Breast-Conserving Therapy for Breast Cancer

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History of Lumpectomy

Essential to the surgical treatment of breast cancer is an understanding of the two critical objectives that have not varied in the last 50 years: (1) local control and (2) accurate staging. While survival may be improved with early detection, its accomplishment is only secured by providing excellent local control of the disease. Every surgeon understands that some cases, though detected early and treated effectively, will go on to metastasize in spite of excellent local control. This substantiates the claim that the disease is systemic in some cases at its earliest development. Therefore, a surgeon's skill and function in the treatment of the disease should be measured by the outcomes of local control and accuracy of staging.

William S. Halsted's description of the radical mastectomy was the great advance at the turn of the last century and remains the mainstay of surgical management for those uncommon cases today of locally advanced breast cancer. The advent of mammography and improved technology has increased the detection rates of very early breast cancer in many instances. Patient advocacy, through the committed efforts of patient advocates such as Rose Kushner, has also greatly helped with advancing breast cancer research funding and the development of a national screening program. Dr. Bernard Fisher, a surgeon, and his brother Dr. Edwin Fisher, a pathologist at the University of Pittsburgh, postulated that breast cancer at these earlier stages could be treated with the combination of local excision to negative margins and the addition of radiation therapy.

To prove this hypothesis, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial began in 1971. The trial compared women undergoing radical mastectomies to those obtaining total mastectomies, with and without radiation therapy. In 1977, the first results were published, which showed no difference in treatment failure or survival and, after 25 years, no difference in long-term outcomes [1, 2]. In 1976, the NSABP B-06 trial, which compared mastectomy to lumpectomy, showed that removing a small portion of the breast along with axillary lymph nodes and radiation therapy was just as

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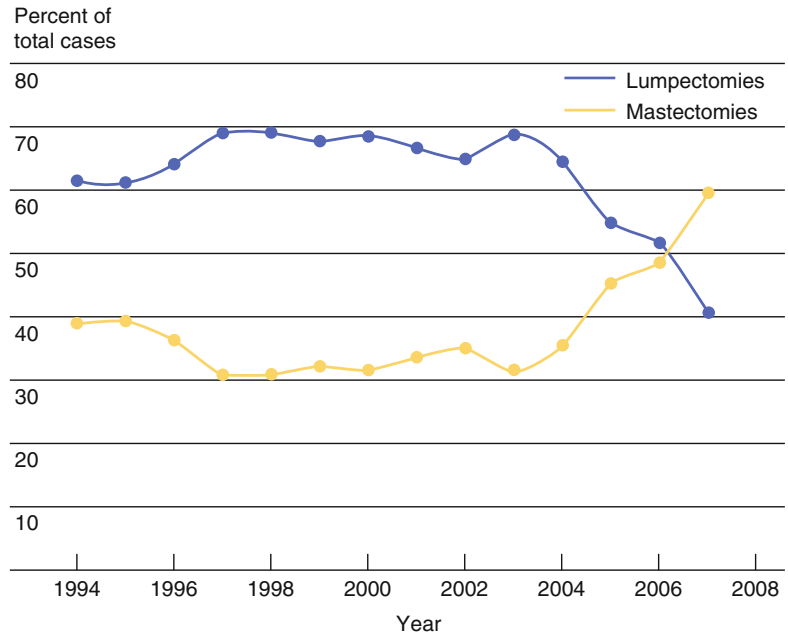

Fig. 13.1 Lumpectomy versus mastectomy (From McGuire et al. [5])

effective as mastectomy. After 20 years of follow-up of the B-06 trial, no significant difference has been found in overall or disease-free survival between those that underwent total mastectomy and lumpectomy [1–3]. Based on the NSABP B-06 trial, breast conservation therapy decreases local recurrences from 39 to 14 % [4].

Lumpectomy, also known as wide local excision or partial mastectomy, combined with sentinel node biopsy and radiation therapy, comprises the package described as "breast conservation therapy" (BCT). Up until 2003, BCT has been the primary treatment option for breast cancer treatment for nearly 60–70 % of all cases treated at major breast cancer treatment centers. A recent decline has been noted in several major programs and a trend back toward mastectomy has occurred (Fig. 13.1). These have been shown to be due primarily to patient-driven decision making and are not physician-driven outcomes [5–7].

Keystone Trials

Over the past 50 years, patient education, screening, and early detection with advancements in mammography, ultrasound, magnetic resonance imaging (MRI), breast-specific gamma imaging (BSGI), and positron emission mammography (PEM) have continued to shape the management of breast cancer. It is the summation of several early studies that have culminated in identifying the equivalency of mastectomy and BCT. For instance, rates of survival of those undergoing a mastectomy in comparison to lumpectomy with radiation achieved no significant differences in outcome. Defined predictors of local recurrence after BCT have led to modifications in surgical and radiation techniques to reduce local recurrence.

NSABP B-06

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, a federally sponsored clinical trial, raised several aspects of comparisons between surgical options, use of radiation, and systemic therapy. In a step further, it compared the efficacy of chemotherapy in patients with positive axillary nodes after surgical treatment, as well as determining the clinical significance of microscopic multicentricity. The study took place between 1976 and 1984, with a total of 1,851 patients with tumors up to 4 cm

in diameter and clinically negative lymph nodes, T1 or T2, N0 or N1, M0. Patients were randomly assigned to a total mastectomy, lumpectomy alone, or lumpectomy with postoperative radiation of the breast. All patients with histologically positive axillary nodes received chemotherapy.

Based on this study, rates of ipsilateral breast cancer recurrence after lumpectomy, with or without breast radiation, were compared. At 20 years follow-up, local recurrence rate in women treated with lumpectomy and radiation was 14.3 % versus those treated with lumpectomy alone with a recurrence rate of 39.2 %. For patients with positive nodes who received chemotherapy, the local recurrence rate was 44.2 % for lumpectomy alone, as opposed to 8.8 % for lumpectomy and radiation therapy. The study concluded that lumpectomy, paired with radiation therapy, and adjuvant chemotherapy in women with positive nodes, was appropriate in patients with tumors equal to or less than 4 cm, placing them at stage I or II disease, provided that the resected margins are free of tumor [2].

EORTC

At about the same time, a similar study compared the overall survival between those patients that underwent a modified radical mastectomy (MRM) and breast conservation therapy (BCT) with radiation. The results would similarly echo those found in the NSABP B-06 trial. The European Organization for Research and Treatment of Cancer Trial 10801 took place between 1980 and 1986, in eight centers in the UK, Netherlands, Belgium, and South Africa. It randomized 868 women to MRM and BCT with radiation. The size of tumors was up to 5 cm, though 80 % of women had tumors larger than 2 cm, and patients with axillary node-negative or axillary node-positive disease were included.

At 20 year follow-up, there was no difference in survival between MRM and BCT with radiation [8]. The overall survival was 44.5 % in MRM group and 39.1 % in the BCT group. There was no difference in time to distant metastases or overall survival by age. The study concluded that as a standard of care, patients with early-stage breast cancer can be offered BCT with radiation as an alternative to MRM.

