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CONTINUING EDUCATION– BREAST ONCOLOGY

The Landmark Series:Breast Conservation Trials (including oncoplastic breast surgery)

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ABSTRACT Significant progress has been made in the treatment and outcome of breast cancer. Some of the most dramatic strides have been in the surgical management of breast cancer. Breast-conserving therapy (BCT), including wide local excision of the tumor followed by irradiation, has become a standard treatment option for women with early-stage invasive breast cancer. Large cooperative group trials have contributed to the paradigm shift from mastectomy to BCT. This review reports the landmark BCT trials that provided the data for current surgical practices. The review also describes the body of literature contributing to the increasing use of oncoplastic techniques for patients undergoing BCT.

For decades, Halsted's radical mastectomy was the surgical standard of care for patients with breast cancer. Some surgeons, including George "Barney" Crile, believed that these operations were too aggressive. From the late 1950s, surgeons at the Cleveland Clinic performed modified radical mastectomies, simple mastectomies, and partial mastectomies, with survival outcomes equivalent to those of more radical surgery or better (Fig. 1).[1]

In 1991, the National Institute of Health Consensus Conference endorsed breast-conserving therapy (BCT) as the preferred treatment for early-stage breast cancer.[2] This endorsement was based on evidence demonstrating that women undergoing BCT for early-stage breast cancer have equivalent survival outcomes compared with mastectomy.[3] Since then, additional studies and follow-up analyses have again confirmed equivalent survival outcomes between the two surgical methods.[4–10] These findings led to the widespread use of BCT as the treatment for early-stage breast cancer during the past two decades and the adoption of BCT as an accepted surgical approach for early-stage breast cancer in the National Comprehensive Cancer Network (NCCN) guidelines. Oncoplastic surgery is a newer surgical option that focuses on preserving a woman's breast form after resection of tumor.

The first descriptions of oncoplastic surgery arose in Europe by Audretsch et al.[11] and Clough et al.[12] Since then, many definitions and classifications have arisen, but in general they have stayed central to the theme that oncoplastic surgery represents resection of breast cancer using plastic surgery techniques to maintain an aesthetically appropriate breast shape.

This article reviews the preeminent studies that serve as the foundation for changes in the surgical approach from mastectomy to BCT. It must be noted that few high-quality, large-scale experimental trials have evaluated oncoplastic techniques. Therefore, this report also includes the landmark observational studies that have contributed to the evolution of these techniques in BCT.

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP) B-06

The NSABP B-06 trial opened in 1976 with the purpose of evaluating the efficacy of BCT for women with stage 1 or 2 breast tumors 4 cm or smaller in diameter.[13] By 1984, when the trial closed to accrual, 2163 women had been enrolled in the study and randomly assigned to one of three treatment arms: total mastectomy, lumpectomy, or lumpectomy followed by whole-breast irradiation. Axillary

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FIG. 1 The progression of breast surgery approaches over time from the (**a**) Halsted mastectomy to (**b**) skin-sparing simple mastectomy to (**c**) oncoplastic breast reduction.

lymph node dissection was performed regardless of the treatment arm. The patients in the lumpectomy arms of the study were required to have pathologically negative margins ("no tumor on ink"), and 10 % of the patients randomly assigned to lumpectomy actually underwent mastectomy because of histologically positive margins.[13]

The three groups did not differ significantly in terms of disease-free survival, distant disease-free survival, or overall survival. This was true at both the initial 5-year follow-up evaluation[14] and the long-term 20-year follow-up assessment.[4] The ipsilateral in-breast recurrence rate was 14% among the women who underwent lumpectomy and

breast irradiation compared with 39% among the women who underwent lumpectomy without irradiation ($p < 0.001$).[4]

One important observation from this trial was that a substantial number of recurrences happened more than 5 years after surgery, supporting the need for long-term follow-up evaluation of breast cancer survivors. In addition, this trial was conducted at a time when only women with positive axillary lymph nodes received adjuvant chemotherapy and the regimens were less effective than the current regimens, which currently are more personalized and include targeted therapies. Despite these limitations in adjuvant treatment at the time B-06 was conducted, the finding that lumpectomy followed by breast irradiation (BCT) is appropriate and equivalent to total mastectomy for women with early-stage breast cancer has remained durable over time.

