Chapter 3
New Trends and Development in Breast Surgery

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3.1 Introduction

Several large, randomized clinical trials have been conducted to define surgical treatment of breast cancer. In this chapter, new trends and developments in breast cancer surgery, including appropriate breast-conserving therapy (BCT), accelerated postoperative irradiation, skin-sparing mastectomy and nipple and areola sparing mastectomy (SSM/NSM) with immediate reconstruction, and sentinel lymph node biopsy (SLNB) for axillary staging, have been described.

3.2 Breast Surgery

BCT comprised the excision of tumors with negative surgical margins, axillary surgery, and postoperative irradiation. In the 1980s, six prospective, randomized clinical trials were conducted worldwide to compare BCT with mastectomy, but none revealed any significant difference in the overall survival (OS) between the two arms for early-stage invasive breast cancer [1–7]. However, in these meta-analyses indicated therapeutic equivalence [8, 9]. BCT has been increasingly accepted as a treatment option for stage I and II and selected stage III breast cancer cases. According to the Japanese Breast Cancer Society Breast Cancer Registry, BCT was performed more frequently compared with mastectomy for early-stage breast cancer patients from 2004 to 2009 in Japan [10].

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The choice of appropriate patients is important for successful BCT. The absolute contraindications for BCT include the following:

1. Multicentric cancers in different quadrants of the breast
2. Diffuse ductal metastasis (diffuse malignant calcifications on mammography)
3. The cases that cannot receive radiotherapy because of radiation-induced acute and late onset toxicities (history of prior radiotherapy or connective tissue diseases such as active systemic lupus erythematosus or scleroderma)
4. Positive surgical margins after multiple re-excisions

Although tumor size itself is not a contraindication for BCT, both adequate resection with negative margins and acceptable cosmetic results should be accomplished for successful BCT. Previous meta-analyses revealed that neoadjuvant chemotherapy can effectively decrease the tumor size and successfully improve the rate of BCT [11].

Few studies have reported that the rate of local–regional recurrence (LRR) is higher following BCT than mastectomy [1, 4]. Although LRR was thought to not affect OS, a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group reported that the higher rate of LRR led to a poorer survival rate [8]; therefore, the risk of LRR should not be overlooked.

One of the most important factors of LRR following BCT is the surgical margin status [12–14]. Although there is no international standard definition of positive surgical margins, in Japan, it has been defined as a positive margin with cancer cells detected at 5 mm or less from the surgical edge. In case of positive margin status (margin exposure $\leq$5 mm), additional re-excision is recommended to achieve a negative margin status. According to the National Comprehensive Cancer Network (NCCN), margins less than 1 mm are considered inadequate [15, 16].

Of the BCT methods discussed so far, only conventional radiotherapy has been evaluated. Conventional radiotherapy delivers 45–50 Gy to the whole breast over 4–5 weeks, which has been considered to effectively decrease the LRR incidence, distant recurrence, and death [17]. Recently, the focus of BCT has increasingly shifted to cosmetic outcome, quality of life, and patient satisfaction; further, accelerated irradiation schedules have increased the convenience of conventional radiation therapy. In a meta-analysis, it was concluded that accelerated irradiation schedules were equivalent to conventional radiation therapy with regard to LRR, OS, breast cosmesis, and early and late onset toxicities [18]. Moreover, because most ipsilateral breast tumor recurrences (IBTRs) occur near the lumpectomy cavity, accelerated partial breast irradiation (APBI) has been developed. APBI delivers higher doses of radiation focused to a limited tissue volume over a shorter period of time to achieve less toxicity, decreased costs, and increased convenience. APBI may enable repeated BCT in case with LRR outside of the previous irradiated cavity. Currently, APBI is being evaluated in a large clinical trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) (NSABP B-39/RTOG 0413).

At present, BCT has become a well-established procedure worldwide, and the other modalities that enable noninvasive treatment of primary tumors, including

percutaneous ablation, radiofrequency ablation, and cryoablation, have been the focus of several clinical trials that are now ongoing worldwide.