Danish Breast Center Cooperative Group

From 1983 to March 1989, the Danish Breast Cancer Cooperative Group (DBCG) conducted a randomized trial comparing breast conservation to mastectomy in patients with invasive breast cancer. From a total of 1,153 women, 905 were placed on either mastectomy or breast conservation. The remaining 248 were not randomized. Those placed in the breast conservation arm obtained radiotherapy afterward. Tumor diameter was more than 2 cm in over 50 % of cases. Patients were excluded based on the following criteria: sarcoma of the breast or carcinoma in situ, fixation of the tumor to the muscles, evidence of metastatic disease, history of other malignancies, signs of multicentricity by palpation or mammography, and concerns in cosmesis, such as a large tumor in a small breast. In this trial, patients had the choice of changing arms in terms of the proposed operation. Hence, 33 patients randomly assigned to a mastectomy chose breast conservation, while 55 chose a mastectomy over breast conservation. Regardless of tumor size and palpable nodes, all patients underwent an axillary dissection. The dissection consisted of removal of at least all level I lymph nodes.

The median follow-up was 40 months for all patients. For the purpose of consistency, both patient and tumor characteristics were similar in both breast conservation and mastectomy group. Overall survival in the breast conservation group was 79 %, compared to that of the mastectomy group of 82 %. The recurrence-free survival at 6 years was similar in both groups, 70 % versus 66 % [9].

Milan National Tumor Institute Trial

Under the guidance of the National Cancer Institute in Milan, between the years of 1973

and 1980, this trial enrolled 701 women with breast cancer up to 2 cm in size for the primary tumor and clinically negative nodes. These patients would undergo either a radical mastectomy or quadrantectomy with axillary dissection and postoperative radiation to the ipsilateral residual breast tissue. Chemotherapy was reserved for patients with pathologically positive nodes. Of the 701 patients, 349 had a mastectomy and 352 a quadrantectomy. Factors such as age, size and site of primary tumor, and axillary metastases were similar in both groups.

At a 20 year follow-up, no differences between the two groups were found in overall or disease-free survival [10]. Interestingly, the contralateral breast cancer rates were similar. These findings contraindicated the previous thought that radiation increased the incidence of contralateral breast cancer. Based on this trial, patients with a breast cancer lesion less than 2 cm in size have the option of either a mastectomy or quadrantectomy, without concern for decrease in survival.

The Institute Gustave-Roussy Trial

The trial randomized 179 women with breast cancer into modified radical mastectomy versus lumpectomy. Eighty eight patients had lumpectomy and radiotherapy, while 91 patients underwent mastectomy. Axillary dissection was performed in all patients regardless of the lack of palpable axillary lymph node. At a 15-year follow-up, no differences were observed between the two surgical groups in risk for death, metastases, contralateral breast cancer, or locoregional recurrence [9].

Patient Selection for Lumpectomy

As the advent of mammography and early detection improved, the average tumor sizes of the 1970s and 1980s fell to 2.5 cm, allowing the majority of women to undergo BCT. BCT is indicated in women with a T1 (<2 cm) tumor, T2 that is ≤5 cm, N0, N1 (ipsilateral moveable axillary nodes), and M0 (no metastasis) tumors, which correlates to clinically stages I and II breast cancer. An important consideration as to which patients are candidates for BCT is practicality and cosmesis. The tumor to breast volume as well as location of the tumor, such as central or lower inner quadrant, may require nipple-areola complex removal or result in significant deformity of the breast and preclude standard approaches to BCT. Newer techniques of oncoplastic surgery described by Clough and Silverstein may allow for the accommodation of BCT in otherwise compromising locations. Nearly all BCT has been done on unifocal lesions with multicentric lesions being a contraindication for BCT [4]. Certain cases of closely approximated or "kissing lesions" have been successfully treated with BCT. More extensive areas when completely excised with oncoplastic techniques can result in excellent outcomes with BCT.

To be eligible for breast-conserving therapy, three conditions must be met. One must be able to obtain negative surgical margins, patient is able to undergo adjuvant radiation therapy, and the result must be cosmetically acceptable. Positive margins, due to lobular invasive or ductal in situ disease, require excision to negativity and are amenable to BCT, as long as they meet the aforementioned criteria [4].

Contraindications of lumpectomy are multicentric disease, persistently positive margins, early pregnancy, diffuse microcalcifications on preoperative mammogram, or prior history of breast radiation. Early pregnancy is a contraindication since whole breast radiation is contraindicated during pregnancy. However, breast cancer detected during pregnancy in the second or third trimester may be able to be treated with lumpectomy and sentinel node biopsy after which chemotherapy can be administered followed by radiation following delivery.

With the advent of accelerated partial breast irradiation (APBI) and intraoperative radiation therapy (IORT), some patients may be offered shielded breast irradiation during the second or third trimester of pregnancy. Multicentric disease is defined as two or more primary tumors in separate quadrants of the same breast and is a contraindication to BCT. However, some patients with out-of-field recurrences are now being offered APBI or

IORT to those new areas of disease. Relative contraindications include whole breast radiation to a very large breast, lobular carcinoma in situ (LCIS), active connective tissue disease (such as systemic lupus erythematosus, scleroderma or radiosensitivity due to inherited ataxia telangiectasia), and a tumor larger than 5 cm in a patient with small breasts (due to a poor cosmetic result) [4].

Surgical Principles: Techniques in Breast Lumpectomy

BCT is routinely performed for malignant breast diseases. Particularly for malignant processes, there are myriad of surgical techniques and complementary therapies being performed. All of these techniques have similar efficacy rates, and selection should be a patient-centered decision.

Needle-Localized Lumpectomy

Preoperative image-guided needle localization of breast masses has been performed since the 1960s [11–13]. After being refined to include a hook wire to prevent needle migration, the technique quickly became the standard of care in excising breast masses [12]. Mammography, ultrasonography, and magnetic resonance imaging are all used to guide needle placement. After placement, standard lumpectomy incisions are used to gain a rectangular or cylindrical block of tissue around the wire. Needle localization is a time-tested method, but effective excision depends both on the precision of radiological placement and surgical technique. Unfortunately, it does add another step in the procedure, which could lead to patient discomfort and inconvenience [13]. Nonetheless, it is arguably the most popular technique among surgeons.

Palpable Mass Excision

Excision of a palpable mass is indicated for those masses that are not visualized on mammography or for those with features that portend malignancy. Incisions should be made to facilitate excision while maintaining a good cosmetic result.

Hematoma Ultrasound-Guided Lumpectomy

Ultrasonography can be utilized to directly visualize lesions and post-biopsy hematomas. The hematoma ultrasound-guided lumpectomy was described in 2001 and has become widely performed [14]. After routine biopsy of breast lesions, a hematoma forms that is sometimes palpable and most of the time is easily visualized under ultrasound guidance. Intraoperative ultrasound is used to localize the lesion, which guides incision placement. The ultrasound can then be used to ensure proper margin-free excision, and ex vivo ultrasonography ensures that the lesion is removed. Hematomas do resorb with time, so operative scheduling should be close to the biopsy date (within 6 weeks). This technique obviates the need for needle localization in many patients, but if lesions are not visualized with sonography, needle localization should be performed [14, 15].