MILAN CANCER INSTITUTE TRIAL

The Milan Cancer Institute trial enrolled 701 women from 1973 to 1980 and randomized them to either radical mastectomy or breast-conserving surgery followed by whole-breast radiation therapy.[5] Two important factors distinguishing this trial from NSABP B-06 were that all the women enrolled had tumors 2 cm in size or smaller and those treated with breast-conserving surgery underwent quadrantectomy. During quadrantectomy, a long radial incision is made, and the tumor is removed together with 2 to 3 cm of normal tissue, skin, and pectoral fascia along with the pectoralis minor muscle.

In this trial, adjuvant chemotherapy was administered to patients with positive axillary nodes, but only to those enrolled after 1976. Follow-up assessment at 20 years showed an ipsilateral in-breast recurrence rate of 8.8% for the women who underwent BCT versus a chest wall local recurrence rate of 2.3% for the women who underwent radical mastectomy.[5] The all-cause mortality rate at 20 years was 41.7% for the women who underwent BCT versus 41.2% for the women who underwent radical mastectomy. The disease-specific mortality rate was 26.1% for the BCT group and 24.3% for the radical mastectomy group.[5] Thus, the long-term survival rate was equivalent between the two groups, further supporting BCT for the surgical treatment of early-stage small breast cancers.

NATIONAL CANCER INSTITUTE (NCI) TRIAL

The NCI trial enrolled 237 patients between 1979 and 1987, randomizing them to either modified radical mastectomy or lumpectomy with axillary dissection and adjuvant whole-breast irradiation.[6] Local or regional recurrences were defined as recurrences in the ipsilateral supraclavicular, axillary, or internal mammary nodal regions as well as chest wall disease in the mastectomy group, or as inoperable recurrence of breast cancer in the BCT group. If a patient in the BCT group had a recurrence in the breast that was successfully treated by mastectomy, it was not considered a local or regional recurrence unless it was followed by a further local or regional event.

Follow-up assessment at 10 years showed an overall survival rate of 75% for the patients in the mastectomy group and 77% for the patients in the BCT group. Disease-free survival was 69% for the mastectomy group and 72% for the BCT group.[6] The local regional recurrence rate was 10 % for the mastectomy group at 10 years and 5% for the BCT group, but this involved the exclusion of patients successfully treated by mastectomy who were censored from the analysis. Importantly, the 10-year disease-free survival rate for the salvage mastectomy subpopulation was 67%, which was not significantly different from that for women assigned to lumpectomy plus irradiation who did not experience a local regional recurrence.[6]

The NCI trial included all patients with T1 or T2 tumors (size $\leq$5 cm), and 8% of the patients in both groups had tumors larger than 4 cm. Thus, this population had larger tumors than the patients in the B-06 trial or the Milan trial. In addition, the NCI trial required only gross tumor excision in the BCT group, and a second excision was allowed to achieve this. The inclusion criteria of larger tumors and surgical margin status may account for the higher in-breast recurrence rate for the BCT patients in the NCI trial than in other trials.[8] After nearly 20 years of follow-up evaluation, overall survival or disease-free survival did not differ between the two groups (respectively 58% and 67% in the mastectomy group vs 54% and 63% in the BCT group).[7]

INSTITUT GUSTAVE-ROUSSY (IGR) TRIAL

The IGR trial enrolled 179 patients between 1972 and 1979 with invasive breast cancers up to 2 cm in size, randomizing them to either modified radical mastectomy or lumpectomy with a 2-cm margin of normal glandular tissue.[8] All the patients also underwent axillary lymph node dissection. For the patients with positive axillary nodes, an additional randomization was performed between lymph node irradiation and no regional lymph node irradiation.

The 5-year results were published in 1984[15] and the 10-year results in 1989.[16] After 15 years of follow-up evaluation, the two groups did not differ in terms of overall survival, distant metastasis, contralateral breast cancer, new primary malignancy, or locoregional recurrence rates.[8] The 15-year rates for first cause of failure were 9% for locoregional recurrence and 16 % for distant recurrence in

the lumpectomy group and 14 % for locoregional recurrence and 20% for distant recurrence in the mastectomy group.[8] Most of the recurrences developed within the first 10 years of follow-up evaluation.

