading to the widespread belief that adjuvant XRT does not contribute to

Table 1. Randomized Trials Comparing Mastectomy and BCT

Trial	Accrual Years	No. of Patients	Maximum Tumor size (cm)	Minimum Lump Margin	Median Follow-Up (years)	OS (%)		LR/IBTR (%)	
						Mastectomy	BCT	BCT	Mastectomy
NSABP B-06[2]	1976-1984	1851	4	Microscopically free at inked edge	20	47	Lump, 46	39.2	10.2
							Lump + XRT, 47	14.3	
Milan Cancer Institute[3]	1973-1980	701	2		20	58.8	58.3	8.8	2.3
NCI[4]	1979-1987	237	5	Grossly negative	18.4	58	54	22*	0*
EORTC[5,6]	1980-1986	868	5	Grossly negative	13.4	66	65	20	12
Institut Gustav Roussy[7]	1970-1982	179	2		10	79	78	4	NR
DBCCG[8]	1983-1989	905	5	Grossly negative	6	82	79	NR	NR
EORTC and DBCCG (pooled results)[9]	1980-1989	1,772	5	Grossly negative	9.8	67	67	9	10

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.

survival. This concept has recently been challenged, however, on the basis of established outcome benefits associated with postmastectomy XRT in high-risk patients[24]; 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,[25] where results were pooled from all prospective, randomized clinical trials of lumpectomy alone versus lumpectomy and breast 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[26] 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 prior to delivery of 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[27-29] 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.[27,28]

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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 tumor foci 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.

Retrospective, prospective, and case-control studies have now shown that invasive lobular cancers[30-35] and cases of LCIS coexisting with an invasive cancer[36-38] 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[39] and infiltrating tumors coexisting with LCIS[40] have an increased risk of in-breast events, but in both scenarios the excess breast events tend to occur over a protracted follow-up. This suggests an increased long-term risk of developing new primary breast lesion.

Margin Status

The margin is characterized as the closest microscopic distance between the inked lumpectomy tissue edge and any cancerous tissue (invasive or ductal carcinoma in situ [DCIS]). Obtaining a negative lumpectomy margin is considered a basic prerequisite for standard-of-care BCT.[41] The conceptual goal is to resect the clinically evident cancer, with the expectation that subsequent radiation therapy will control residual foci of occult microscopic disease present elsewhere in the breast. Microscopic disease resulting from a positive margin is more problematic because theoretically, cancer cells entrapped in the relatively hypoxic environment of the lumpectomy scar bed will be resistant to radiation therapy. Furthermore, inability to achieve negative margins may be a marker of an excessive tumor burden in the treated breast. Numerous studies[33,42-51] have correlated lumpectomy margin status with risk of local recurrence (LR); these are reviewed in detail elsewhere.[52,53]

Although margin status has been repeatedly (but not invariably) associated with local control in conservatively treated breast cancer, there is no universally accepted definition for the optimal tumor-free margin. A common approach 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[54-56] 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% *v* 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.[43,48,57] In general, a microscopic margin of at least 2 mm seems to insure reasonable likelihood that that local failure rates will be less than 5% at 5 years.[58-60] 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,[61] 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

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recurrence by Schnitt et al[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,[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.[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[67] reported outcome for 181 BCT cases from the JCRT where rigorous margin re-evaluation 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[68] and Smitt et al[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.[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.[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.[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.[75-79] Tan et al,[80] Fischer et al,[81] and Lee et al[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[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[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[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[86] reported that of 25 breast cancers excised with intraoperative ultrasound guidance, negative margins were obtained in 92%. Rahusen et al[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

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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 al[91] 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 al[93] 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 al[94] 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 al[96] 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

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Table 2. Selected Studies of BCT in Patients With *BRCA1/BRCA2* Mutations