Radioisotope (Seed) Localization Lumpectomy

Tc^{99m} radioisotope sulfur colloid is used to identify draining lymph nodes of the primary tumor. It follows that if a different radioisotope could be inserted into target lesions, excision could be similarly guided by gamma counts. This has been performed and widely published since the early 2000s [16]. Radiological or ultrasound placement of radioactive I^{125} seeds can be used to localize the malignant lesion, and any of the gamma detection probes set on the I^{125} setting can detect the seed even in the presence of the Tc^{99m} which has been injected for lymphatic mapping of sentinel nodes. A gamma counter is used to guide both the incision and the extent of excision. This technique does require a preoperative radiological implantation, but improvements in margin negativity have cemented the use of this procedure in the breast surgeon's armamentarium [17].

Cryoablation-Assisted Lumpectomy

Cryoablation can be used in conjunction with intraoperative ultrasound to guide lumpectomy. Essentially, the lesion is visualized under ultrasound guidance and a cryoablation of the area is performed, followed by an ultrasound-guided lumpectomy of the area that was ablated. Margin negativity is acceptable using this technique for lesions less than 18 mm [18]. Larger lesions are more difficult to adequately ablate, and the ablation process makes postoperative pathological analysis more difficult [19]. To further analyze the ability of cryoablation to eradicate intraductal carcinoma, the Cryoablation Trial Z0172 is in clinical Phase II trials at present.

Lumpectomy with Radiofrequency Ablation

Intraoperative radiofrequency ablation of the lumpectomy bed was examined in the early part of year 2000. Performance of this technique requires some specialized equipment and surgical precision, but the consistent 1 cm margin of ablation confirmed on post-ablation cavity wall biopsy could prevent re-excision rates for specimen margin positivity. After lumpectomy, RFA probe is secured in the lumpectomy bed with a purse-string suture. Care is taken to keep the probe from causing skin burns, and Doppler ultrasonography can be used to manipulate the probe to prevent this [20]. It is possible that this could be definitive breast conservation therapy for some patients with favorable lesions, but this requires more evaluation [21].

Lumpectomy with Brachytherapy

Some patients with favorable tumors can avoid whole breast radiation therapy and undergo accelerated partial breast irradiation (APBI) [22] (see Table 13.1). This entails 1 week of radiation therapy that is often delivered through exteriorized catheters placed into or through the lumpectomy cavity. Surgeons can assist with partial breast irradiation by placing brachytherapy catheters through externalized catheters placed into or through the lumpectomy cavity devices into the lumpectomy cavity either intraoperatively or in the office after lumpectomy. The catheter can be cumbersome for some patients, but given that the total radiation time is 1 week, it is widely tolerated [23]. Techniques of multiple polyethylene catheters placed in an array through and through the breast tissue traversing the lumpectomy cavity were first implemented over 30 years ago. Subsequent balloon catheter devices (MammoSite, ClearPath) were developed as well as bundled and strutted device with multiple polyethylene catheters (SAVI) device. Treatment programs of 34 Gy delivered in 10×3.4 Gy fractions twice daily have been employed (see Table 13.2).

Lumpectomy with Intraoperative Radiation Therapy

Intraoperative radiation therapy is a development in the spectrum of breast conservation therapy. This collaboration between breast surgeons and radiation oncologists begins by localizing and removing the tumor. Next, the radiation device (Intrabeam, Xoft) is placed within the lumpectomy cavity and secured the radiation is delivered to the tumor and peritumoral tissues in a single fraction of 20 Gy. Proper therapy can be completed even in noncompliant patients given the one stage lumpectomy and radiation [25]. While intraoperative cost is higher, this eliminates the long-term radiation therapy costs and ensures patient compliance with therapy [26]. The recent results of the TARGIT trial demonstrate excellent short-term results with single 20 Gy doses of IORT.

Margin Assessment

Obtaining adequate margins is of the utmost importance in breast-conserving surgery. Excision of the lesion in its entirety with adequate margins is vital to minimizing the risk of a local tumor recurrence. However, overzealous

Table 13.1 Professional medical society consensus guidelines for patient selection for APBI

	ABS[a]	ASBS[b]	ACRO[c]	ASTRO[d]		
				Suitable	Cautionary	Unsuitable
Age	≥50	≥45	≥45	≥60	50–59	<50
Diagnosis	Unifocal, invasive ductal carcinoma	Invasive ductal carcinoma or DCIS	Invasive ductal carcinoma or DCIS	Invasive ductal or other favorable subtypes (i.e., mucinous, tubular, colloid)	Pure DCIS ≤3 cm EIC ≤3 cm	–
Tumor size (cm)	≤3	≤3	≤3	≤2	2.1–3.0	>3
Surgical margins	Negative microscopic margins of excision	Negative microscopic margins of excision	Negative microscopic margins of excision	Negative by at least 2 mm	Close (<2 mm)	Positive
Nodal status	NØ	NØ	NØ	NØ (i–, i+)	–	Positive

There continues to be growing interest in the use of accelerated partial breast irradiation. To provide additional direction for patients and physicians regarding the use of APBI, consensus guidelines have been issued by the major physician professional societies

[a]Breast Brachytherapy Task Group, American Brachytherapy Society (ABS), February 2007

[b]Consensus statement for accelerated partial breast irradiation. American Society of Breast Surgeons (ASBS), October 7, 2008

[c]American College of Radiation Oncology (ACRO) Statement on Partial Breast Irradiation, September 2008

[d]American Society for Radiation Oncology (ASTRO) Consensus Statement on Partial Breast Irradiation, July 2009

Table 13.2 APBI data review

Institution	# of cases	Median F/U (months)	Local recurrence (%)	Cosmesis good/ excellent (%)
ASBS MammoSite Registry	1,440	60.5	1.8	90
Virginia Commonwealth University	483	24	1.2	91
National Institute of Oncology, Hungary Phase III Trial[a]	APBI 127 WBI 131	66	APBI 4.7 WBI 3.4	APBI 81 WBI 62
William Beaumont Hospital	199	71	1.6	92
Ochsner Clinic	164	65	3	75
RTOG 95–17	99	51	4	Not reported
Mass General Hospital	48	84	2	68
National Institute of Oncology, Hungary Phase I/II Trial	45	80	6.7	84
MammoSite FDA Trial	43	66	0	83
Tufts/Brown	33	84	6.1	88
Total	2,681	65	APBI 3.1 WBI 2.8	84

Adapted from Polgar et al. [24]

Not only does brachytherapy allow for a dramatic change in the treatment schedule from several weeks to just 5 days, it also is associated with fewer radiation-related toxicities and an improved cosmetic outcome. This chart summarizes a multitude of clinical trials evaluating the efficacy of brachytherapy

[a]Conclusion: Partial breast irradiation using interstitial HDR implants or EB to deliver radiation to the tumor bed alone for a selected group of early-stage breast cancer patients produces 5-year results similar to those achieved with conventional WBI. Significantly better cosmetic outcome can be achieved with carefully designed HDR multi-catheter implants compared with the outcome after WBI

resection may lead to a less than desirable cosmetic outcome. Although there is no clear consensus as to what constitutes a negative margin, many authors define a positive margin as tumor at the inked margin and a close margin as tumor less than 2 mm from the inked margin. Definition for an adequate margin in the breast literature ranges from no tumor at ink to 10 mm.