THE DANISH BREAST CANCER COOPERATIVE GROUP (DBCG) TRIAL

The DBCG trial enrolled 1153 women between the years of 1983 and 1989, with 905 of the women randomized to either breast-conserving surgery or mastectomy. The remaining 248 patients were allowed to choose their surgical approach.[9]

All the patients underwent axillary lymph node dissection. Adjuvant radiation therapy was administered to all the patients undergoing BCT and to those in the mastectomy group who had axillary lymph node involvement. The two treatment groups did not differ significantly in terms of 10-year recurrence-free survival (57.4% for the BCT group vs 61.7% for the mastectomy group) or 20-year overall survival (53.7% for the BCT group vs 49.1% for the mastectomy group). This was true for both the overall cohort and the randomized subgroups.[9] The pattern of recurrences did not differ significantly between the two groups, but the authors did observe that new primary breast cancer was more common in the BCT group.

THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) 10801 TRIAL

From 1980 through 1986 in the EORTC 10801 trial, 902 patients with tumors up to 5 cm in size were enrolled and randomized to either modified radical mastectomy or lumpectomy with axillary lymph node dissection.[10] An attempted 1-cm margin of normal tissue was recommended for the lumpectomy group, but margins were not routinely inked to assess microscopic margins, and only gross macroscopic disease at the margins resulted in re-excision. The patients in both treatment arms underwent irradiation of the parasternal lymph node region if the tumors were centrally or medially located. Adjuvant chemotherapy was administered to all patients up to 55 years of age and to those with positive axillary lymph node metastases.[10]

After 10 years of follow-up evaluation, the two groups did not differ in terms of overall survival (66% for the mastectomy arm vs 65% for the BCT arm) or distant metastasis-free survival (66% for the mastectomy arm vs 61% for the BCT arm). However, locoregional recurrence differed significantly between the two groups at 10 years (12% for the mastectomy arm vs 20% for the BCT arm; $p = 0.01$).[10] The authors reported that the higher locoregional recurrence rates for the patients undergoing BCT appeared to be due to younger age, increased involvement of axillary lymph nodes, and larger tumor size. However, the overall small number of patients with locoregional recurrence precluded formal analysis. In addition to the authors' hypothesis, one potential confounder was the lack of microscopic margin assessment. Despite these limitations in this multicenter randomized trial, the survival rates were equivalent between the surgical treatment arms.

ONCOPLASTIC SURGICAL TECHNIQUES DURING BCT

Randomized controlled trials specifically examining oncoplastic surgery are scarce. As a result, current guidance for oncoplastic treatment decision-making is based on retrospective case-matched cohort comparison studies. Given that one part of oncoplastic surgery includes a partial mastectomy, this technique borrows from the randomized controlled trials demonstrating oncologic safety from the classic trials described earlier. Presumptively, the lack of a clear definition for oncoplastic surgery until recently may be the reason why so few randomized studies exist.

In 2019, The American Society of Breast Surgeons (ASBrS) defined oncoplastic surgery as "breast-conservation surgery incorporating an oncologic partial mastectomy with ipsilateral defect repair using volume displacement or volume replacement techniques with contralateral symmetry surgery as appropriate."[17] This consensus definition also came with a classification system describing level 1 volume displacement as resection that removes less than 20% of breast tissue, level 2 volume displacement as resection that removes 20% to 50 % of breast tissue, and volume replacement techniques as resections that remove more than 50% of breast tissue (Table 1).<T1> The paper underscored oncoplastic surgery as a form of breast conservation, noting that before this consensus definition and classification system, at least 30 definition articles had existed, with several of the definitions contradicting each other. Having a consensus definition therefore allowed appropriate communication of surgical technique, enabling the surgeon to communicate a plan to a patient, colleague, or trainee.

ONCOPLASTIC ONCOLOGIC OUTCOMES

Although survival benefits compared with mastectomy can be extrapolated as equivalent using the randomized controlled trials described earlier because an intrinsic nature of an oncoplastic operation includes a partial mastectomy, local and regional recurrence rates may differ. De Lorenzi et al.[18] published their case-matched cohort