Study	Breast Cancer Patient Subsets	Median Follow-Up (years)	Local Recurrence (%)		OS (%)
			BCT	Mast	
Verhoog, 1998[97]	BRCA1: n=47(18 BCT; 29 Mast)	NR	10% at 2 years 14% at 5 years	NR	78% at 2 years* 63% at 5 years*
	Sporadic: n=186(90 BCT; 96 Mast)	NR	9% at 2 years 16% at 5 years	NR	88% at 2 years* 69% at 5 years*
Robson, 1999[93]	BRCA 1/2: n=35 (all BCT)	10	22% at 10 years	NA	72% at 10 years
	Sporadic: n=294 (all BCT)		7% at 10 years	NA	87% at 10 years
Pierce, 2000[95]	BRCA 1/2: n=71 (all BCT)	5	2% at 5 years	NA	86% at 5 years
	Sporadic: n=213 (all BCT)	5	4% at 5 years	NA	91% at 5 years
Eccles, 2001[98]	BRCA 1: n=75 (36 BCT; 39 Mast)	6	17	10	80% at 5 years*†
	FH positive, BRCA status unknown: n=67 (36 BCT; 31 Mast)	9	28	19	90% at 5 years*†
	Sporadic: n=162 (83 BCT; 79 Mast)	7	24	17	80% at 5 years*†
Haffty, 2002[94]	BRCA 1/2: n= 22 (all BCT)	13	49	NA	NR
	Sporadic: n=105 (all BCT)	14	21	NA	NR
Pierce, 2003[96]	BRCA 1/2: n=170 (all BCT)	8	13	NA	No significant difference
	Sporadic: n=469 (all BCT)	6	9	NA	No significant difference
Delaloge, 2003[99]	BRCA1: n=37 (all BCT)	10	9‡	NA	80
	BRCA2: n=16 (all BCT)	10	37‡	NA	76
	FH positive, BRCA negative: n=43 (all BCT)	10	12‡	NA	88
El-Tamer, 2004[100]	BRCA1: n=30(13 BCT; 17 Mast)	8	23	6	91%, 5-year OS*
	BRCA2: n=21(8 BCT; 13 Mast)	5	13	0	91%, 5-year OS*
	Sporadic: n=436(220 BCT; 216 Mast)	2	6	4	95%, 5-year OS*
Seynaeve, 2004[101]	BRCA 1/2: n=26 (all BCT)	6	15	NA	Mortality hazard, 1.76 (95% CI, 0.72 to 4.30) compared to sporadic cases
	Unspecified hereditary breast cancer: n=61 (all BCT)	6	25	NA	Mortality hazard, 0.88 (95% CI, 0.42 to 1.87) compared to sporadic cases
	Sporadic: n=174 (all BCT)	6	12	NA	Comparison mortality hazard, 1.00
Robson, 2004[102]	BRCA1: n=43 (all BCT)	10	12	NA	67
	BRCA2: n=14 (all BCT)	10			
	Sporadic: n=440 (all BCT)	10	8	NA	86

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.

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 for improved operability and provides an in vivo assessment of chemosensitivity. However, concerns that downsized tumors might leave a field of satellite nodules rather than shrink concentrically led to skepticism regarding BCT eligibility. This uncertainty motivated Singletary et al[105] to conduct a feasibility study of BCT in 143 locally advanced breast cancer patients, all of whom received induction CTX. Meticulous pathology review of their mastectomy specimens revealed that 23% had been converted to BCT candidates by virtue of having residual unifocal tumors no larger than 4 cm and complete resolution of skin changes.

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 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 trial[114-116] randomly assigned more than 1,500 women with stages I to IIIA breast cancer to receive preoperative versus postoperative chemotherapy. 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

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

Study	Accrual Years	No. of Patients	Stages	Median Follow-Up (months)	BCT Rate (%)		Local Recurrence After BCT (%)		Overall Survival at Median Follow-Up (%)	
					PreOp CTX	PostOp CTX	PreOp CTX	PostOp CTX	PreOp CTX	PostOp CTX
Institut Bergonie[106,107]	1985-1989	272	II-IIIA (T>3 cm)	124	63.1	0	XRT: 34 L/ALND/XRT: 23	NA	55*	55*
Institut Curie[108-110]	1983-1990	414	IIA-IIIA	66	82	77	24	18	86	78
Royal Marsden[111-113]	1990-1995	309	I-IIIB	48	89	78	3†	4†	80*	80*
NSABP[114-116]	1988-1993	1,523	I-IIIA	108	60	68	10.7	7.6	69‡	70‡
EORTC[117]	1991-1999	698	I-IIIA	56	37	21	NR	NR	NR	NR
ECTO[118]	2001	892	I-IIIA	23	71	35	NR	NR	NR	NR
ABCSG[119]	1991-1996	423	I-IIIB	NR	67	60	NR§	NR§	NR§	NR§

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.