It is important to ensure a negative margin at the time of the initial resection. Although re-excision is possible and often performed for positive margins, this adds patient discomfort, cost and further anesthesia, and surgical risk. Currently re-excision rates for positive margin status vary greatly in the literature. A recent multi-institutional study of 2,206 women undergoing partial mastectomy found an overall re-excision rate of 22.9 %, with 9.4 % of patients requiring re-excision of two or more re-excisions with 8.5 % of patients ultimately requiring a total mastectomy. The study found that younger women (age <35), thinner women (BMI <18.5), and those with initial margins of less than 1 mm are more likely to require a re-excision.

A study by Morrow et al. analyzing the SEER data from several institutions nationwide demonstrated a stunning 40 % re-excision rate. DCIS, lobular carcinoma, and lymphovascular invasion also had higher re-excision rates. Obtaining a negative margin is important because margin status affects the rate of local and overall recurrence. Local recurrence rates with negative margins found in the literature vary between 2 and 13 % and increase to 6–31 % if the margins are positive. However, it is important to remember that negative margins do not guarantee total eradication of disease but that the residual tumor burden is low enough to be treated with chemoradiation. Thus, factors such as intrinsic tumor biology and clinical stage play an important role in the risk of overall recurrence.

Margin assessment is especially difficult in clinically non-palpable lesions or lesions with poorly defined borders. Various techniques have been used to assess specimen margins to ensure adequate resection including optical assessment, intraoperative frozen section, and imprint cytology. Ensuring an adequate margin begins with preoperative imaging. Standard imaging such as mammography, ultrasound, and MRI should be used to determine the size, location, and character of the tumor. Ultrasound- or mammography-guided needle localization or clip placement near non-palpable tumors is helpful in identifying suspicious regions. However, this technique does not define the borders of the lesion in a three-dimensional setting and thus does not ensure a negative margin. After careful surgical dissection, the specimen should be orientated and marked carefully as to ensure facile re-excision if necessary. A gross visual inspection of the specimen is always necessary to assess macroscopic disease. In addition, a number of surgeons use a variety of techniques to ensure adequate margins intraoperatively. Portable radiography systems, such as the Faxitron® and Kubtec® (XPERT 40) systems, allow for immediate radiographic analysis of specimen margins following needle-localized excisions. The images can be sent immediately to radiology for further evaluation.

Although wire-guided localization has traditionally been viewed as the standard of care for localizing non-palpable breast lesions in breast-conserving therapy. Various new technologies have been introduced to augment and even substitute its role in localization and margin assessment. Intraoperative specimen mammography provides an immediate image of the entire excised specimen. This allows radiographic visualization of suspicious areas and allows the surgeon to excise additional margins at the time of lumpectomy, thus decreasing the rate of re-operative surgery. In Bathla et al.'s study of the utility of Faxitron mammographically guided intraoperative re-excision, 84.3 % of patients who underwent primary lumpectomy using this method had histologically clear margins at initial excision versus national rates of 55–68 % [27]. A total of 17.6 % of excisions had positive margins despite the use of 2D Faxitron imaging. The sensitivity and specificity of intraoperative margin assessment via 2D Faxitron imaging for patient with primary breast cancer quoted in this study were 58.5 and 91.8 %, respectively, with a positive predictive value of 82.7 % and negative predictive value of 76.7 %. Thus, although intraoperative specimen mammography improves the rate of negative margins at initial excision, it does not always predict negative histological margin. It should be used carefully in conjunction with the already established assessment tools available to ensure a negative margin.

Intraoperative ultrasonography can also be used to aid margin assessment. Ultrasound localization can be used alone for non-palpable lesions or used as an adjunct to the standard needle localization procedure. Although some studies have shown a superior negative margin rate for ultrasound-guided excision versus needle localization, this technique is only useful for lesions clearly visualized by the ultrasound and is often not useful in DCIS where lesions are diagnosed as calcifications on mammography.

Various other techniques have been used in an attempt to optimize margin negativity. Cryoprobe-assisted location (CAL) is one such method which uses liquid nitrogen or argon to freeze the lesion using an ultrasound-guided cryoprobe, transforming the non-palpable lesion to a solid palpable mass easily viewed by ultrasound. This technique was shown to have similar positive margin rates compared to needle-wire localization lumpectomy while excising a smaller specimen. CAL also showed a benefit in ease of lumpectomy, surgical cosmesis, and procedure time. However, the freezing process associated with this procedure alters the tumor morphology and interferes with pathological analysis of the specimen including tumor grade, distinguishing between in situ and invasive components, assessment of mitoses and lymphovascular invasion, and expression of hormone receptors.

Radio-guided localization (RGL) has emerged as a novel method for localization of non-palpable breast lesions with the promise of improved margin clearance. This technology uses a radioactive tracer placement into the occult breast mass in order to aid with excision. Radio-guided occult lesion localization (ROLL) and radio-guided seed localization (RSL) are two approaches to this technology that has become increasingly popular. ROLL involves injecting (99m)Tc-labeled particles of human serum albumin (7–10 MBq) into the lesion under stereotactic mammographic or ultrasonic guidance then carrying out breast-conserving surgery with the aid of a handheld gamma-detecting probe. After excision, the specimen may be examined by either ultrasonography or mammography to verify complete lesion prior to histological evaluation.

RSL is utilized in a similar fashion but uses an implantable ^{125}I encapsulated titanium seed as the radioactive guide. The seed used in RSL has the added advantage of being easily visible on both mammography and ultrasound. The radioactive seed used in RSL has a relatively long half-life (60 days) compared to that of the Tc-labeled albumin used in ROLL (6 h), so it does not need to be performed on the day of surgery. Furthermore, RSL does not use the same radiotracer (^{99m}Tc) as SLN mapping and causes less confusion when performing both procedures than ROLL. Recent data has shown at least equivalent outcomes between radio-guided localization and wire localization in terms of margin status. It shows promise as a useful tool in the future of breast conservation surgery.

Although the various technologies mentioned above have facilitated complete excision of breast lesions, definitive margin assessment is through pathological analysis. Some surgeons utilize frozen section in an attempt to confirm negative margins at the time of the operation. Frozen section is fairly accurate, with sensitivity and specificity quoted in the literature at approximately 90 and 100 %, respectively [28, 29]. However, this technique can be costly, time consuming, and labor intensive, and its use is often limited by these factors.

