The Multidisciplinary Approach to Breast Cancer Management

17

Sarah M. DeSnyder and Kelly K. Hunt

Introduction

Breast cancer remains the second leading cause of cancer mortality among women in the United States. The field of breast cancer treatment is rapidly changing, and as the treatment evolves, it is more important than ever for physicians involved in the diagnosis and treatment of breast cancer to work as a collaborative team. It is through multidisciplinary treatment planning that breast cancer patients are able to achieve the best possible outcomes.

Management of Ductal Carcinoma In Situ

Significant changes have occurred in the past 30 years with respect to the detection, understanding, and management of ductal carcinoma in situ (DCIS). Prior to the utilization of screening mammography, DCIS accounted for less than 1 % of all breast cancer cases and was identified most often as a palpable mass, bloody nipple discharge, or the development of Paget's disease [1]. The routine use of screening mammography has resulted in a dramatic increase in the number of women diagnosed with DCIS. In 2011, the American Cancer Society estimated that DCIS accounted for 20 % of newly diagnosed breast cancers in the United States [2].

The natural history of DCIS has been reported by several groups who followed patients with a diagnosis of DCIS without any specific therapy other than diagnostic biopsy. Approximately 25–35 % of women with DCIS experience progression to invasive carcinoma within 10 years [3–5]. Those with low-grade lesions were noted to have a longer interval without disease progression compared to those with higher-grade lesions.

S.M. DeSnyder, MD • K.K. Hunt, MD (✉)
Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Unit 1484, Houston, TX 77030, USA
e-mail: sdesnyder@mdanderson.org; khunt@mdanderson.org

Although DCIS lesions are in situ or noninvasive carcinomas, they have traditionally been treated largely the same as invasive carcinomas. Initially, patients with DCIS were treated with mastectomy. However, randomized trials demonstrating equivalent overall survival (OS) in patients with invasive carcinoma treated with mastectomy and those treated with breast-conserving surgery followed by radiation therapy (breast-conserving therapy; BCT) raised questions about the necessity of mastectomy to treat all breast cancers. This led to clinical trials of breast conservation in patients with DCIS. As a result, selected patients with DCIS now have a wide variety of treatment options, including mastectomy either with or without reconstruction; BCT; and, in some highly selected patients, breast-conserving surgery alone.

Key Clinical Trials

In the 1970s and 1980s, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial and five other randomized trials were conducted in women with early-stage invasive carcinoma and demonstrated the OS equivalence of mastectomy and BCT [6–11]. Although the NSABP B-06 trial was designed to compare total mastectomy, BCT, and breast-conserving surgery alone in women with invasive carcinoma, central pathology review revealed that 78 patients actually had pure DCIS [6, 12]. Despite significant differences in local-regional recurrence rates, no OS difference was noted between patients with DCIS who underwent mastectomy and those who underwent BCT. Thus, the NSABP B-06 trial helped to establish the equivalence of mastectomy and BCT in women with DCIS.

The NSABP conducted the B-17 trial in order to assess the need for radiation following breast-conserving surgery in the management of DCIS. Patients with localized DCIS were randomly assigned to BCT or breast-conserving surgery alone [13]. After a mean follow-up time of 90 months, rates of both ipsilateral noninvasive and invasive recurrences were significantly lower in the group who received radiation. This study demonstrated the importance of postoperative radiation following surgical excision of DCIS.

M.K. Shetty (ed.), *Breast Cancer Screening and Diagnosis: A Synopsis*,
DOI 10.1007/978-1-4939-1267-4_17, © Springer Science+Business Media New York 2015

The benefit of BCT over breast-conserving surgery alone for DCIS was also demonstrated in several other randomized trials including the European Organization for Research and Treatment of Cancer (EORTC) protocol 10853; the United Kingdom, Australia, New Zealand DCIS Trial (the "UK Trial"); and the Swedish Trial [14–17]. However, it is important to recognize the current standards for specimen examination and processing—including correlation with imaging, inking of margins, and detailed pathologic examination with reporting of margin width—were not standard at the time these randomized trials were conducted.

A retrospective study by Silverstein and colleagues demonstrated that highly selected patients with DCIS may safely undergo breast-conserving surgery alone. This study examined the relationship between margin status and local control for women with DCIS [18]. The authors showed that women with margins greater than 10 mm did not benefit from radiation therapy. Women with margins between 1- and 10-mm had a relative risk of local recurrence of 1.49, compared to 2.54 for women with margins less than 1 mm. Although this was a single institution retrospective analysis, it suggested that appropriately selected patients with DCIS might not require postoperative radiation therapy.

The Radiation Therapy Oncology Group (RTOG) sought to define those patients with "good risk" DCIS who could be identified to safely undergo breast-conserving surgery alone. Eligible patients included those with unicentric, low- or intermediate-grade DCIS measuring 2.5 cm or less with a margin of 3 mm or more obtained at the time of breast-conserving surgery. Patients were randomized to whole-breast irradiation (WBI) versus no radiation. Although the trial was closed due to failure to meet required accrual numbers, the results for the 585 analyzable patients have been reported at a median follow-up was 6.46 years [19]. The local failure rate at 5 years was 0.4 % for those patients randomized to receive WBI and 3.2 % for those randomized to no radiation. This trial demonstrated a significant reduction in the local failure rate with WBI. Continued follow-up for enrolled patients is planned.

Similar to the RTOG, the Eastern Cooperative Oncology Group also prospectively evaluated patients to identify those who could safely undergo breast-conserving surgery alone [20]. Eligible patients included those with low- or intermediate-grade DCIS measuring 2.5 cm or less excised with a margin of at least 3 mm and those with high-grade DCIS measuring 1 cm or less excised with a margin of at least 3 mm. At a median follow-up of 6.2 years, those with low- or intermediate-grade DCIS had an ipsilateral breast event rate of 6.1 %, while those with high-grade DCIS had an ipsilateral breast event rate of 15.3 %. This study identified an acceptable ipsilateral breast event rate for those with low- or intermediate-grade DCIS who underwent excision alone with a margin width of at least 3 mm. In contrast, those with high-grade DCIS were not deemed to be acceptable candidates for breast-conserving surgery alone.

Selection of Surgical Therapy

Selection of therapy for patients with DCIS depends on clinical and pathologic factors, including tumor size, tumor grade, mammographic appearance, and patient preference. For most women with DCIS, the choice is between breast-conserving therapy and mastectomy. There is no single correct surgical treatment and many patients will require extensive counseling to make a decision regarding surgical therapy.

Breast-Conserving Surgery or Mastectomy

Careful selection of patients for breast-conserving surgery alone is critical to optimizing outcomes. At The University of Texas MD Anderson Cancer Center, patients with small (less than 1 cm) low-grade lesions excised with a margin of 5 mm or greater are considered candidates for breast-conserving surgery without radiation therapy [21]. The majority of patients with DCIS are candidates for BCT. However, if potential contraindications to radiation therapy exist, such as prior irradiation or the presence of collagen vascular disease, preoperative evaluation by a radiation oncologist may be indicated.

Patients with extensive suspicious calcifications identified on mammography, multicentric DCIS, close or positive margins after multiple re-excisions, prior WBI, or active collagen vascular disease should be considered candidates for mastectomy. Patients with DCIS who require mastectomy are typically candidates for skin-sparing mastectomy with immediate breast reconstruction. Certain patients are eligible for mastectomy that spares the nipple-areolar complex: patients with tumors located more than 2.5 cm from the border of the areola with smaller breast size, minimal ptosis, no prior breast surgeries requiring periareolar incisions, body mass index less than 40 kg/m^2, no active tobacco use, no prior breast irradiation, and no evidence of collagen vascular disease.

In patients eligible for BCT, the surgeon must extensively counsel the patient about the risks and benefits of BCT. It is important that patients understand that BCT is associated with a slightly higher risk of local recurrence than mastectomy, but that despite this, there is no OS difference between BCT and mastectomy.

Patient factors that may drive the decision for BCT include desire to preserve native breast tissue, desire to maintain breast and nipple sensation, and desire to minimize surgical intervention. Patient factors that may drive the decision for mastectomy include anxiety regarding recurrence, desire to minimize the need for continued imaging surveillance, concern about breast symmetry, and desire to avoid radiation therapy.

Axillary Staging

The role of axillary staging in patients with DCIS is limited. Since DCIS is a noninvasive carcinoma, it does not have the propensity to spread, and thus lymph node involvement is not expected. Despite this, for patients undergoing mastectomy as well as those with large, high-grade, or palpable tumors, axillary staging with

sentinel lymph node biopsy (SLNB) may be recommended. Since most lesions are diagnosed with needle core biopsy, there is about a 20 % incidence of finding invasive breast cancer on final pathology. As it is not feasible to perform lymphatic mapping and SLNB after mastectomy, most surgeons will recommend that patients undergo SLNB at the time of mastectomy for DCIS. The technique for SLNB is described later in this chapter.

Surgical Technique

Breast-Conserving Surgery

Patients undergoing breast-conserving surgery for nonpalpable DCIS require image-guided localization of the tumor. The lesion is excised with the goal of achieving optimal cosmesis (Fig. 17.1). Incision placement is of the utmost importance to achieving this goal. For tumors located in the superior pole of the breast, creation of an incision following Langer's lines is best, while for tumors located in the inferior pole of the breast, a radial incision may be best [22]. The tumor is excised with a rim of normal breast tissue. Following excision, the specimen is oriented and sent to the pathology department, where it is imaged with specimen radiography, inked (Fig. 17.2a), sectioned (Fig. 17.2b), and reimaged. If close margins are identified on specimen radiography, re-excision is performed, and the excised tissue is sent to the pathology department for permanent-section examination. The border of the surgical cavity should be marked with radiopaque clips to facilitate radiation therapy planning. This intraoperative assessment of margins helps to achieve negative margins at the initial surgery and reduce the need for reoperation for margin control.