TABLE 1 Oncoplastic surgery definitions

Oncoplastic surgery: a form of breast-conservation surgery that includes oncologic resection with a partial mastectomy, ipsilateral reconstruction using volume displacement, or volume-replacement techniques with possible contralateral symmetry surgery when appropriate	
Oncoplastic surgery classification	
Volume displacement	Examples
Level 1: <20% breast tissue removed	Local tissue rearrangement
	Crescent mastopexy
	Doughnut mastopexy
Level 2: 20% to 50% breast tissue removed	Circumvertical mastopexy design
	Reduction mammoplasty designs (including free nipple graft)
Volume replacement	Examples
>50 % breast tissue removed	Implant-based reconstruction
	Local/regional flap reconstruction: thoracodorsal artery perforator, etc

comparison study of larger cancers (T2) with a 7.4-year average follow-up period and found no statistically significant differences in local or regional recurrences between patients undergoing oncoplastic surgery and those undergoing mastectomy. Their overall and disease-free survival rates also were similar. The oncoplastic surgery arm had a higher rate of local recurrences than the mastectomy arm, which had a higher rate of regional recurrences, although the differences were not statistically significant.[18] These findings may be attributable to the fact that the remaining breast tissue after oncoplastic surgery could translate toward a trend of increased local recurrence. The adjuvant radiation in the oncoplastic arm compared with the mastectomy arm likely explains the lower regional recurrence trend after oncoplastic surgery.

POSITIVE MARGINS AFTER ONCOPLASTIC BCT

A rationale exists for a lower positive margin rate, especially when larger partial mastectomies are performed using level 2 volume displacement or volume replacement designs. Two large meta-analyses, by De La Cruz et al.[19] and Losken et al.,[20] describe a lower positive margin rate for oncoplastic surgery than for standard partial mastectomy. In examining 6011 patients from 55 different articles, De La Cruz et al.[19] noted a 9.8 % rate when oncoplastic surgery was performed for T1 and T2 breast cancers. Losken et al.[20] evaluated 62 publications of 8659 patients undergoing oncoplastic BCT and found that oncoplastic surgery group had a statistically lower positive margin rate (12 %) than the standard partial mastectomy group (21 %). The oncoplastic group included patients who underwent level 2 volume displacement ("oncoplastic reduction") and volume replacement ("oncoplastic flaps").

ONCOPLASTIC BCT COMPLICATION RATES

Prior authors have contributed to the growing techniques of oncoplastic breast surgery in terms of technique and complication rates.[21–24] Clough et al.[21] described a quadrant-by-quadrant atlas for oncoplastic surgery in 2010, categorizing specific techniques according to the location of the tumor in the breast. Compared with standard partial mastectomy, oncoplastic surgery tends to have a higher short-term complication rate, which occurs secondary to the more extensive dissection needed during surgery with an oncoplastic design. Jonczyk et al.[25] evaluated this in a National Surgical Quality Improvement Program (NSQIP) database analysis and demonstrated that the short-term overall complication rates for standard partial mastectomy were lower (2.25 %) than those for oncoplastic surgery (3.2%).

Well-designed, long-term comparison studies of oncoplastic surgery and standard partial mastectomy in comparable patient populations are needed. Newer methods to overcome defects created by large partial mastectomies have been described.[23,24] Losken et al.[24] compared 111 patients who underwent the newer auto-augmentation oncoplastic techniques with a standard oncoplastic group of 222 patients. These newer auto-augmentation techniques use an extended pedicle (e.g., an extended superomedial pedicle) or a secondary pedicle (e.g., an inferolateral segment of the Wise incision in addition to a primary pedicle). No statistically significant difference in overall complication rates was observed between the oncoplastic-only group (15.5%), the extended pedicle group (19.6%), and the secondary pedicle group (20 %).[24]

TABLE 2 Survival and recurrence rates for mastectomy and breast-conserving therapy from landmark trials[a]

Trial	Patients (*n*)	Mean follow-up (years)	OS (%)	DSS (%)	LRR (%)	DR (%)
NSABP B-06 (4)	2163	20	M (47)	M (49)	M 14.8)	M (22.4)
			L (46)	L (45)	L (17.5)[b]	L (24.9)
			L + R (46)	L + R (46)	L + R (8.1)	L + R (26.0)
Milan [5]	701	20	M (58.3)	M (73.9)	M (8.8)	M (24.3)
			L + R (58.8)	L + R (75.7)	L + R (2.3)	L + R (23.3)
NCI [6]	237	18	M (58)	M (67)	M (6.9)	M (23.3)
			L + R (54)	L + R (63)	L + R (22)[c]	L + R (24.8)
IGR [7]	179	15	M (64)	N/A	M (16.5)	M (20)
			L + R (72)	N/A	L + R (13.6)	L + R (13)
Danish [8]	1153	20	M (50.6)	M (59.5)	M (11.5)	M (18.7)
			L + R (57.8)	L + R (61.1)	L + R (8.4)	L + R (25.6)
EORTC [9]	902	13.4	M (66.1)	M (66.3)	M (12.2)	M (26.7)
			L + R (65.2)	L + R (60.5)	L + R (19.7)	L + R (26.8)

[a]All p value comparisons within cells are nonsignificant except where noted.