Intraoperative touch prep or imprint cytology offers a quicker and easier alternative to intraoperative frozen section. Using this method, each surface of the specimen is touched to a glass slide then stained and air dried. The slides are then screened to look for malignant epithelial cells, with the premise that malignant cells stick to the slide while benign cells do not. Therefore, a negative margin will show no epithelial cells or rare benign epithelial or non-epithelial cells, while a positive margin will show atypical or malignant epithelial cells. This method is useful in determining positive margins but does not indicate when margins are close. Current data shows that imprint cytology demonstrates sensitivities of 80–100 %, specificities of 83–100 %, and diagnostic accuracies of 73–100 %. In addition, the efficacy of intraoperative imprint cytology has been well established in a large series of 1,713 patients published by Weinberg et al. [30].

The study showed that imprint cytology provided an accurate evaluation of lumpectomy margins and was associated with an overall decrease in overall 5-year local recurrence from 8.8 to 2.8 % compared to frozen section.

Recurrence After Lumpectomy

Recurrence after breast-conserving therapy must be broken down into local (occurring in the conserved ipsilateral breast), regional (occurring in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes), and distant (outside of the ipsilateral breast and lymph nodes). BCT has been shown to be equivalent compared to MRM in terms of disease-free and overall survival. The overall recurrence rates have been found to be 0.5–2 % per year. Two large randomized studies, the Milan trial and NSABP trial, demonstrated these findings with short- and long-term follow-up for patients with stages 0, I, and II disease. The NSABP B-06 trial evaluated the effectiveness of lumpectomy with and without radiation versus modified radical mastectomy in patients with tumors ≤ 4 cm. The recurrence rate at 5 years for lumpectomy with radiation was 7.7 % [31]. By 8 years after treatment, this was up to 10 % [32]. However, the patients treated with lumpectomy alone (no radiation) had a recurrence rate of nearly 40 %. Patients who had positive nodes and were treated with chemotherapy, radiation, and lumpectomy had a local recurrence rate of only 6 %. Twenty-year follow-up data of this trial has found a hazard ratio for death of 1.05 (lumpectomy without radiation compared to mastectomy) and 0.97 (lumpectomy with radiation compared to mastectomy) [3].

Despite the risk of death being nearly equal, the risk of local recurrence was significantly higher in the lumpectomy without radiation group (39.2 %) compared to the lumpectomy with radiation (14.3 %) and the mastectomy (10.2 %). Over 73 % of the recurrences in the lumpectomy without radiation group occurred within the first 5 years, while 40 % of those undergoing lumpectomy plus radiation had a recurrence within the same time span. The 20-year follow-up data for the Milan trial [10] differs from the NSABP trial suggesting a higher incidence of local recurrence in the breast conservation group (8.8 % ± 3.2) compared to the mastectomy group (2.3 % ± 0.8). Despite the difference in recurrence rates, both treatment options showed comparable overall survival as well as risk of death from breast cancer (26.1 % vs. 24.3 %, respectively). These results were later confirmed in a large meta-analysis of nearly 42,000 patients [33].

Imprint cytology has shown to decrease the risk of recurrence in patients undergoing breast conservation therapy. In a study published in 2004 [30], recurrences after BCT performed at an outside institution using frozen and permanent sections to determine margins were compared to those performed at the Moffitt Cancer Center where imprint cytology was used to determine margins. The results were dramatic, with imprint cytology reducing the recurrence rate from 8.8 to 2.8 % for all types of breast cancer. The breakdown for each type of cancer can be seen in Table 13.3.

While BCT certainly has advantages to the patient compared to a traditional MRM, there are a number of risk factors that have to be considered prior to surgery that can increase the risk of recurrence in patients undergoing BCT. The most common risk factors debated among the literature are large tumor size, multiple tumors, axillary lymph node involvement, young age, high nuclear grade, hormone receptor status, lack of radiation, and margin status. Of these risk factors, achieving a clear surgical margin is the only factor that can be controlled by the surgeon. Some studies suggest that it is not the width of the negative margin, but the mere status of having a negative margin. It is common practice of many surgeons to perform a re-excision if the cancer is within 2 mm of the margin when examined by the pathologist. Age less than 40 years has been shown to increase the risk of recurrence by 1.8 % while being ER negative increases it by 1.5 % [34]. Their study also confirms what has been shown in many other studies that adjuvant radiation therapy after lumpectomy significantly decreases the chance of recurrence (HR 0.39). Of note, other groups feel the age that worsens prognosis is less than 35 years old [35].

Table 13.3 BCT recurrence rates without and with imprint cytology (IC)

Recurrence	OSH without IC	Moffitt with IC	*P* value
Overall	8.8 %	2.8 %	<0.0001
DCIS	8.8 %	4.0 %	0.105
IDC	9.5 %	2.7 %	<0.0001
ILC	5.1 %	1.5 %	0.166
Mixed	0	2.9 %	0.558

Adapted from Weinberg et al. [30]
DCIS ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *Mixed* mixed ductal and lobular carcinoma

Treatment of recurrence after BCT depends on the initial operation and location of recurrence. For local recurrence, patients who undergo BCT with radiation should return to the OR for a total mastectomy with repeat sentinel node biopsy. If follow-up has demonstrated regional or local and regional recurrence in the axilla, the patient should be evaluated for possible resection and then be evaluated for chest wall, supraclavicular, infraclavicular, and axillary radiation. If the regional recurrence is in the supraclavicular or internal mammary nodes, surgical resection may be indicated and the patient should receive localized radiation therapy. When recurrent disease is systemic, then no surgical intervention is warranted and the patient should be evaluated for chemotherapy.

Oncoplastic Reductions

As BCT became an acceptable option for many women instead of a mastectomy, the concept of oncoplastic breast surgery evolved from its early attempts to preserve breast tissue. Over time, BCT has been regarded as a minimalist approach, with the assurance that the cancerous lesion is excised in its entirety. Oncoplastic surgery provides a range of possibilities to allow a more "cosmetic" result. A range of applications stem from breast reduction, skin and nipple sparing, and autologous reconstruction. It combines oncologic principles with plastic surgery techniques, requiring vision of symmetry and aesthetics and understanding of breast anatomy and contour.

For those women with large breasts and breast tumor, the volume of breast tissue allows for tumor resection and reduction mammoplasty. After the tumor has been excised with sufficient tissue to ensure negative margins, large breasts allow for a better aesthetic result. Papp et al. [36] observed an overall improved aesthetic outcome with patients in the immediate mammoplasty group compared to those with delayed reconstruction. Indications for bilateral reduction mammoplasty are large, pendulous breasts, tumor location to allow for negative margins, tumor located in lower quadrants, significant area of redundant skin remaining after tumor resection, and tumor location in area where a poor aesthetic result is likely (for instance, underneath the nipple) [37].