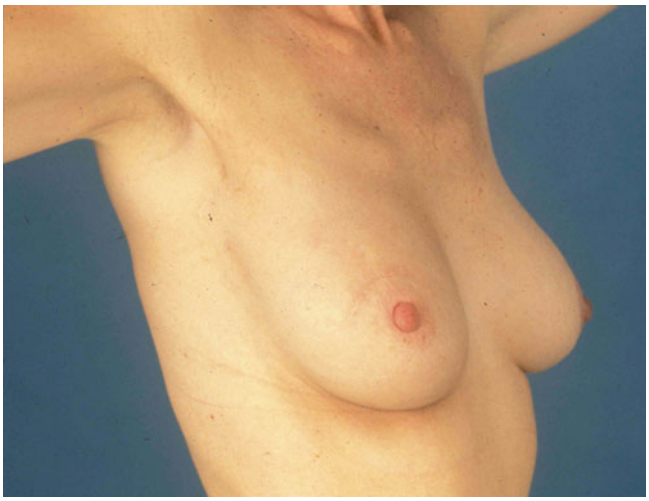

Fig. 17.1 Long-term cosmetic outcome after breast-conserving surgery performed using a periareolar incision

Various techniques may be utilized to minimize contour defects following breast-conserving surgery. For larger defects, the deep parenchyma may be re-approximated. However, if a large cosmetic defect is anticipated preoperatively, it may be beneficial to involve a plastic surgeon to perform local tissue rearrangement and possibly a procedure on the contralateral breast to achieve symmetry.

The findings on the final pathology review dictate whether additional surgical therapy will be needed. At MD Anderson, margins are re-excised if the tumor is less than 2 mm from the inked margin. As discussed previously, inability to obtain negative margins after multiple re-excisions is an indication for mastectomy.

Mastectomy

Patients undergoing mastectomy for DCIS may be considered for total mastectomy, skin-sparing mastectomy with immediate reconstruction (Fig. 17.3a), or nipple-areolar-complex-sparing mastectomy with immediate reconstruction (Fig. 17.3b).

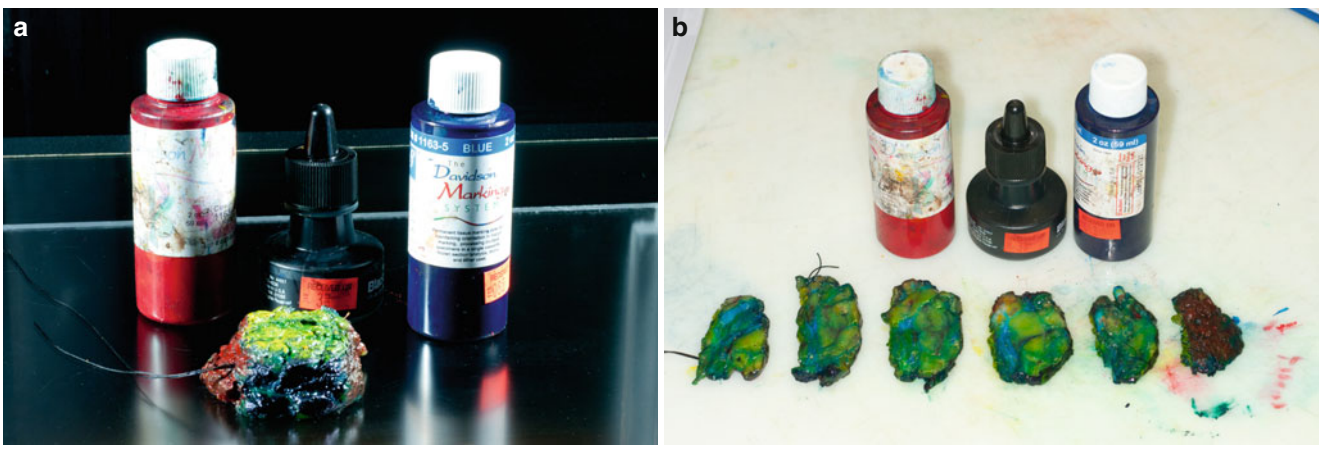

Fig. 17.2 (**a**) Segmental mastectomy specimen shown after different colors of ink have been applied to designate the anatomic margins. (**b**) Segmental mastectomy specimen shown following inking and sectioning. Both the whole specimen and the sectioned specimen are radiographed, and careful examination is performed by the pathologist and the radiologist

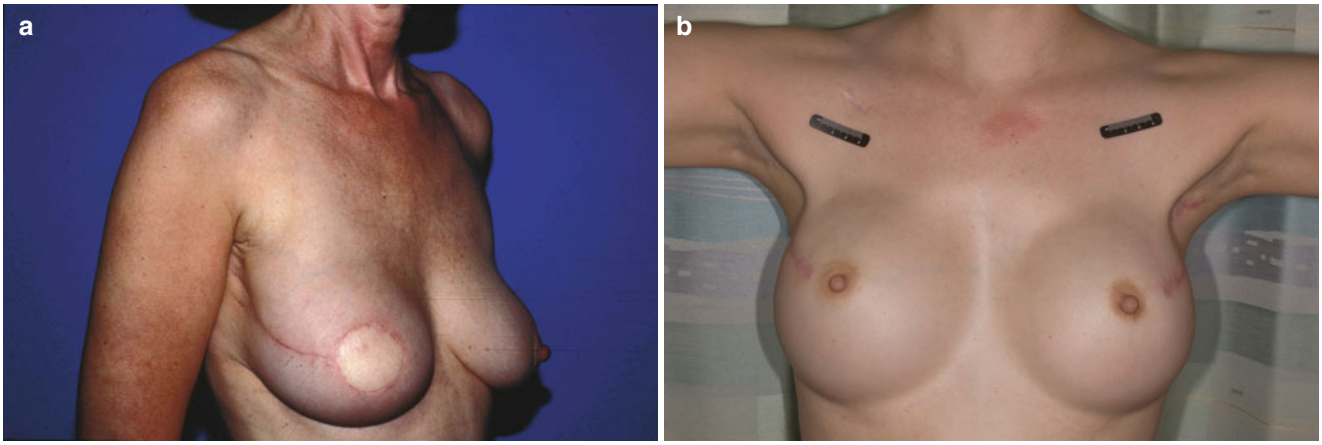

Fig. 17.3 (**a**) Skin-sparing mastectomy with TRAM flap reconstruction prior to nipple reconstruction. (**b**) Bilateral nipple-areolar-complex-sparing mastectomy with implant reconstruction

Although extensive DCIS is not a contraindication to skin-sparing mastectomy, patients with DCIS close to the skin may require excision of additional skin to achieve negative margins. Intraoperative specimen radiography is performed to determine the adequacy of margins. Excision of additional skin may be necessary if superficial disease is identified.

As discussed previously, careful selection of patients for nipple-areolar-complex-sparing mastectomy is crucial to optimize outcomes. A variety of incisions may be chosen for this type of mastectomy, including a radial incision, a lateral incision, or an inframammary incision. Incision placement may be dictated by the location of the tumor, prior biopsy scars, or patient or surgeon preference. Following excision of the breast tissue, the specimen is oriented, and clips are placed at the circumference of the areolar margin at the 3, 6, 9, and 12 o'clock positions as well as directly underneath the nipple to focus the pathologic examination. As with skin-sparing mastectomy, intraoperative specimen radiography is performed to determine the adequacy of margins. Excision of additional skin may be necessary if superficial disease is identified. If there is suspicion of disease in the tissue beneath the nipple, tissue from the area or areas of interest is subjected to intraoperative frozen section examination. The nipple-areolar complex should be excised if malignant cells are identified on frozen section examination.

Radiation Therapy

Radiation therapy is an important component of therapy for most women with DCIS who choose to undergo BCT. It is important to note that adequate surgical therapy is required to achieve superior outcomes with BCT. Radiation therapy cannot adequately compensate for inadequate surgery.

The benefit of radiation therapy for patients with DCIS undergoing breast-conserving surgery has been well established by prospective randomized trials. The NSABP B-17 trial included 814 patients with DCIS [13]. Following margin-negative tumor excision, patients were randomized to two groups, WBI and observation. Patients in the WBI group received 50 Gy to the whole breast without a boost to the tumor bed. Although there was no difference in OS between the WBI and observation groups at a mean follow-up time of 8 years, significant reductions were observed in the rates of both ipsilateral DCIS (12.1 % vs. 26.8 %, $P=0.007$) and invasive recurrence (3.9 % vs. 13.4 %, $P<0.000005$).

The EORTC 10853 trial included 1,010 patients with DCIS and was similar in design to the NSABP B-17 trial [14, 15]. Patients were randomized to WBI or observation after margin-negative tumor excision. As in the NSABP B-17 trial, patients in the WBI group received 50 Gy to the whole breast. However, in contrast to what was done in the NSABP B-17 trial, 5 % of patients in the WBI group received a boost to the tumor bed. At a median follow-up time of 10.5 years, no OS difference was seen between the two groups. However, patients randomized to postoperative WBI had fewer recurrences, including both DCIS and invasive recurrences, than patients randomized to observation (74 % vs. 85 %, $P<0.0001$). It is important to note that all patient subgroups in this trial benefited from postoperative WBI.