[b]$p < 0.001$ for lumpectomy alone vs lumpectomy with adjuvant irradiation

[c]$p = 0.001$

OS, overall survival; DSS, disease-specific survival; LRR, locoregional recurrence; DR, distant recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project B-06 trial; NCI, National Cancer Institute trial; IGR, Institut Gustave-Roussy trial; EORTC, European Organization for Research and Treatment of Cancer trial; M, mastectomy; L, lumpectomy alone without irradiation; L + R, lumpectomy with adjuvant irradiation

PATIENT-REPORTED OUTCOMES FOR ONCOPLASTIC BCT

Kelsall et al.[26] using a case-matched cohort comparison design, evaluated 286 patients undergoing oncoplastic surgery and compared them with 281 patients undergoing mastectomy and immediate reconstruction (both implant and autologous reconstruction). Using validated patient-reported outcomes (PROs), this study found that patients undergoing oncoplastic surgery had statistically higher body image scores and self-rated breast appearance scores than patients undergoing mastectomy and immediate reconstruction. Specifically, higher PROs were noted for the women with larger breasts, who presumptively benefited not only from the oncologic resection of cancer, but also from the symptomatic relief conferred by macromastia. Similarly, Chand et al.[27] compared 58 women who underwent level 2 volume-displacement oncoplastic surgery (oncoplastic mammoplasty) with 92 women who underwent mastectomy with autologous reconstruction using a latissimus dorsi miniflap design and found that those in the oncoplastic surgery group were significantly more satisfied with the shape and feel of their breast and less likely to report upper back pain. Finally, Stein and Zhang.[28] used the BREAST-Q, a validated questionnaire designed to evaluate the outcomes of reconstructive breast surgery from the patient perspective,[29] with both short- and long-term follow-up evaluation to show that patients undergoing oncoplastic surgery reported better PROs than those undergoing mastectomy with immediate reconstruction, specifically when asked about satisfaction with breasts and sexual well-being.

CONCLUSION

Breast-conserving therapy is widely accepted as an effective treatment option for patients with early-stage breast cancer, a disease that no longer requires radical surgery or significant associated morbidity. The shift away from mastectomy toward BCT saw its largest surge in the 1980s, initiated by the landmark trials described in this report. Although these landmark trials differed with respect to their size, the disease characteristics of the patients and the nuances of the surgical procedure all have demonstrated similar survival rates for the patients receiving BCT and those receiving the more extensive mastectomy approaches. Importantly, the survival equivalency has been durable for more than four decades. The minimization of surgical extent and preservation of cosmetic outcomes are the hallmarks of our modern approaches to the surgical treatment of breast cancer. The emergence of oncoplastic techniques extend these surgical goals while maintaining excellent oncologic outcomes.

THE FUTURE

This report describes the landmark trials that have transformed the surgical treatment of patients with early-stage breast cancer (Table 2). However, the paradigm shifts that have occurred between the Halsted radical mastectomy and BCT or oncoplastic BCT are unlikely to be terminal events in the surgical care of our patients with breast cancer. We continue to see innovation in this area, with percutaneous intact specimen excision, ablative techniques, and improvements in our neoadjuvant and adjuvant systemic and local therapies. Furthermore, more recent studies suggest that patients undergoing BCT may have better overall survival and disease-specific survival than those undergoing mastectomy.[30,31]

Future randomized trials are needed to investigate subgroups for which BCT may prove superior to mastectomy. The immediate future of breast-conserving surgery likely will focus on the increasing adoption of oncoplastic surgery and training models that allow for its spread. Ideally, collaboration between societies such as the American Society of Breast Surgeons and the American Society of Plastic Surgeons can create fellowship pathways to ensure that future oncoplastic surgeons master the appropriate techniques to make them both safe and capable in both the oncologic and reconstructive methods. Such a single surgeon model would allow several pathways (e.g., from general surgery or plastic surgery) into subspecialty breast oncoplastic training programs, which would benefit from the knowledge introduced by a multidisciplinary lineage.

Surgery remains the standard for women with early-stage breast cancer. However, what we currently consider to be unacceptable or unproven techniques may become the standard of care in the future because of ongoing and future landmark trials.

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