The option to provide a bilateral reduction mammoplasty at the same time of the oncologic resection does increase the overall surgical time. In certain patients with multiple comorbidities, a lengthened anesthetic state may not be suitable. Radiation therapy for certain patients after their reconstruction causes some degree of fibrosis and retraction of tissue [38]. Furthermore, postoperative complications in terms of wound healing can pose a delay in adjuvant therapy. Poor healing can lead to wound dehiscence, fat necrosis, flap necrosis, nipple-areola complex necrosis, wound infection, hematoma, and seroma [39]. A conservative approach to wound dehiscence consists of local debridement and revision if necessary. However, flap necrosis and nipple-areola complex necrosis are due to poor vascularity to area and tension in flap. These complications can be prevented by preservation of perforator vessels and beveling of the flap.

The key concepts to a reduction mammoplasty are to preserve adequate vascular supply to the nipple-areola complex as well as to the remaining breast parenchyma. The Wise pattern, also referred to as the "keyhole" approach, creates the classic inverted T- or anchor-shaped incision. The first line marker is from the suprasternal notch advancing inferiorly as it intersects with a midclavicular line at a point where the current nipple exists. The distance between the midline and new nipple should be approximately 9–10 cm, and the lines from the suprasternal notch and the new

nipples on both sides should form a right triangle [40]. The tumor location is marked and a keyhole marks the excision area to include the area of breast to be removed. A pedicle width is chosen, approximately 8–10 cm, based on the tumor location. The inferior- or superior-based pedicle should be within 1.5 cm from the areola. After the tumor is resected, an incision is created along the markings and de-epithelization is performed to create the pedicle. Thickness of the pedicle is between 4 and 8 cm at the base and 3–5 cm at the nipple-areola complex. Flaps are created and the parenchymal tissue is excised, followed by transposition of the pedicle and the flaps aligned and approximated to these new margins of skin [41].

Similarly to the Wise pattern for reduction mammoplasty, a vertical pattern offers similar results. Once the tumor is excised, the breast is pushed medially and laterally against a vertical line. The medial and lateral incision lines delineate the areas of resection. The inferior margin of the excision is 4 cm superior to the inframammary fold. A pedicle 8–10 cm in width with a 1.5 cm margin around the areola is designed. The dermal pedicle is de-epithelialized, parenchymal tissue is excised, and the dermal pedicle is transposed, advancing and closing the skin flaps as performed with the Wise pattern [42].

As to oncologic and adjuvant treatment benefits, for instance, radiation, immediate mammoplasty reduction allows for an overall better tissue composition. In patients with large, pendulous breasts, clinical series note increased complications after radiation, in comparison to smaller breasts [43]. The increased fat content in large breasts, the fatty tissue, results in more fibrosis after radiation therapy. Increased skin retraction and asymmetry is noted in this group of patients, preventing a better cosmetic result.

From an oncologic perspective, the ability to resect and remove further tissue allows for a greater possibility of negative margins. In patients with oncologic mammoplasty reduction, the core of the tumor and substantial excision of surrounding tissue permits a negative resection margin [44]. The reduction allows a larger mean volume of breast tissue, potentially reducing the incidence of margin involvement. One drawback of these oncoplastic approaches is the fact that once the excision has occurred and the breast tissues are rearranged, the margins that remain positive can be nearly impossible to accurately locate and re-excise. The solution to this dilemma has been solved in the authors' experience by placing a Cavity Evaluation Device (CED) into the lumpectomy cavity at the time of primary excision. It is then embedded into the breast, bringing the fill valve just under the skin at a position that would make subsequent catheter-based APBI an appropriate treatment in this population of patients. If indeed the margins remain positive on final pathology, it is relatively easy to go back through the prior incisions to the balloon cavity and re-resect the appropriate margin(s). Again, you must await final pathology, finally exchanging the CED for an APBI treatment catheter.

This method provides a number of advantages: accurate excision of the tumor-bearing area with wide margins, accurate identification of the lumpectomy site for subsequent radiation therapy, accurate identification of margins in the event of a pathologically positive margin, the ability to accurately find and re-excise the margin, and ultimately the ability to apply APBI treatment options. The latter is associated with less breast deformity and shrinkage to a group of patients that have undergone plastic reductive procedures for improved cosmesis that can be greatly altered by the long-term consequences of whole breast irradiation. For those patients with the criteria necessary for whole breast irradiation, the placement of the CED and subsequent APBI for tumor bed boost dosing enhances the accuracy and effectiveness of that treatment. In women with large, pendulous breasts, oncoplastic reduction provides the ability to fully excise the existing tumor without leaving a significant defect from its resection, while remodeling the surrounding breast tissue to provide an aesthetic as well as functional outcome.

Controversial Topics in Breast Conservation Therapy

Breast conservation therapy has an equivalent efficacy when compared with mastectomy for early-stage breast cancers. As surgical techniques

and medical treatments advance, more patients are becoming candidates for BCT which is obscuring the boundaries between lumpectomy and mastectomy.

Breast Conservation for Large Tumors

Lumpectomy and radiation had traditionally been offered for tumors less than 20 mm in size. NSABP B-06 included patients with up to 40 mm tumors, and subsequent series of patients with larger tumors have been published. Dongen et al. published a series in 2000 with inclusion criteria up to 50 mm in size [8]. Their series had nearly 900 patients and a 13.4-year median follow-up. With regard to overall survival and distant disease, there was no difference between the BCT and mastectomy groups. However, local recurrence in this series was higher in the BCT group (20 %) than in the group who had mastectomy (12 %). Even for T3/T4 cancers, BCT outcomes were found to be acceptable when compared with mastectomy. In one series with 196 patients, overall survival, breast cancer-related survival, and local recurrence-free survival were equivalent between BCT and mastectomy [45].

Much like large tumors, centrally located tumors have traditionally been treated with mastectomy because the oncoplastic result has previously been in question. A head to head comparison of BCT for central tumors with BCT for tumors on the breast periphery involving 1,485 patients showed no difference in 5-year overall, local, or distant recurrence-free survival between the groups [46]. Furthermore, oncoplastic techniques have improved the cosmesis after these operations. One subset of patients where lumpectomy has shown to be feasible for large tumors includes those women with breast hypertrophy/macromastia. One series used partial mastectomy with immediate reduction mammoplasty to treat tumors 0.05–8.9 cm large. There was no difference in recurrence or complication rate attributable to tumor size [37]. Advances in neoadjuvant therapy and oncoplastic techniques are being explored, and these will continue to allow for broadened indications for BCT, even in the setting of locally advanced disease.

Lumpectomy After Neoadjuvant Therapy

As with other malignancies, neoadjuvant therapy is being utilized to downstage tumors in breast cancer with a couple of goals in mind. The first goal is to offer more patients breast conservation therapy as neoadjuvant therapy pushes tumor size into nationally acceptable parameters. The other is to use response to predict patient outcomes. Large series have been completed, and these have shown that BCT with neoadjuvant therapy has resulted in acceptable rates of recurrence. In a series of 340 patients at MD Anderson Cancer Center, neoadjuvant therapy was used prior to BCT, with 96 % of these patients with initial stage II or stage III disease. BCT after neoadjuvant therapy in their study produced acceptable rates of local recurrence and ipsilateral breast recurrence, but they did notice a subset of patients for whom BCT was less effective in controlling disease. These were patients with nodal involvement at diagnosis, multifocal disease pattern, lymphovascular invasion, and large residual tumor. Consequently, they developed a prognostic index to predict successful BCT after neoadjuvant therapy [47].