The UK Coordinating Committee on Cancer Research trial included 1,030 patients with DCIS or microinvasive disease (invasive disease measuring less than 1 mm) [16]. Patients were randomized to postoperative radiation therapy or observation following margin-negative tumor excision. Some patients in each group received adjuvant tamoxifen therapy. Patients randomized to postoperative radiation therapy received 50 Gy to the whole breast without a boost to the tumor bed. At a median follow-up time of 4.8 years, the incidence of recurrence in the ipsilateral breast was significantly reduced in the patients randomized to postoperative radiation therapy (6 % vs. 14 %, $P<0.001$). Although tamoxifen use

was not associated with a reduced risk of ipsilateral invasive disease, it was associated with a reduced risk of ipsilateral DCIS recurrence.

In the SweDCIS trial, 1,046 women were randomized to postoperative radiation therapy or observation [17]. Patients randomized to postoperative irradiation had a 5-year incidence of ipsilateral recurrence of 7 %, compared to 22 % in the observation group ($P<0.0001$). No difference was seen in OS.

Despite these data from prospective, randomized trials supporting the benefit of postoperative radiation therapy following margin-negative tumor excision, some investigators have supported excision alone for DCIS because of the lack of OS benefit from postoperative radiation therapy. Thus, patients who are unlikely to benefit from postoperative radiation therapy may be selected for breast-conserving surgery only. The MD Anderson Cancer Center selection criteria for breast-conserving surgery alone have been discussed earlier in this chapter.

Limited data exist to support the use of accelerated partial breast irradiation (APBI) for patients with DCIS. APBI is administered two times daily over 5 days. A variety of methods exist for administration of APBI, including the use of balloon catheters or interstitial multicatheter brachytherapy devices and 3-dimensional conformal external beam radiation therapy. The published consensus statement from the American Society for Radiation Oncology (ASTRO) categorizes patients aged 50 years or older with DCIS measuring 3 cm or less in the "cautionary" group for APBI use; patients younger than 50 years of age and those with DCIS larger than 3 cm are considered to be "unsuitable" for APBI [23]. The ASTRO task force asserted that the paucity of data on the use of APBI in patients with DCIS has resulted in uncertainty regarding its use. The ASTRO guidelines encouraged enrollment of patients with DCIS measuring less than 3 cm in the RTOG 04-13/NSABP B-39 clinical trial. This clinical trial was opened in March 2005 and has recently completed accrual. The goal of this trial is to examine the efficacy of APBI modalities compared to each other as well as to WBI.

Adjuvant Tamoxifen

Results from studies to date indicate that following counseling regarding the risks and benefits of tamoxifen therapy, women with estrogen receptor (ER)-positive DCIS without contraindications to tamoxifen therapy should be offered adjuvant tamoxifen for a duration of 5 years.

The NSABP B-24 trial demonstrated a significant reduction in ipsilateral tumor events with adjuvant tamoxifen therapy for patients with DCIS [24]. This trial included 1,804 women with DCIS regardless of ER status. Women were randomized to BCT with tamoxifen or BCT without tamoxifen. At a median follow-up time of 74 months, the rate of breast cancer events was lower in the tamoxifen group (8.2 % vs. 13.4 %, $P=0.0009$).

Allred and colleagues retrospectively evaluated 41 % of patients with DCIS in the NSABP B-24 trial to determine the relationship between DCIS ER status and the effects of tamoxifen [25]. In this study, 76 % of women had DCIS that was ER positive. Patients with ER-positive DCIS had a greater reduction in ipsilateral breast tumor recurrence with tamoxifen than patients with ER-negative DCIS (11 % vs. 5.2 %, $P<0.001$).

Management of Early-Stage Breast Cancer

Early-stage (stage I and II) breast cancer may be managed successfully with either BCT or mastectomy.

Key Clinical Trials

Trials Comparing BCT and Mastectomy

The NSABP B-06 trial established the survival equivalence of BCT and mastectomy for patients with early-stage breast cancer [6]. This trial compared lumpectomy and axillary lymph node dissection (ALND) either with or without WBI to modified radical mastectomy in patients with a tumor size of 4 cm or less and either N0 or N1 nodal status. A total of 2,163 patients were randomized. No difference was noted between the treatment groups in disease-free survival (DFS) or OS. This was maintained at 20 years of follow-up [26]. Notably, there were significant differences in the local control rates. Patients treated with lumpectomy without WBI had an in-breast recurrence rate of 39.2 %, those treated with lumpectomy with WBI had an in-breast recurrence rate of 14.3 %, and those treated with mastectomy had a chest wall recurrence rate of 10.2 %. In addition to the NSABP B-06 trial, five other randomized trials have demonstrated no difference in DFS and OS between BCT and mastectomy for patients with early-stage disease [7–11].

Axillary Staging

Axillary lymph node status remains the most important prognostic factor for women with operable breast cancer. Much like the treatment of the primary breast tumor, staging and treatment of the axilla has become less invasive over the past several decades. Historically, ALND was required for axillary staging. However, randomized trials evaluating less invasive techniques for operable breast cancer demonstrated that elective ALND had no survival benefit over ALND performed in a delayed fashion once clinically palpable axillary disease became evident [26, 27]. The routine use of ALND for staging of the axilla overtreats the 75 % percent of women with operable breast cancer in whom the axillary lymph

nodes are histologically negative. These findings prompted the development of lymphatic mapping and SLNB for breast cancer patients with a clinically negative axilla [28].

In 1991, Giuliano and colleagues initiated a pilot study to examine the use of SLNB for patients with breast cancer. Of the 174 patients enrolled, 114 (65.5 %) had a SLN successfully identified. In 109 of these 114 patients (95.6 %), the status of the SLN accurately predicted the status of the axilla. The results of this pilot study, reported in 1994, revolutionized axillary surgery. Today, SLNB is recognized as a minimally invasive and accurate technique to stage the axilla with the advantage of decreased morbidity [28, 29].

The NSABP B-32 trial compared clinically node-negative patients undergoing SLNB followed by ALND with patients undergoing SLNB with ALND only if a SLN was positive for metastatic disease [30]. A total of 5,611 patients were randomized. The SLN identification rate was 97 %, and the false-negative rate was 9.7 %. Twenty-six percent of patients in the trial had positive SLNs. Over 60 % of patients with metastatic disease in the SLNs had no further positive lymph nodes within the ALND specimen. The NSABP B-32 clinical trial and other randomized trials demonstrated no difference in DFS, OS, and local-regional control rates between patients with negative SLNs who underwent SLNB alone and those who underwent ALND [31, 32]. In addition, patients who undergo SLNB alone have been noted to have decreased morbidity and improved quality of life compared to patients who undergo ALND [32, 33].

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial evaluated the utility of ALND in patients with clinical T1-2, N0 breast cancer with one or two positive SLNs for whom BCT with WBI was planned [34]. Patients were not eligible if they received neoadjuvant chemotherapy or neoadjuvant hormonal therapy or if their treatment plan included mastectomy, lumpectomy without radiation, or lumpectomy with alternative forms of radiation delivery such as APBI. WBI was administered using standard tangential fields without additional fields. Patients with one or two positive SLNs were randomized to completion ALND or no further surgery. Decisions regarding adjuvant therapy were left to the treating clinicians. The primary endpoint was OS, and the secondary endpoint was local-regional recurrence. After a median follow-up time of over 6 years, no difference was noted between patients randomized to completion ALND and those randomized to no further surgery in terms of OS (91.9 and 92.5 %, respectively; $P=0.25$) or DFS (82.2 and 83.8 %, respectively; $P=0.14$).

Data from the ACOSOG Z0011 trial also demonstrated that patients randomized to SLNB alone were less likely to have adverse effects than were patients randomized to completion ALND (25 % vs. 70 %, $P\leq0.001$) [35]. Patients in the SLNB-alone group were less likely to have wound infections (3 % vs. 8 %, $P\leq0.0016$), seromas (6 % vs. 14 %, $P\leq0.0001$), paresthesias (9 % vs. 39 %, $P<0.0001$), and subjectively reported lymphedema (2 % vs. 13 %, $P<0.0001$).

Prior to the reporting of the ACOSOG Z0011 data, completion ALND was the standard of care for patients with metastatic disease identified within SLNs. Following publication of the ACOSOG Z0011 trial, the National Comprehensive Cancer Network (NCCN) added a footnote to its published breast cancer guidelines stating that there was no OS difference for patients with one or two positive SLNs treated with BCT who underwent completion ALND and those who underwent no further surgery [36]. In addition, the American Society of Breast Surgeons issued a consensus statement that supported the omission of completion ALND for patients who meet the ACOSOG Z0011 criteria [37]. The results of the ACOSOG Z0011 trial have revolutionized treatment of the axilla in selected patients with axillary metastasis.

The International Breast Cancer Study Group (IBCSG) 23-01 trial had a design similar to that of the ACOSOG Z0011 trial [38]. In the IBCSG 23-01 trial, patients with micrometastatic disease within the SLN were randomized to ALND versus no further surgery. Unlike the ACOSOG Z0011 trial, the IBCSG 23-01 trial did not exclude patients undergoing mastectomy. Approximately 9 % of patients in each arm of the trial were treated with mastectomy. The investigators recently published the results and showed no differences in OS or local-regional recurrence between the study arms [39].