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 PET[129,130] 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 al[131] in a multicenter series of 30 patients revealing an 8-year disease-free survival of 95%.

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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,[139-141] especially if it is invasive rather than in situ, large,[142-144] associated with skin involvement,[142,145,146] or is detected after a short disease-free interval.[140,147-149]

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.[150] 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 (intracavitary, brachytherapy, intensity-modulated radiation therapy, etc) have motivated Kuerer et al[158] 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.[159] 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[160-162] 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 nonpalpable lesions.

Table 4. Selected Studies of Breast Conservation Therapy in Patients With Multiple Primary Tumors

Study	No. of Cases	Median Follow-Up (months)	Margin Status	Local Recurrence	
				No.	%
Leopold, 1989[133]	10	64	Unclear; all lesions completely excised grossly	4	40
Kurtz, 1990[132]	61	71	Positive/unknown: 39 cases; negative: 22 cases	Overall: 15 Negative margin cases: 1	25 5
Wilson, 1993[134]	13	71	Unclear; all lesions completely excised grossly	3	23
Hartsell, 1994[135]	27	53	Grossly negative in all cases; microscopically positive in 4 cases	1	3.7
Cho, 2002[136]	15	77	Microscopically negative in all cases	0	0
Kaplan, 2003[137]	36	98	Microscopically negative in all cases	1	2.8
Okumura, 2004[138]	34	45	> 2 mm in 21 cases; positive/close: 13 cases	1	2.9

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Table 5. Studies Reporting Breast-Preserving Management for Local Recurrence After BCT for Breast Cancer

Study	No. of Cases	Local Therapy for Recurrent Breast Tumor	Median Time to LR After Initial BCT for Cancer	Median Size of Recurrent Breast Tumor (cm)	Median Follow-Up After Recurrence	LR (%)*	Survival*
Recht, 1989[150]	3	Wide excision (two patients); wide excision + iridium-192 implant (one patient)	NR NR	NR NR	NA NA	0 0	NED at 14 and 25 months Expired NED at 72 months
Kurtz, 1991[151]	50	Wide excision	NR	< 2	51 months	32	67% at 5 years
Abner, 1993[152]	16	Wide excision	NR	NR	NR	31	38% at 39-99 months
Maulard, 1995[153]	38	Tumorectomy + 30 Gy brachytherapy (n = 15)	29 months	2.4 (mean)	48 months (mean)	26	61% at 5 years
		60-70 Gy brachytherapy (n=23)	35 months	3.9	36 months (mean)	17	50% at 5 years
Dalberg, 1998[154]	14	Wide excision	4 years	NR	6 years	50	NR
Voogd, 1999[142]	20	Wide excision (n=13) Wide excision + irradiation (n=7)	3.6 years	< 1	NR	NR	NR
Salvadori, 1999[155]	57	Wide excision	> 4 years	≤ 1	73 months	14	85%
Deutsch, 2002[156]	39	Wide excision + 50 Gy in 25 fractions	63 months	NR	52 months	21	78% at 5 years
Resch, 2002[157]	17	Wide excision + pulse dose rate brachytherapy	50 months	1.5 (mean)	59 months	24	59% disease-free at 59 months

Abbreviations: LR, local recurrence; BCT, breast conservation therapy; NR, no response; NA, not applicable; NED, no evidence of disease.
*Refers to outcome after management of initial local recurrence; survival refers to live patients (overall survival) at median follow-up unless otherwise specified.

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 straight forward, 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 al[163] found an accuracy of 97.3% in use of touch-preps for margin analysis, and Klimberg et al[164] estimated a margin assessment sensitivity at 100%. In a subsequent review of 701 lumpectomy specimens evaluated at the Moffitt Cancer Center (Tampa, FL), Cox et al[165] reported a local recurrence rate of 2.7% for women whose lumpectomy margins were evaluated by touch-prep cytology, compared to 14.6% in referral cases whose margins were analyzed by conventional histopathology. A subset of 347 Moffitt Cancer Center cases had correlation between frozen section, touch-prep cytology, and permanent histopathology 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 specimen serial sections, as has been reported by Rubio et al[168] 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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