A 325-patient study out of Vienna analyzed use of neoadjuvant therapy and BCT in patients with lobular carcinoma [48]. There was no difference in local recurrence in those patients with ductal versus lobular carcinoma. Fifty-three month follow-up showed no difference in local recurrence between those lobular carcinoma patients who had mastectomy and BCT. Furthermore, neoadjuvant therapy made BCT an option in 45 % of patients originally scheduled for mastectomy. Likewise, others have seen neoadjuvant therapy enable BCT in nearly 50 % of patients, while also delineating how response to therapy does impact overall survival [49]. Five-year survival was 100 % for those who achieved a complete response, while partial and nonresponders had 74 and 48 % 5-year survival, respectively. The general trend has been for more widespread use of neoadjuvant therapy. This has been predicated upon the fact that it has allowed more patients to undergo BCT, in addition to enabling assessment of tumor response to therapy as an important prognostic tool for survival.

References

1. Fischer JE. Fischer's mastery of surgery. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
2. Wickerham DL, Costantino JP, Mamounas EP, Julian TB. The landmark surgical trials of the national surgical adjuvant breast and bowel project. World J Surg. 2006;30(7):1138–46. doi:10.1007/s00268-005-0552-5.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233–41. doi:10.1056/NEJMoa022152.
4. Sabiston DC, Townsend CM. Sabiston textbook of surgery: the biological basis of modern surgical practice. 19th ed. Philadelphia: Elsevier/Saunders; 2012.
5. McGuire KP, Santillan AA, Kaur P, Meade T, Parbhoo J, Mathias M, Shamehdi C, Davis M, Ramos D, Cox CE. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. Ann Surg Oncol. 2009;16(10):2682–90. doi:10.1245/s10434-009-0635-x.
6. Balch CM, Jacobs LK. Mastectomies on the rise for breast cancer: "the tide is changing". Ann Surg Oncol. 2009;16(10):2669–72. doi:10.1245/s10434-009-0634-y.
7. Katipamula R, Degnim AC, Hoskin T, Boughey JC, Loprinzi C, Grant CS, Brandt KR, Pruthi S, Chute CG, Olson JE, Couch FJ, Ingle JN, Goetz MP. Trends in mastectomy rates at the Mayo Clinic Rochester: effect of surgical year and preoperative magnetic resonance imaging. J Clin Oncol. 2009;27(25):4082–8. doi:10.1200/JCO.2008.19.4225.
8. van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, van der Schueren E, Helle PA, van Zijl K, Bartelink H. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 2000;92(14):1143–50.
9. Blichert-Toft M, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW, Mouridsen HT. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. Journal of the National Cancer Institute Monographs. 1992;11:19–25.
10. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32. doi:10.1056/NEJMoa020989.
11. Hall FM, Frank HA. Preoperative localization of nonpalpable breast lesions. AJR Am J Roentgenol. 1979;132(1):101–5. doi:10.2214/ajr.132.1.101.
12. Hall FM, Kopans DB, Sadowsky NL, Homer MJ. Development of wire localization for occult breast lesions: Boston remembrances. Radiology. 2013;268(3):622–7. doi:10.1148/radiol.13121943.
13. Ernst MF, Avenarius JK, Schuur KH, Roukema JA. Wire localization of non-palpable breast lesions: out of date? Breast. 2002;11(5):408–13. doi:10.1054/brst.2002.0444.
14. Thompson M, Henry-Tillman R, Margulies A, Thostenson J, Bryant-Smith G, Fincher R, Korourian S, Klimberg VS. Hematoma-directed ultrasound-guided (HUG) breast lumpectomy. Ann Surg Oncol. 2007;14(1):148–56. doi:10.1245/s10434-006-9076-y.
15. Arentz C, Baxter K, Boneti C, Henry-Tillman R, Westbrook K, Korourian S, Klimberg VS. Ten-year experience with hematoma-directed ultrasound-guided (HUG) breast lumpectomy. Ann Surg Oncol. 2010;17 Suppl 3:378–83. doi:10.1245/s10434-010-1230-x.
16. Cox CE, Furman B, Stowell N, Ebert M, Clark J, Dupont E, Shons A, Berman C, Beauchamp J, Gardner M, Hersch M, Venugopal P, Szabunio M, Cressman J, Diaz N, Vrcel V, Fairclough R. Radioactive seed localization breast biopsy and lumpectomy: can specimen radiographs be eliminated? Ann Surg Oncol. 2003;10(9):1039–47.
17. Gray RJ, Pockaj BA, Karstaedt PJ, Roarke MC. Radioactive seed localization of nonpalpable breast lesions is better than wire localization. Am J Surg. 2004;188(4):377–80. doi:10.1016/j.amjsurg.2004.06.023.
18. Sabel MS, Kaufman CS, Whitworth P, Chang H, Stocks LH, Simmons R, Schultz M. Cryoablation of early-stage breast cancer: work-in-progress report of a multi-institutional trial. Ann Surg Oncol. 2004;11(5):542–9. doi:10.1245/ASO.2004.08.003.
19. Bland KL, Gass J, Klimberg VS. Radiofrequency, cryoablation, and other modalities for breast cancer ablation. Surg Clin North Am. 2007;87(2):539–50. doi:10.1016/j.suc.2007.02.003, xii.
20. Klimberg VS, Kepple J, Shafirstein G, Adkins L, Henry-Tillman R, Youssef E, Brito J, Talley L, Korourian S. eRFA: excision followed by RFA-a new technique to improve local control in breast cancer. Ann Surg Oncol. 2006;13(11):1422–33. doi:10.1245/s10434-006-9151-4.
21. Wilson M, Korourian S, Boneti C, Adkins L, Badgwell B, Lee J, Suzanne Klimberg V. Long-term results of excision followed by radiofrequency ablation as the sole means of local therapy for breast cancer. Ann Surg Oncol. 2012;19(10):3192–8. doi:10.1245/s10434-012-2476-2.
22. NSABP B-39, RTOG 0413. A Randomized Phase III Study of conventional whole breast irradiation versus partial breast irradiation for women with stage 0, I, or II breast cancer. Clinical advances in hematology & oncology. H&O. 2006;4(10):719–21.