Recently, the ACOSOG Z1071 trial examined the role of SLNB in patients who presented with N1-2 nodal disease and received neoadjuvant chemotherapy [40]. This trial included patients with clinical T1-4, N1-2 breast cancer who received neoadjuvant chemotherapy. All patients underwent SLNB followed by completion ALND. Complete resolution of axillary disease was noted in 40 % of patients. SLNB identified the nodal status correctly in 84 % of patients; the false-negative rate was 12.4 %. Although this false-negative rate was higher than the predefined acceptable rate of 10 %, removal of two or more SLNs at the time of SLNB reduced the false-negative rate. The results of this trial were recently published in the Journal of the American Medical Association. This trial may significantly impact treatment of the axilla in patients with axillary nodal disease at presentation in whom axillary disease resolves following neoadjuvant chemotherapy.

Selection of Surgical Therapy

BCT or Mastectomy

Selection of therapy for patients with early-stage breast cancer depends on a variety of tumor and patient factors, including the ratio of tumor size to breast size, the presence of multicentric disease, whether the patient can tolerate radiation therapy, and patient preference. Patients with a large tumor in relation to the size of the breast may not achieve an

adequate cosmetic outcome after BCT and may be better served by mastectomy. BCT is typically reserved for patients with a tumor size of 4 cm or less. However, BCT with a good cosmetic outcome may also be achievable in women with larger tumors and relatively large breasts. Patients with larger tumors who wish to pursue BCT may be candidates for either neoadjuvant chemotherapy or neoadjuvant hormonal therapy to decrease the tumor size and thus permit BCT. In addition, patients with larger tumors who opt for BCT may be candidates for local tissue rearrangement or placement of myocutaneous tissue flaps to repair the defect resulting from BCT. Patients with multicentric disease are better served by mastectomy as they are considered to have an increased risk of recurrence after BCT.

It is also important to recognize that BCT requires adjuvant radiation therapy. Thus, patients for whom BCT is planned should be evaluated by a radiation oncologist if they have undergone prior irradiation of the breast or a region close to the breast or have a collagen vascular disease. In addition, patients for whom BCT is planned must be willing and able to attend all planned radiation therapy appointments.

Breast Reconstruction After Mastectomy

Mastectomy for early-stage breast cancer may be performed either with or without breast reconstruction. Many patients with early-stage breast cancer who undergo mastectomy are candidates for breast reconstruction.

For many patients, reconstruction can be performed immediately at the time of mastectomy. Immediate reconstruction allows for skin-sparing mastectomy which preserves the patient's own skin, thus optimizing cosmetic outcomes. Highly selected women with early-stage breast cancer may be candidates for immediate reconstruction with preservation of the nipple-areolar complex. Eligibility for this procedure has been described previously in this chapter. Patients for whom adjuvant radiation therapy is planned are not ideal candidates for nipple-areolar-complex-sparing mastectomy because of the effects of radiation on the preserved nipple. In addition to providing improved cosmesis resulting from preservation of the skin and/or the nipple-areolar complex, immediate reconstruction provides a psychological benefit for the patient. Patients undergoing immediate reconstruction also benefit from completing therapy and reconstruction in one surgery.

If no postoperative radiation therapy is planned, patients may have immediate reconstruction performed using implants or autologous tissue; tissue flaps that can be used include the transverse rectus abdominis myocutaneous flap, deep inferior epigastric perforator flap, latissimus dorsi flap with an implant, and other tissue flaps. However, if adjuvant radiation therapy may be required, a tissue expander should be placed. A tissue expander allows for preservation of the skin at the time of mastectomy, and the expander can be deflated at the time of radiation therapy to permit adequate irradiation of the chest wall and regional nodal basins. Removal of the tissue expander and reconstruction with either an implant or autologous tissue takes place approximately 1 year after completion of radiation therapy.

Axillary Staging

Axillary staging is required for all patients with early-stage breast cancer. Information about the axillary nodal status is valuable prognostic information and assists in tailoring adjuvant therapies. For example, for patients with small tumors without lymph node involvement, adjuvant chemotherapy may not be recommended; however, detection of lymph node involvement in a patient with a small tumor would prompt a recommendation for chemotherapy. In addition, detection of axillary lymph node involvement in a patient younger than 40 years or more than four involved axillary lymph nodes in any patient would prompt a recommendation for adjuvant radiation therapy in patients treated with mastectomy, whereas in the absence of nodal metastases, postmastectomy radiation therapy (PMRT) would not be recommended.

Thus, patients with clinically node-negative breast cancer should undergo SLNB for staging of the axilla. Patients with a positive SLN should be appropriately selected for completion ALND versus no further surgery according to the principles outlined previously.

At MD Anderson, patients for whom BCT with WBI is planned and who meet the eligibility criteria used in the ACOSOG Z0011 trial undergo intraoperative lymphatic mapping with SLNB at the time of segmental mastectomy. At the time of SLNB, the SLNs are sent to the pathology department for permanent-section examination. Patients with one or two positive SLNs who have negative tumor margins proceed to adjuvant systemic therapy and WBI with no further surgery.

The current MD Anderson practice regarding completion ALND was established during a multidisciplinary conference held to discuss the results of the ACOSOG Z0011 trial and apply these results safely to patients [41]. This conference included clinicians from the Departments of Surgical Oncology, Radiation Oncology, Breast Medical Oncology, Diagnostic Radiology, and Pathology. The participants reached a consensus that omission of completion ALND was appropriate for patients with clinical T1-2, N0 breast cancer and one or two positive SLNs expected to undergo BCT with WBI but not for patients expected to undergo mastectomy or APBI or for patients who underwent neoadjuvant chemotherapy or neoadjuvant hormonal therapy. Special consideration was given to patients with lobular histology as patients with lobular carcinoma were underrepresented in the ACOSOG Z0011 trial and small-volume axillary disease may be of clinical relevance in patients with lobular histology. Both of these factors should be taken into consideration when patients with lobular histology

are counseled about completion ALND. Hormone receptor status is also an important consideration as 83 % of ACOSOG Z0011 participants had ER-positive disease. Although ER status was not significantly associated with local-regional recurrence on multivariable analysis, at MD Anderson, hormone receptor status is considered within a broad context of factors when patients are counseled about completion ALND. Age is another important factor to consider. More than 62 % of patients in each arm of the ACOSOG Z0011 trial were older than 50 years. In addition, age younger than 50 years was a significant predictor of local-regional recurrence on multivariable analysis. Thus, patients younger than 50 years should be carefully counseled regarding completion ALND. Nodal burden may also play an important role in risk determination. At MD Anderson, a nomogram that incorporates the size of SLN metastases and the ratio of positive to negative nodes harvested at SLNB may be used to counsel patients regarding the need for completion ALND [42]. At MD Anderson, patients with a positive SLNB expected to undergo mastectomy and those expected to undergo BCT with alternative forms of radiation therapy undergo completion ALND.

Surgical Techniques

Breast-Conserving Surgery

Patients undergoing breast-conserving surgery for nonpalpable early-stage breast cancer require image-guided localization of the tumor.

Incision placement is key to achieving optimal cosmetic outcomes. The tumor is excised with a rim of normal breast tissue. The specimen is then oriented and sent to the pathology department, where it is imaged with specimen radiography, inked, sectioned, and reimaged. If close margins are identified on specimen radiography, re-excision is performed, and the excised tissue is sent to the pathology department for permanent-section examination. The border of the surgical cavity is marked with radiopaque clips to facilitate radiation therapy planning.

Patients with larger defects after tumor excision may benefit from involvement of a plastic surgeon for local tissue rearrangement (Fig. 17.4a) or reconstruction using a latissimus dorsi flap (Fig. 17.4b). If necessary, a procedure may be performed on the contralateral breast to achieve symmetry, either during the same surgery when the tumor is excised or following completion of radiation therapy at a second surgery.

The findings on the final pathology review dictate whether additional surgical therapy will be needed. As described previously, at MD Anderson, a margin of less than 2 mm prompts consideration for a return to the operating room for re-excision. If negative margins cannot be achieved after multiple re-excisions, mastectomy is indicated.

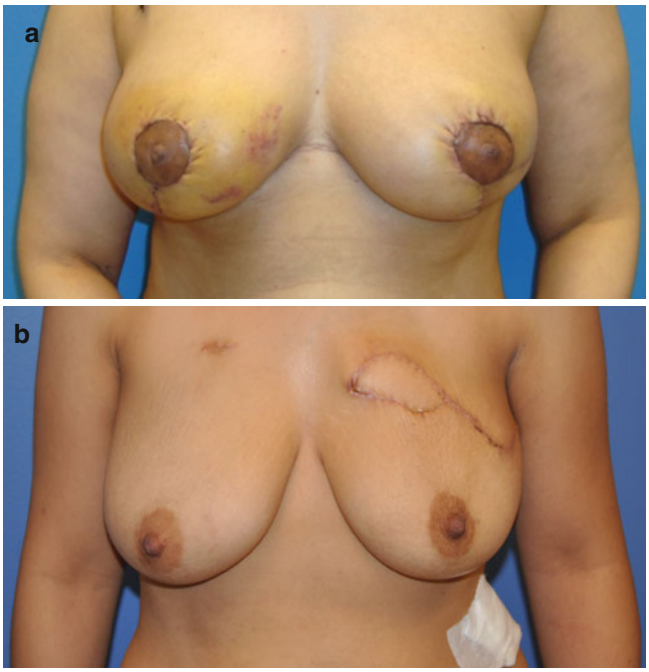

Fig. 17.4 (**a**) Cosmetic outcome in a patient requiring re-excision for margin control with local tissue rearrangement and contralateral symmetry procedure. (**b**) Breast-conserving surgery with repair of the partial mastectomy defect using a latissimus dorsi flap for volume replacement (Photos courtesy of Dr. David M. Adelman)

Mastectomy

Surgical options for patients undergoing mastectomy for early-stage breast cancer include total mastectomy, skin-sparing mastectomy, and, for some highly selected patients, nipple-areolar-complex-sparing mastectomy.