SSM for breast cancer has been widely applied to preserve a majority of the natural skin envelope of the breast. With this procedure, immediate reconstruction is possible to improve the cosmetic outcome [19]. A meta-analysis of such retrospective studies reported no significant difference in the local recurrence rates between patients undergoing SSM with immediate reconstruction and those undergoing conventional mastectomy without reconstruction [20]. More recently, in carefully selected patients, NSM has been performed to preserve the entire natural skin envelope of the breast and allow immediate reconstruction. However, no randomized trials with long-term follow-up periods have been conducted to examine the utility and safety of SSM/NSM; therefore, it is necessary to carefully select patients suitable for SSM/NSM.

3.3 Axillary Staging

Axillary status is one of the most important prognostic factors to predict the outcomes of breast cancer treatment. ALND remains the standard method in clinically node-negative patients and is important for LRR, but its impact on OS is unclear.

The NSABP B-04 trial was performed as two parallel trials, one for clinically node-negative patients and the other for clinically node-positive patients (Fig. 3.1)

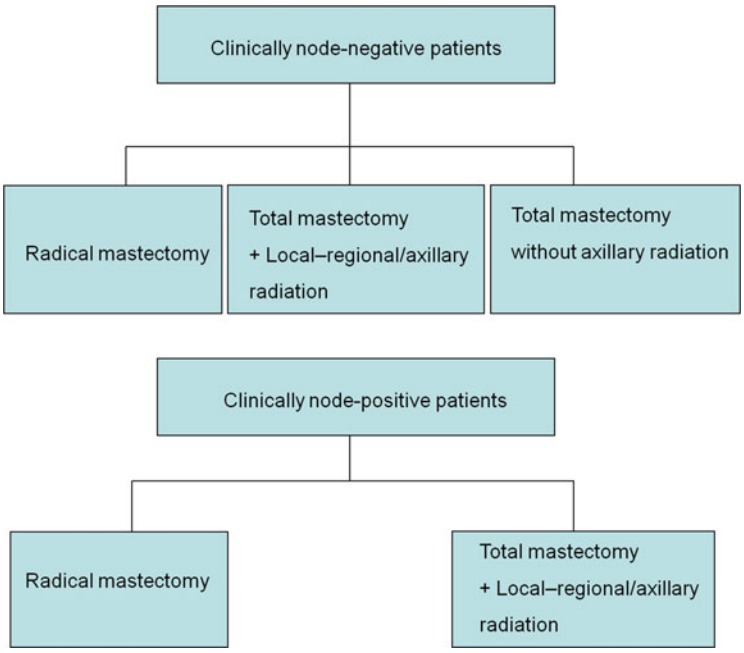

Fig. 3.1 Schema for NSABP B-04 trial

to compare radical mastectomy with less extensive surgical treatments [21]. Between 1971 and 1974, 1079 patients with clinically node-negative disease were randomized to undergo radical mastectomy ($N = 362$), total mastectomy plus local–regional/axillary radiation ($N = 352$), or total mastectomy without axillary radiation ($N = 365$), whereas 586 patients with clinically node-positive disease were randomized to undergo radical mastectomy ($N = 292$) or total mastectomy plus radiation ($N = 294$). None of the patients received systemic treatment [21]. In 2002, 25-year follow-up data were reported, which revealed no significant differences with respect to disease-free survival (DFS), distant disease-free survival (DDFS), and OS among the three groups of patients with clinically node-negative disease or the two groups of patients with clinically node-positive disease [22]. In the clinically node-negative arm, the LRR incidence was lower in the patients who underwent total mastectomy plus radiation (5 %) than in those who underwent radical mastectomy (9 %) or total mastectomy alone (13 %; $P = 0.002$). In the clinically node-positive arm, the LRR incidence revealed no significant difference: 16 % in patients who underwent radical mastectomy and 14 % in those who underwent total mastectomy plus radiation ($P = 0.67$). In this trial, 40 % clinically node-negative patients who underwent radical mastectomy revealed pathological lymph node involvement; therefore, it can be assumed that 40 % clinically node-negative patients who underwent total mastectomy without radiation also had pathological lymph node involvement; however, only 19 % (68/365) patients subsequently experienced nodal recurrence and then underwent ALND. The median time from mastectomy to identification of axillary metastases was 15 months (range, 3–135 months), and most cases were identified within 2 years from the initial surgery. These patients remained in the same arm for survival analyses.