23. Benitez PR, Keisch ME, Vicini F, Stolier A, Scroggins T, Walker A, White J, Hedberg P, Hebert M, Arthur D, Zannis V, Quiet C, Streeter O, Silverstein M. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Am J Surg. 2007;194(4):456–62. doi:10.1016/j.amjsurg.2007.06.010.
24. Polgar C, Fodor J, Major T, Nemeth G, Lovey K, Orosz Z, Sulyok Z, Takacsi-Nagy Z, Kasler M. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma–5-year results of a randomized trial. Int J Radiat Oncol Biol Phys. 2007;69(3):694–702. doi:10.1016/j.ijrobp.2007.04.022.
25. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sutterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010;376(9735):91–102. doi:10.1016/S0140-6736(10)60837-9.
26. Veronesi U, Orecchia R, Luini A, Galimberti V, Zurrida S, Intra M, Veronesi P, Arnone P, Leonardi MC, Ciocca M, Lazzari R, Caldarella P, Rotmensz N, Sangalli C, Sances D, Maisonneuve P. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. Breast Cancer Res Treat. 2010;124(1):141–51. doi:10.1007/s10549-010-1115-5.
27. Bathla L, Harris A, Davey M, Sharma P, Silva E. High resolution intra-operative two-dimensional specimen mammography and its impact on second operation for re-excision of positive margins at final pathology after breast conservation surgery. Am J Surg. 2011;202(4):387–94. doi:10.1016/j.amjsurg.2010.09.031.
28. Olson TP, Harter J, Munoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. Ann Surg Oncol. 2007;14(10):2953–60. doi:10.1245/s10434-007-9437-1.
29. Weber WP, Engelberger S, Viehl CT, Zanetti-Dallenbach R, Kuster S, Dirnhofer S, Wruk D, Oertli D, Marti WR. Accuracy of frozen section analysis versus specimen radiography during breast-conserving surgery for nonpalpable lesions. World J Surg. 2008;32(12):2599–606. doi:10.1007/s00268-008-9757-8.
30. Weinberg E, Cox C, Dupont E, White L, Ebert M, Greenberg H, Diaz N, Vercel V, Centeno B, Cantor A, Nicosia S. Local recurrence in lumpectomy patients after imprint cytology margin evaluation. Am J Surg. 2004;188(4):349–54. doi:10.1016/j.amjsurg.2004.06.024.
31. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, Fisher E, Wolmark N, Deutsch M, Montague E, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312(11):665–73. doi:10.1056/NEJM198503143121101.
32. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, Fisher E, Deutsch M, Caplan R, Pilch Y, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1989;320(13):822–8. doi:10.1056/NEJM198903303201302.
33. Group EBCTC. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med. 1995;333(22):1444–55. doi:10.1056/NEJM199511303332202.
34. Miles RC, Gullerud RE, Lohse CM, Jakub JW, Degnim AC, Boughey JC. Local recurrence after breast-conserving surgery: multivariable analysis of risk factors and the impact of young age. Ann Surg Oncol. 2012;19(4):1153–9. doi:10.1245/s10434-011-2084-6.
35. Matthews RH, McNeese MD, Montague ED, Oswald MJ. Prognostic implications of age in breast cancer patients treated with tumorectomy and irradiation or with mastectomy. Int J Radiat Oncol Biol Phys. 1988;14(4):659–63.
36. Papp C, Wechselberger G, Schoeller T. Autologous breast reconstruction after breast-conserving cancer surgery. Plast Reconstr Surg. 1998;102(6):1932–6; discussion 1937–8.
37. Chang E, Johnson N, Webber B, Booth J, Rahhal D, Gannett D, Johnson W, Franzini D, Zegzula H. Bilateral reduction mammoplasty in combination with lumpectomy for treatment of breast cancer in patients with macromastia. Am J Surg. 2004;187(5):647–50. doi:10.1016/j.amjsurg.2004.01.002; discussion 650–1.
38. Gray JR, McCormick B, Cox L, Yahalom J. Primary breast irradiation in large-breasted or heavy women: analysis of cosmetic outcome. Int J Radiat Oncol Biol Phys. 1991;21(2):347–54.
39. Brierley JD, Paterson IC, Lallemand RC, Rostom AY. The influence of breast size on late radiation reaction following excision and radiotherapy for early breast cancer. Clin Oncol. 1991;3(1):6–9.
40. Yang JD, Lee JW, Kim WW, Jung JH, Park HY. Oncoplastic surgical techniques for personalized breast conserving surgery in breast cancer patient with small to moderate sized breast. J Breast Cancer. 2011;14(4):253–61. doi:10.4048/jbc.2011.14.4.253.
41. Berry MG, Fitoussi AD, Curnier A, Couturaud B, Salmon RJ. Oncoplastic breast surgery: a review and systematic approach. J Plast Reconstr Aesthet Surg. 2010;63(8):1233–43. doi:10.1016/j.bjps.2009.05.006.
42. Smith ML, Evans GR, Gurlek A, Bouvet M, Singletary SE, Ames FC, Janjan N, McNeese MD. Reduction mammaplasty: its role in breast conservation surgery

for early-stage breast cancer. Ann Plast Surg. 1998;41(3):234–9.
43. Losken A, Elwood ET, Styblo TM, Bostwick 3rd J. The role of reduction mammaplasty in reconstructing partial mastectomy defects. Plast Reconstr Surg. 2002;109(3):968–75; discussion 976–7.
44. Kaur N, Petit JY, Rietjens M, Maffini F, Luini A, Gatti G, Rey PC, Urban C, De Lorenzi F. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol. 2005;12(7):539–45. doi:10.1245/ASO.2005.12.046.
45. Fitzal F, Riedl O, Wutzl L, Draxler W, Rudas M, Pluschnig U, Handl-Zeller L, Dubsky P, Bachleitner-Hofmann T, Steger G, Jakesz R, Gnant M. Breast-conserving surgery for T3/T4 breast cancer: an analysis of 196 patients. Breast Cancer Res Treat. 2007;103(1):45–52. doi:10.1007/s10549-006-9325-6.
46. Fitzal F, Mittlboeck M, Trischler H, Krois W, Nehrer G, Deutinger M, Jakesz R, Gnant M. Breast-conserving therapy for centrally located breast cancer. Ann Surg. 2008;247(3):470–6. doi:10.1097/SLA.0b013e31815b6991.
47. Akay CL, Meric-Bernstam F, Hunt KK, Grubbs EG, Bedrosian I, Tucker SL, Kuerer HM, Hoffman KE, Babiera GV, Strom EA, Buchholz TA, Mittendorf EA. Evaluation of the MD Anderson Prognostic Index for local-regional recurrence after breast conserving therapy in patients receiving neoadjuvant chemotherapy. Ann Surg Oncol. 2012;19(3):901–7. doi:10.1245/s10434-011-2006-7.
48. Fitzal F, Mittlboeck M, Steger G, Bartsch R, Rudas M, Dubsky P, Riedl O, Jakesz R, Gnant M. Neoadjuvant chemotherapy increases the rate of breast conservation in lobular-type breast cancer patients. Ann Surg Oncol. 2012;19(2):519–26. doi:10.1245/s10434-011-1879-9.
49. Spanheimer PM, Carr JC, Thomas A, Sugg SL, Scott-Conner CE, Liao J, Weigel RJ. The response to neoadjuvant chemotherapy predicts clinical outcome and increases breast conservation in advanced breast cancer. Am J Surg. 2013;206(1):2–7. doi:10.1016/j.amjsurg.2012.10.025.