Regardless of the type of mastectomy, intraoperative specimen radiography is performed to determine the adequacy of margins. Excision of additional skin may be necessary if superficial disease is identified.

As discussed previously, careful selection of patients for nipple-areolar-complex-sparing mastectomy is crucial to optimize outcomes. If there is suspicion of disease beneath the nipple or areola, intraoperative assessment of the tissue underlying the circumference of the areolar margin at 3, 6, 9, and 12 o'clock as well as directly underlying the nipple may be performed by the pathologist using frozen section examination. The nipple-areolar complex should be excised if malignant cells are identified on frozen section examination.

Patients undergoing skin-sparing mastectomy or nipple-areolar-complex-sparing mastectomy undergo initiation of reconstruction with placement of a tissue expander. If the likelihood of adjuvant radiation therapy is very small, immediate reconstruction can be performed using an implant or a myocutaneous flap.

Axillary Lymph Node Staging

In patients with a clinically negative axilla, axillary staging should be performed with SLNB. SLNB requires lymphatic mapping, which can be accomplished with blue dye or a radioactive tracer, and SLN dissection. Some surgeons choose to have patients undergo preoperative lymphoscintigraphy as well to identify patterns of lymphatic drainage.

For patients undergoing preoperative lymphoscintigraphy, lymphoscintigraphy is most often performed with injection of high-dose technetium-labeled sulfur colloid (2.5 mCi) on the day prior to surgery. The technetium-labeled sulfur colloid can be injected peritumorally or under the areola. Patients with nonpalpable tumors require imaging guidance for peritumoral injection. Peritumoral injection has the advantage of identifying drainage patterns of the tumor outside of the axilla, such as drainage to the internal mammary lymph nodes. Lymphoscintigraphy is performed 15–30 min following radiocolloid injection and then at 30- to 60-min intervals thereafter until drainage to the SLN is identified. The inability of lymphoscintigraphy to identify a SLN on the day before surgery does not necessarily indicate failure of mapping; in some patients, drainage to SLNs will occur, and a SLN will be identified with a handheld gamma probe at the time of surgery. However, if drainage is not identified on lymphoscintigraphy performed the day before surgery, consideration should be given to reinjection of low-dose technetium-labeled sulfur colloid on the day of surgery.

On the day of surgery, patients injected the day before surgery with high-dose technetium-labeled sulfur colloid are taken directly to the operating room. Patients who did not undergo injection of high-dose technetium-labeled sulfur colloid the day before surgery should be injected with a low dose (0.5–1 mCi) of technetium-labeled sulfur colloid 1–4 h before they are taken to the operating room. If dual-modality SLN mapping is planned (i.e., use of both blue dye and radiotracer), prophylaxis for allergic reactions to the blue dye solution should be administered intravenously in the operating room. This prophylaxis includes diphenhydramine, steroids, and famotidine. Five milliliters of lymphazurin blue dye should be injected peritumorally for patients undergoing breast-conserving surgery or either peritumorally or under the areola for patients undergoing mastectomy. The breast should be massaged for 5 min to facilitate lymphatic drainage. A handheld gamma probe is used to transcutaneously localize the SLN within the axilla. A transverse incision is made close to the transcutaneously identified node along the standard ALND incision line below the axillary hairline. The gamma probe may be utilized to guide the dissection. Alternatively, blue-stained lymphatics may be used to guide the dissection. SLNs are defined as blue-stained lymph nodes and lymph nodes containing radioactivity as identified by the gamma probe.

Patients in whom mapping is more likely to fail to identify a SLN include patients who have undergone prior breast surgery, patients over 70 years of age, and obese patients. Patients who do not have a SLN identified should undergo ALND. The technique for ALND is described later in this chapter.

Radiation Therapy

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has examined all of the randomized trials where breast conservation was performed with or without radiation therapy [43]. At 15 years of follow-up, the absolute reduction in mortality with radiation therapy after breast-conserving surgery was 5.1 % in node-negative patients and 7.1 % in node-positive patients. These data suggest that the addition of radiation not only improves local control but also improves survival.

Two randomized trials have suggested that in selected older patients with small, low-grade tumors, breast-conserving surgery without radiation therapy may be appropriate [44, 45]. The Cancer and Leukemia Group B (CALGB) C9343 trial included women over 70 years of age with T1N0 breast cancer and randomized them to breast-conserving surgery with or without radiation therapy. All women, 97 % of whom had ER-positive tumors, were treated with adjuvant tamoxifen. No differences in DFS and OS were seen although the local recurrence rate was lower in patients randomized to radiation (1 % vs. 4 %, $P<0.001$). The Canadian trial was similar to the CALGB C9343 trial. Although the Canadian trial was open to women 50 years of age and older, the mean age was 68 years, and 80 % of women had ER-positive tumors. At a median follow-up time of 5.6 years, no difference was seen in DFS or OS although the local recurrence rate was lower in patients randomized to radiation (0.6 % vs. 7.7 %, $P<0.001$). Generally, patients with early-stage breast cancer selected for breast-conserving surgery without radiation include women 70 years of age or older with an expected survival of less than 10 years with T1, N0, ER-positive breast cancer.

APBI is an option for carefully selected patients with early-stage breast cancer. A variety of methods exists for administration of APBI as have been described previously in this chapter. Proponents of APBI argue that the majority of breast cancer recurrences occur in or adjacent to the tumor bed; the abbreviated course of treatment may increase the feasibility of BCT for many women; and the abbreviated course of treatment may improve radiation therapy compliance. The previously discussed RTOG 04-13/NSABP B-39 trial, which directly compares WBI to APBI in early-stage breast cancer, will provide data on local recurrence and survival and assess differences in outcomes between the two radiation treatment strategies.

While the results of this trial are awaited, a consensus statement from ASTRO was developed to guide the use of APBI outside of the context of a clinical trial [23]. According to the consensus statement, patients suitable for APBI include patients 60 years of age or older with a unifocal, T1, ER-positive tumor with no lymphovascular invasion and resection margins of at least 2 mm. Patients for whom ASTRO was not certain about the appropriateness of APBI include patients with invasive lobular histology, a tumor size of 2.1 cm to 3 cm, ER-negative disease, focal lymphovascular invasion, or margins less than 2 mm. Patients considered unsuitable for APBI include those with T3 or T4 disease, ER-negative disease, multifocality, multicentricity, extensive LVI, or positive margins.

Adjuvant Systemic Therapy

Adjuvant chemotherapy, biologic therapy, and hormonal therapy have all contributed to improved outcomes for breast cancer patients. The timing of systemic therapy may alter surgical therapy options and provide valuable prognostic information. Thus, it is important that the timing of therapies be determined using a multidisciplinary approach.

Chemotherapy may be administered as either neoadjuvant or adjuvant treatment. The NSABP B-18 trial demonstrated that neoadjuvant and adjuvant chemotherapy are equivalent with respect to DFS and OS [46]. However, in that trial, 12 % of patients who were initially not candidates for BCT were candidates for BCT at the conclusion of their neoadjuvant chemotherapy. In addition, administering chemotherapy in the neoadjuvant setting allows clinicians to assess the tumor's sensitivity to the regimen, which in turn allows clinicians to alter regimens for tumors that appear resistant, limiting the administration of ineffective chemotherapeutics.

The NCCN guidelines on breast cancer treatment, available at www.nccn.org, provide expert opinion based on synthesis of the available evidence. For patients with early-stage breast cancer, the most current NCCN guidelines, published in 2013, recommend neoadjuvant chemotherapy for patients with stage IIA (T2N0) and IIB (T2N1, T3N0) disease who are not initially candidates for BCT but desire to undergo BCT [47]. For patients with stage II disease who desire mastectomy, chemotherapy may be administered as adjuvant therapy or as neoadjuvant therapy.

Adjuvant chemotherapy has the potential to benefit all patients with early-stage breast cancer. However, most patients with stage I disease have a small risk of local recurrence, metastasis, and death due to breast cancer and thus a smaller potential benefit from adjuvant chemotherapy. Chemotherapy may be appropriate for some patients with stage I disease. However, when patients with stage I disease are counseled about adjuvant therapy options, it is important to consider tumor characteristics such as ER status, tumor size, and other prognostic factors.

Patients with ER-positive disease and a tumor smaller than 1 cm are unlikely to derive significant benefit from chemotherapy. In contrast, patients with ER-positive disease and a tumor size of 1–2 cm should be considered for adjuvant systemic therapy. Patients with ER-positive disease should be administered endocrine therapy for 5 years. Premenopausal patients should be recommended tamoxifen, while postmenopausal patients should be considered for an aromatase inhibitor.

Patients with ER-negative disease smaller than 0.5 cm are not usually recommended to receive adjuvant therapy. Those with ER-negative disease measuring 0.6–1 cm and unfavorable features such as young age, high tumor grade, and LVI should be considered for adjuvant chemotherapy. Patients with ER-negative disease larger than 1 cm should also be considered for adjuvant chemotherapy.

The NCCN guidelines recommend trastuzumab-based therapy for all patients with node-positive HER2-positive disease and patients with node-negative HER2-positive tumors larger than 1 cm. The guidelines also recommend that trastuzumab-based therapy be considered for patients with HER2-positive disease measuring 0.6–1 cm.