Similarly, in the meta-analysis to compare patients with clinically node-negative disease with or without ALND, ALND did not confer a survival advantage, although the rate of axillary recurrence was decreased [23]. These data suggested that routine ALND for clinically node-negative patients is unnecessary and that ALND after the diagnosis of clinically evident disease in the axilla did not have a significant negative impact on OS. However, ALND was associated with lymphedema, shoulder dysfunction, pain, and paresthesias [24–26]. In addition, in clinically node-negative patients, the rate of nodal metastases was only 20–35 % [27–29]. The results of these trials promoted a shift to more noninvasive breast and axillary surgery.

SLNB was developed as an accurate method to evaluate the axillary status with less morbidity compared with ALND. The concept of SLNB, which was the first method designed to drain lymph nodes, was proposed as a treatment modality for melanoma in the late 1980s and early 1990s [30, 31]. Since Giuliano et al. first reported the results of SLNB for breast cancer treatment [32], larger trials have been conducted to evaluate SLNB as a staging procedure for clinically node-negative breast cancer. The NSABP B-32 trial was a large randomized clinical trial conducted between 1999 and 2004, which randomized 5611 patients into two groups: SLNB plus ALND (group 1) or SLNB plus ALND (only if SLN was positive; group 2) (Fig. 3.2). The primary endpoints were OS, regional control, and morbidity, whereas

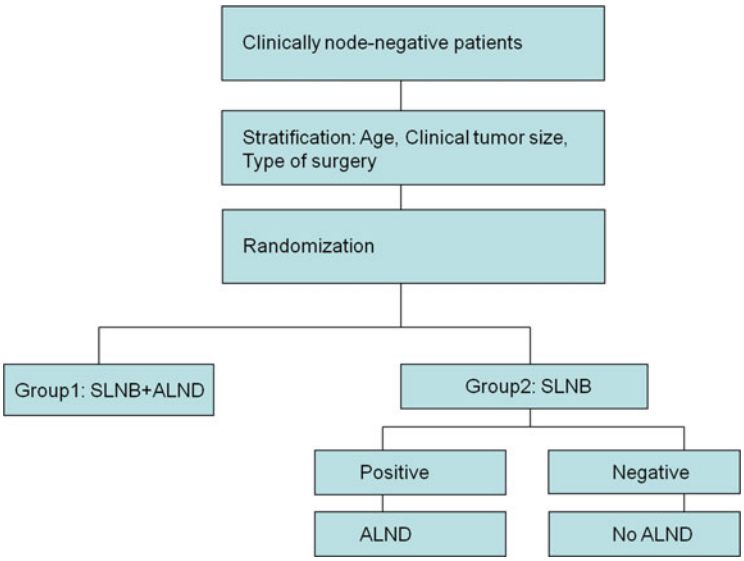

Fig. 3.2 Schema for NSABP B-32 trial

the secondary endpoints were accuracy and technical success [33]. The initial results of technical success and accuracy in 5536 patients were reported in 2007, which revealed that SLN was identified in 5379 patients (97 %) and was positive in 26 % patients in both groups. In group 1, the accuracy of SLNB was 97 %, and the false negative rate was 9.8 %. The OS results were reported in 2010 [33]. A total of 3986 patients with pathologically negative SLN were compared. The two groups were well balanced with regard to age, clinical tumor size, and type of surgery. The use of systemic therapy and radiation was similar between the groups. The 5-year Kaplan–Meier estimates for OS were 97 % and 95 % in groups 1 and 2, respectively, and the 8-year estimates were 92 % and 90 %, respectively ($P = 0.12$). Further, the 8-year estimates for DFS were 82 % in both groups, and the rates of regional control were similar as well. Because the OS, DFS, and regional control rates between these treatment groups were equivalent, it was concluded that if SLN is negative, SLNB alone (without ALND) is appropriate for axillary status staging.