To individualize therapy decisions, it is important to consider the anticipated benefit for each patient. For patients for whom the NCCN guidelines recommend consideration of chemotherapy, tools to assist with decision making about systemic therapy may be helpful. These tools include Adjuvant! Online (Adjuvant! Inc.), Oncotype DX® (Genomic Health, Inc.), and MammaPrint® (Agendia). Adjuvant! Online is a computer model based on the Surveillance, Epidemiology, and End Results registry that estimates the 10-year risk of recurrence and death due to breast cancer according to age, comorbidities, ER status, tumor size, tumor grade, and nodal status. The Adjuvant! Online website creates easy-to-understand charts to assist with patient counseling. Adjuvant! Online does have limitations, however. Because it is based on registry data, inaccuracies may exist with respect to the data captured. In addition, information on women younger than 35 years and information on HER2 status was not captured, and thus, the use of Adjuvant! Online does not provide the best outcome information for these patients. Oncotype DX is a 21-gene assay developed to quantify the risk of recurrence and predict the benefit from chemotherapy for patients with ER-positive, node-negative disease [48, 49]. Oncotype DX also provides easy-to-understand graphics to assist in patient counseling. The MammaPrint assay, another tool used to predict both prognosis and the benefit of adjuvant therapy, is a 70-gene assay that categorizes patients as being at either low or high risk for recurrence, regardless of ER status.

Management of Locally Advanced Breast Cancer

Patients with locally advanced breast cancer must undergo multimodality treatment including systemic therapy, surgery, and radiation therapy to optimize outcomes. This patient group includes patients without clinically detected metastatic disease with tumors larger than 5 cm, tumors that invade the chest wall, tumors that involve the overlying breast skin, fixed or matted axillary lymph nodes, internal mammary involvement, or supraclavicular lymph node involvement.

Selection of Surgical Therapy

Traditionally, patients with locally advanced breast cancer required modified radical mastectomy; however, in a select group of patients, neoadjuvant chemotherapy may shrink the primary tumor enough to render patients candidates for BCT. Neoadjuvant chemotherapy is now the standard of care for patients with locally advanced disease.

In patients with internal mammary lymph node involvement, supraclavicular lymph node involvement, or chest wall invasion, neoadjuvant chemotherapy may render the disease resectable. In patients with locally advanced breast cancer considered operable at initial evaluation, neoadjuvant chemotherapy may make surgical intervention technically less difficult. In patients with large primary tumors who desire BCT, neoadjuvant chemotherapy may shrink the primary tumor enough to render patients candidates for this therapy. Patients who experience a decrease in the size of the primary tumor but still have a contour defect at the time of surgery may benefit from involvement of a plastic surgeon at the time of breast-conserving surgery to perform local tissue rearrangement or myocutaneous flap placement to restore volume and minimize the defect.

In a study to assess the feasibility of BCT for patients with locally advanced disease, patients who received neoadjuvant chemotherapy for locally advanced disease underwent pathologic examination of their mastectomy specimens [50]. Mastectomy specimens from 143 patients were examined, and 33 patients (23 %) were found to be appropriate candidates for BCT with ALND following completion of neoadjuvant chemotherapy. Requirements for BCT with ALND in this study included resolution of skin edema, residual tumor size less than 5 cm, lack of multicentricity, lack of extensive lymphovascular invasion, and lack of extensive suspicious microcalcifications.

More recently, an assessment of patients undergoing BCT following neoadjuvant chemotherapy, including patients with locally advanced disease, demonstrated that appropriately selected patients with locally advanced breast cancer can undergo BCT with an acceptable rate of local recurrence [51]. The 5-year ipsilateral breast tumor recurrence-free survival rate did not differ significantly between patients with T1, T2, T3, and T4 tumors. However, it is important to note that patients with T3 and T4 tumors were offered BCT according to their response to neoadjuvant chemotherapy. In addition, patients with multifocal T3 and T4 disease had a worse 5-year ipsilateral breast tumor recurrence-free survival rate than patients without multifocal disease (80 % vs. 97 %, $P = 0.0008$).

The administration of neoadjuvant chemotherapy to patients with chest wall involvement or extensive skin involvement may result in resolution of this involvement, thus permitting resection with modified radical mastectomy. However, if chest wall or extensive skin involvement does not resolve following neoadjuvant chemotherapy, chest wall resection or extensive skin resection may be required. Chest wall or extensive skin resection necessitates a multidisciplinary surgical team including a surgical oncologist, a plastic surgeon, and a thoracic surgeon. If skeletal resection is required, complex planning is necessary to achieve optimal outcomes, as resection of the chest wall may result in instability, exposure of underlying vital structures, and respiratory difficulty.

Chest wall reconstruction stabilizes the chest wall, protects underlying structures, and prevents paradoxical chest wall movement. A variety of mesh products and even metal plates may be considered for repair of chest wall defects. In addition, consideration of various soft tissue reconstruction options is important. These are necessary to provide coverage after chest wall resection as well as to provide closure after extended skin resection. Options for soft tissue closure range from skin graft placement to local tissue transfer to use of a myocutaneous flap.

Surgical Techniques

Breast-Conserving Surgery

It is of the utmost importance for patients with locally advanced breast cancer to undergo placement of a marker prior to initiation of neoadjuvant chemotherapy. This marker ensures that it will be possible to localize the tumor if a complete imaging response occurs. Patients with a nonpalpable tumor following neoadjuvant chemotherapy require image-guided localization of the tumor at the time of surgery. The technique for BCT has been described earlier in this chapter.

Mastectomy

Surgical options for patients who undergo mastectomy for locally advanced breast cancer include total mastectomy and, for a highly selected group of patients, skin-sparing mastectomy. The decision to proceed with skin-sparing mastectomy should be a joint decision of the breast surgeon, the plastic surgeon, and the radiation oncologist. Continued skin involvement after neoadjuvant chemotherapy, including

edema, chest wall involvement, or diffuse, suspicious-appearing calcifications close to the overlying skin, indicates the need for total mastectomy. Intraoperative specimen radiography is performed to determine the adequacy of margins. Excision of additional skin may be necessary if superficial disease is identified.

Patients undergoing skin-sparing mastectomy have initiation of reconstruction with placement of a tissue expander. The use of a tissue expander allows for administration of PMRT as deflation of the expander permits adequate targeting of the chest wall and regional nodal basins. Patients should not have immediate reconstruction with either an implant or a myocutaneous flap as patients with locally advanced breast cancer will require PMRT.

Axillary Lymph Node Dissection

In patients who undergo a total mastectomy, ALND is performed through the lateral portion of the elliptical incision. In patients who undergo BCT or a skin-sparing mastectomy, ALND is performed through a separate axillary incision. Skin flaps are raised superiorly, medially, laterally, and inferiorly within the axilla. Posterolaterally, the anterior border of the latissimus muscle is identified. Anteromedially, the lateral border of the pectoralis major muscle is identified. The axillary vein is then identified cephalad. Using these landmarks as the anatomic boundaries, a level I and II ALND is performed. Dissection proceeds from cephalad to caudad along the latissimus muscle up to the axillary vein. Dissection then proceeds from lateral to medial along the axillary vein. The thoracodorsal nerve and vessels are identified and protected from injury. Branches of the axillary vein are ligated with either ties or clips. The long thoracic nerve is identified as it travels within the investing fascia of the serratus anterior muscle and protected from injury. The fascia along the lateral border of the pectoralis muscle is then incised, and the fatty lymphatic contents are swept off the posterior axilla and chest wall, with care taken to leave the serratus fascia intact (Fig. 17.5).

Standard ALND does not include the level III axillary lymph nodes. Routine excision of level III axillary nodes provides little benefit and increases the risk of lymphedema. However, if palpable lymphadenopathy exists at the axillary apex, the tendinous portion of the pectoralis minor muscle may be divided at its insertion to allow excision of level III lymph nodes.

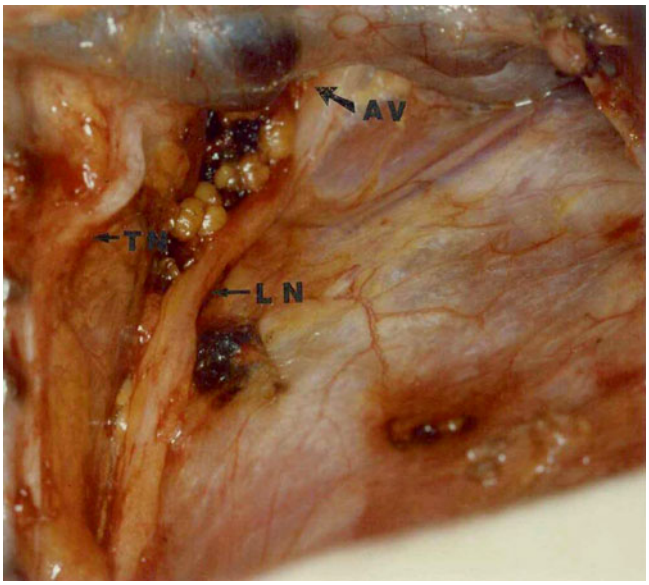

Fig. 17.5 Vital structures identified during axillary lymph node dissection including the axillary vein (*AV*), thoracodorsal nerve (*TN*), and long thoracic nerve (*LN*)

Radiation Therapy

The administration of WBI in patients with locally advanced breast cancer requires a skilled radiation oncologist. The use of multiple adjacent fields is complex, and incorrect planning of such treatment may result in either inadequate coverage of the chest wall and regional lymphatics or administration of elevated doses with burning of the tissue. However, in the hands of an experienced radiation oncologist, BCT is feasible for patients with locally advanced breast cancer with a good response to neoadjuvant chemotherapy and successful breast-conserving surgery.

In patients treated with mastectomy, PMRT is well known to effectively reduce the burden of residual local-regional disease. The Danish Breast Cancer Cooperative Group's protocol 82b randomized premenopausal women with high-risk breast cancer who underwent modified radical mastectomy to either chemotherapy or chemotherapy with radiation therapy [52]. Patients with a primary tumor larger than 5 cm, positive lymph nodes, skin invasion, or pectoralis fascia invasion were considered high risk. Radiation was delivered to the chest wall and regional nodal basins. At a median follow-up time of 114 months, patients who received PMRT had a significantly lower local-regional recurrence rate (9 % vs. 32 %) and higher DFS (48 % vs. 35 %) and OS rates (54 % vs. 45 %) compared to patients who did not receive PMRT.

The Danish Breast Cancer Cooperative Group's protocol 82c examined postmenopausal women with high-risk breast cancer who underwent modified radical mastectomy and randomized them to either tamoxifen or tamoxifen with PMRT [53]. At a median follow-up time of 10 years, patients in the PMRT group had a significantly lower local-regional recurrence rate (8 % vs. 35 %) and significantly higher DFS (36 % vs. 24 %) and OS rates (45 % vs. 36 %).

The British Columbia trial randomized premenopausal node-positive breast cancer patients who had undergone modified radical mastectomy to adjuvant chemotherapy alone versus adjuvant chemotherapy with PMRT [54]. At a

median follow-up time of 20 years, patients randomized to receive adjuvant chemotherapy with PMRT had a significantly lower local-regional recurrence rate (13 % vs. 39 %) and significantly higher DFS (48 % vs. 31 %) and OS rates (47 % vs. 37 %).

The Danish and British Columbia trials demonstrate that patients at high risk for local-regional recurrence have disease that cannot be addressed solely by systemic therapy and surgery. These patients clearly benefit from PMRT, which reduces the local-regional recurrence rate, thereby improving both DFS and OS.

The EBCTCG examined the effect of radiation versus no radiation on local recurrence and 15-year survival in patients treated on randomized trials [43]. Among patients with node-positive disease, those who underwent PMRT had significantly decreased rates of local-regional recurrence at 15 years (8 % vs. 29 %). Not surprisingly, larger reductions in the local-regional recurrence rate were seen in subgroups of patients with higher-risk disease. The EBCTCG concluded that treatments that significantly lower the risk of local-regional recurrence would over the course of 15 years prevent one breast cancer death for every four local recurrences prevented, thus resulting in an improved 15-year OS rate.

It is important that PMRT be applied appropriately to avoid toxic effects for patients at low risk of local-regional recurrence. Katz and colleagues examined patients treated with systemic therapy without PMRT to better define patients at intermediate and high risk of local-regional recurrence, who would benefit from PMRT [55, 56]. Patients with metastases in more than three axillary lymph nodes had a greater than 20 % risk of local-regional recurrence. Patients with one to three positive axillary lymph nodes with a tumor larger than 4 cm, gross extranodal extension, inadequate ALND, skin or nipple invasion, or inadequate margins also had rates of local-regional recurrence that warranted PMRT. These studies helped to define the patients for whom the benefit of PMRT outweighs the risk of toxic effects.

Patients undergoing neoadjuvant chemotherapy and modified radical mastectomy should be carefully evaluated for PMRT after mastectomy is complete and final pathology is available. In general, all patients who present with stage III disease will receive PMRT regardless of response to chemotherapy. Patients who present with stage II disease may not require PMRT, depending on the response to chemotherapy and the amount of residual disease in the breast and regional lymph nodes. Buchholz and colleagues demonstrated that patients who met criteria for PMRT prior to neoadjuvant chemotherapy and patients with more than three axillary lymph nodes positive for disease on final pathology benefit from PMRT [57]. It is important to note that even patients who met the criteria for PMRT at diagnosis but experienced a pathologic complete response to neoadjuvant chemotherapy were at high risk of local–regional recurrence and benefited from PMRT.

Systemic Therapy

Many patients with locally advanced breast cancer have inoperable disease at diagnosis. Delivering neoadjuvant systemic therapy may allow patients with disease initially deemed inoperable to become candidates for surgical resection. In addition, administration of neoadjuvant systemic therapy allows direct observation of tumor response, which provides valuable prognostic information and allows for alterations in ineffective chemotherapy regimens, limiting exposure to ineffective agents. Patients who experience a pathologic complete response to neoadjuvant chemotherapy have survival outcomes superior to those of patients who experience a partial response or no response; patients who experience progression of disease during neoadjuvant chemotherapy have the worst survival outcomes [58].

The effectiveness of chemotherapy regimens in the management of breast cancer are usually tested first in the metastatic setting. Once an agent has been shown to be effective in the metastatic setting, it is tested in adjuvant therapy trials to determine the impact on OS and DFS. Similar chemotherapy regimens will be utilized for neoadjuvant therapy in locally advanced breast cancer as are utilized in the adjuvant setting for patients with earlier stage disease. An EBCTCG update published in 2005 reviewed the results of all the randomized trials with different regimens to provide the evidence for adjuvant treatment decisions [59]. The EBCTCG concluded that polychemotherapy regimens such as CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), and FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) along with some polychemotherapy regimens containing taxanes were more effective than single-agent chemotherapy in reducing breast cancer recurrence and mortality. It is important to note that HER2 status was not considered in this analysis. The use of trastuzumab to treat HER2-positive breast cancer has been demonstrated to significantly improve both DFS and OS. Currently, the NCCN guidelines include several regimens containing trastuzumab for both neoadjuvant and adjuvant chemotherapy [47].

Endocrine therapy also may be administered as neoadjuvant therapy in patients with hormone-receptor-positive breast cancer, particularly for elderly women who are deemed to be poor candidates for chemotherapy. Review of the NSABP B-14 and B-20 data demonstrated that less benefit was derived from chemotherapy with increasing age [60]. ER concentration, nuclear grade, histologic grade, tumor type, and proliferation markers should be considered in the decision between chemotherapy and endocrine therapy. Patients who may benefit from neoadjuvant endocrine therapy include those with locally advanced breast cancer that may become operable, those with large tumors who with a good response to neoadjuvant therapy may become eligible

for BCT, and those with a short life expectancy for whom neoadjuvant endocrine therapy can provide long-term disease control.

All patients with hormone-receptor-positive disease should be offered adjuvant endocrine therapy as part of their multidisciplinary treatment. The EBCTCG analysis demonstrated benefit with the use of adjuvant tamoxifen therapy in patients with hormone-receptor-positive disease but not hormone-receptor-negative disease [59]. The recommended duration of therapy is 5 years. Although American Society of Clinical Oncology (ASCO) guidelines support using an aromatase inhibitor in postmenopausal women, as aromatase inhibitors are superior to tamoxifen in postmenopausal women with respect to DFS and toxic effects, it is important to note that tamoxifen is effective in both premenopausal and postmenopausal women with hormone-receptor-positive tumors [61].

Surveillance for Breast Cancer Patients Who Have Completed Curative Treatment

The American Cancer Society estimated that 230,480 new cases of invasive breast cancer and 57,650 new cases of in situ breast cancer were diagnosed in US women in 2011 [2]. Because of continued improvements in the detection and treatment of breast cancer together with the increasing population of the United States, the number of breast cancer survivors continues to increase. As a result, surveillance for breast cancer patients who have completed curative treatment and survivorship programs to address the physical and emotional needs of breast cancer survivors have become more important than ever before.

In 1994, a multicenter randomized controlled trial was published that examined the impact of two follow-up protocols on breast cancer survival and health-related quality of life in patients treated for breast cancer with curative intent [62]. The study enrolled 1,420 women with stage I, II, and III breast cancer. Women were randomized to an intensive surveillance group or a control group. Patients in the intensive surveillance group had routine visits with imaging including bone scan, liver echography, chest radiography, and laboratory studies at predefined intervals, while patients in the control group had follow-up visits at the same intervals with additional testing only if clinically indicated. No significant differences were seen in survival or time to detection of recurrence between the two groups at 71 months. In addition, no difference in quality of life was noted between these two groups. As a result, the investigators concluded that routine testing during breast cancer surveillance should be discouraged.

The National Research Council Project on Breast Cancer conducted a similar study that addressed the question of surveillance intensity for survivors [63]. A total of 1,243 patients were randomized to either clinical follow-up with physical examination and mammography or intensive follow-up with additional chest radiography and bone scan every 6 months. Although patients in the intensive follow-up group had earlier detection of recurrence, no difference in overall survival was noted. As a result, clinical follow-up was recommended over intensive follow-up.

Guidelines for Follow-up After Breast Cancer Treatment

The NCCN guidelines recommend that patients treated for DCIS have a history and physical examination every 6–12 months for the first 5 years after the completion of treatment and then annually, along with annual mammography [47]. Patients treated with BCT should have their initial follow-up mammogram 6–12 months after the completion of radiation therapy. The NCCN recommends that patients treated for invasive breast cancer be followed up by members of the treatment team. Clinical follow-up with history and physical examination should be performed every 4–6 months for the first 5 years and then annually. Mammograms should be performed annually. These guidelines clearly state that routine laboratory studies and imaging are not recommended for asymptomatic patients.

Women taking tamoxifen who have not undergone hysterectomy should have an annual gynecologic evaluation, and any vaginal spotting in a postmenopausal woman on tamoxifen therapy should be investigated promptly because of the risk of endometrial carcinoma.

Women with ovarian failure taking aromatase inhibitors should undergo baseline bone mineral density testing followed by testing at regular intervals. If bisphosphonate treatment is initiated, baseline dental examination and preventive dental care should be done prior to initiation of treatment. Patients treated with bisphosphonates should take calcium and vitamin D supplements.

Updated guidelines from ASCO are similar to those of the NCCN [64]. ASCO recommends a history and physical examination every 3–6 months for the first 3 years, every 6–12 months for the next 2 years, and then annually. Mammography is recommended annually. Patients who underwent BCT should have their first posttreatment mammogram 6 months after the completion of radiation therapy and then annually. ASCO specifies that laboratory studies and imaging are not recommended for asymptomatic patients. Routine gynecologic follow-up is recommended for all women. The ASCO guidelines state that surveillance care may take place under the direction of a primary care physician beginning 1 year after diagnosis for women with a tumor size less than 5 cm and less than four positive axillary lymph nodes. If a primary care physician takes over surveillance

care, the primary care physician as well as the patient should be informed of recommended surveillance guidelines.

Actual Practice Patterns

Although clear guidelines have been established for surveillance in breast cancer patients who have undergone therapy with curative intent, actual practice patterns vary markedly. This has been illustrated by Margenthaler and colleagues, who surveyed ASCO members to determine how they perform breast cancer surveillance [65]. The results of this survey demonstrated wide deviation from the guidelines. The surveillance strategy most commonly recommended by the respondents was history and physical examination, mammography, and laboratory studies, although the frequency with which these various elements of surveillance were performed varied considerably. Over 80 % of ASCO members surveyed recommended laboratory studies at least annually even though the ASCO recommendations oppose the use of such tests. In addition, 7–15 % of those surveyed recommended various imaging studies at least annually even though the guidelines specifically oppose the use of imaging surveillance.

As the number of breast cancer survivors increases, the need to educate those performing surveillance for these patients has become increasingly important. The use of imaging studies only for patients who are symptomatic is the most appropriate and cost-effective strategy. With the economics of healthcare attracting increased attention, providers who fail to perform surveillance according to the NCCN and ASCO guidelines may experience decreasing reimbursement for unnecessary tests.

NCCN Guidelines for Breast Cancer Survivors

The 2013 version of the NCCN practice guidelines for breast cancer included new guidelines for addressing survivorship issues [47]. The NCCN defines a survivor as "an individual… from the time of diagnosis, through the balance of his or her life." As screening improves, treatment modalities become more effective, and as the population ages, the population of breast cancer survivors grows. Breast cancer survivors have many special needs besides cancer surveillance. The NCCN survivorship guidelines focus on "the potential impact on health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing." For survivors, the NCCN recommends performing healthcare assessments at regular intervals to screen for and provide interventions to address survivorship issues.

Acknowledgments The authors are grateful to Stephanie Deming for editorial assistance with the manuscript.

References

1. Nemoto T, Vana J, Bedwani RN, Baker HW, McGregor FH, Murphy GP. Management and survival of female breast cancer: results of a national survey by the American College of Surgeons. Cancer. 1980;45(12):2917–24.
2. Breast cancer facts & figures 2011–2012. Atlanta: American Cancer Society, Inc. www.cancer.org/acm/graips/content/eepidemiologysurverlance/document/acspc-030975.pdf.
3. Page D, Rogers L, Schuyler P, et al. The natural history of ductal carcinoma in situ of the breast. In: Silverstein MS, Recht A, Lagios MD, eds. Ductal carcinoma in situ of the breast. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 17–21.
4. Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005;103(12):2481–4.
5. Rosen PP, Senie R, Schottenfeld D, Ashikari R. Noninvasive breast carcinoma: frequency of unsuspected invasion and implications for treatment. Ann Surg. 1979;189(3):377–82.
6. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, 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.
7. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. 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.
8. Blichert-Toft M, Nielsen M, During M, Moller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. Acta Oncol. 2008; 47(4):672–81.
9. Jacobson JA, Danforth DN, Cowan KH, D'Angelo T, Steinberg SM, Pierce L, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med. 1995;332(14):907–11.
10. Sarrazin D, Le MG, Arriagada R, Contesso G, Fontaine F, Spielmann M, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol. 1989;14(3):177–84.
11. van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J Natl Cancer Inst Monogr. 1992;11:15–8.
12. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, 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.
13. Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16(2):441–52.
14. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000;355(9203):528–33.
15. Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, Julien JP, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853–a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24(21):3381–7.

16. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003;362(9378):95–102.
17. Emdin SO, Granstrand B, Ringberg A, Sandelin K, Arnesson LG, Nordgren H, et al. SweDCIS: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol. 2006;45(5):536–43.
18. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med. 1999; 340(19):1455–61.
19. McCormick B. RTOG 9804: a prospective randomized trial for "good risk" ductal carcinoma in situ (DCIS), comparing radiation (RT) to observation (OBS). J Clin Oncol. 30(suppl);abstr 1004.
20. Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(32):5319–24.
21. Hunt K, Meric-Bernstam F. Surgical options for breast cancer. In: Hunt KK, Robb GL. Strom EA, Ueno NT, editors. Breast cancer. 2nd ed. New York: Springer; 2008. p. 198–232.
22. Brunnert K. The Osnabrueck experience with reconstruction of the partial mastectomy defect. In: Spear S, editor. Surgery of the breast: principles and art. Philadelphia: Lippincott-Raven; 1998. p. 197–220.
23. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). J Am Coll Surg. 2009;209(2):269–77.
24. Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet. 1999;353(9169):1993–2000.
25. Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol. 2012;30(12):1268–73.
26. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567–75.
27. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med. 1985;312(11):674–81.
28. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994;220(3):391–8; discussion 398–401.
29. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg. 1995;222(3):394–9; discussion 399–401.
30. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007;8(10):881–8.
31. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003; 349(6):546–53.
32. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010;251(4):595–600.
33. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol. 2010;102(2):111–8.
34. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569–75.
35. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol. 2007;25(24):3657–63.
36. National Comprehensive Cancer Center (NCCN) Clinical practice guidelines in oncology: Breast, version 1.2012. Available from: www.nccn.org/professionals/physician_/gls/pdf/breast.pdf.
37. The American Society of Breast Surgeons position statement on management of the axilla in patients with invasive breast cancer. Available from: http://www.breastsurgeons.org/statements/PDF_Statements/Axillary_Management.pdf.
38. Galimberti V, Cole BF, Zurrida S, et al. S3-1: update of International Breast Cancer Study Group trial 23-01 to compare axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node. Cancer Res. 2011;71(24 Supplement):S3–1.
39. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297–305.
40. Boughey JC, Suman VJ, Mittendorf EA, et al. The role of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0-4, N1-2) who receive neoadjuvant chemotherapy – results from the ACOSOG Z1071 trial. Cancer Res. 2012;72 (24 Supplement):S2–1.
41. Caudle AS, Hunt KK, Kuerer HM, Meric-Bernstam F, Lucci A, Bedrosian I, et al. Multidisciplinary considerations in the implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 study: a practice-changing trial. Ann Surg Oncol. 2011;18(9):2407–12.
42. Mittendorf EA, Hunt KK, Boughey JC, Bassett R, Degnim AC, Harrell R, et al. Incorporation of sentinel lymph node metastasis size into a nomogram predicting nonsentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node. Ann Surg. 2012;255(1):109–15.
43. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 366(9503):2087–106.
44. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004;351(10):963–70.
45. Hughes KSSL, Berry D, Cirrincione C, McCormick B, Shank B, Wheeler J, Champion LA, Smith TJ, Smith BL, Shapiro C, Muss HB, Winer E, Hudis C, Wood W, Sugarbaker D, Henderson IC, Norton L, Cancer and Leukemia Group B, Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004;351:971–7.
46. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15(7):2483–93.

47. National Comprehensive Cancer Center (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer Version 2.2013. nccn.org. Available from: www.nccn.org/professionals/physician_/gls/pdf/breast.pdf.
48. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351(27):2817–26.
49. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006; 24(23):3726–34.
50. Singletary SE, McNeese MD, Hortobagyi GN. Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer. 1992;69(11):2849–52.
51. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J Clin Oncol. 2004;22(12):2303–12.
52. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337(14):949–55.
53. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999;353(9165):1641–8.
54. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116–26.
55. Katz A, Strom EA, Buchholz TA, Theriault R, Singletary SE, McNeese MD. The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. Int J Radiat Oncol Biol Phys. 2001;50(3):735–42.
56. Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol. 2000;18(15):2817–27.
57. Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol. 2002; 20(1):17–23.
58. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol. 1999; 17(2):460–9.
59. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.
60. Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER, et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet. 2004;364(9437):858–68.
61. Burstein HJ, Griggs JJ, Prestrud AA, Temin S. American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Oncol Pract. 2010;6(5):243–6.
62. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA. 1994;271(20):1587–92.
63. Rosselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA. 1994;271(20):1593–7.
64. Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(7):961–5.
65. Margenthaler JA, Allam E, Chen L, Virgo KS, Kulkarni UM, Patel AP, et al. Surveillance of patients with breast cancer after curative-intent primary treatment: current practice patterns. J Oncol Pract. 2012;8(2):79–83.