Although omission of ALND in patients with a negative SLN has become standard, ALND is recommended for SLN-positive patients [34, 35]. However, the results of the NSABP B-04 trial indicated no survival advantage for patients who received ALND at the time of the initial surgery; further, considering the improvements in systemic treatment, ALND may not be necessary in all SLN-positive patients. To determine whether SLN-positive patients require ALND, the American College of Surgeons Oncology Group (ACOSOG) conducted the Z-0011 trial, which enrolled patients with clinical T1 or T2, N0, M0 breast cancer who underwent BCT and revealed one or two positive SLNs by hematoxylin and eosin staining (Fig. 3.3). These patients were randomized into two arms: those in arm 1 underwent ALND,

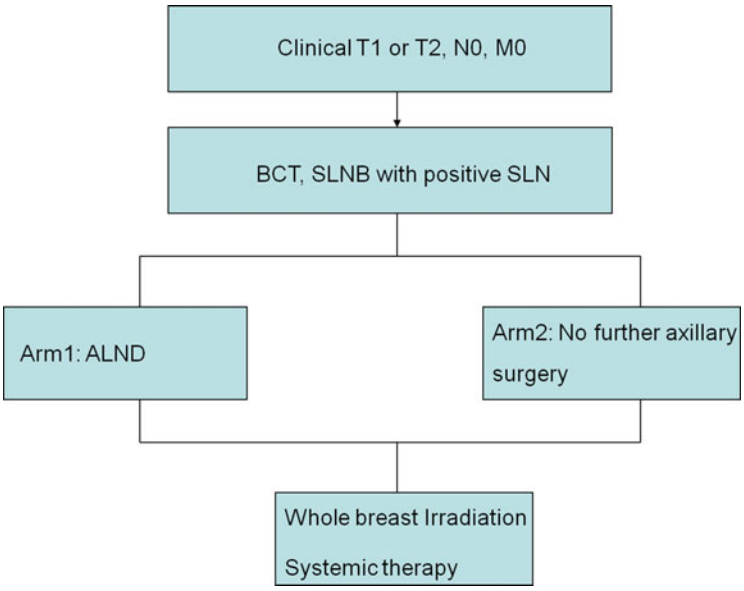

Fig. 3.3 Schema for ACOSOG Z0011 trial

whereas those in arm 2 received no further axillary surgery. All the patients received postoperative whole breast irradiation and were recommended for systemic treatment. The primary endpoint was OS, and the secondary endpoint was DFS. Although this trial was designed for 1900 patients, and enrollment in the trial was initiated in 1999, it was closed in early 2004 after 891 patients were enrolled and randomized (arm 1, 445 patients; arm 2, 446 patients). The reasons for early closure were slow accrual and a lower event rate than anticipated at the time of the study design. Micrometastases were identified in SLNs of 45 % patients in arm 1 and 38 % patients in arm 2. Additional positive lymph nodes were identified in 27 % patients in arm 1. Adjuvant systemic treatment was administered in 96 % patients (chemotherapy, 58 %; hormonal treatment, 46 %) in arm 1 and 97 % patients (chemotherapy, 58 %; hormonal therapy, 47 %) in arm 2. After a median follow-up period of 6.3 years, only 29 incidences of LRR were reported among all patients. The local recurrence rate was 4 % in arm 1 and 2 % in arm 2. Recurrence of the ipsilateral axilla was very rare (0.5 % and 0.9 % in the arms 1 and 2, respectively) [36], and there were no differences in OS or DFS between the two groups. On the basis of these results, the ACOSOG investigators concluded that ALND may be safely omitted in selected patients in line with the eligibility criteria of this trial; however, this trial did not include the following patients: those with T3 tumors, those who underwent mastectomy, those who received neoadjuvant chemotherapy, or those who were administered APBI. Therefore, the ACOSOG investigators cautioned that ALND remains the standard treatment for SLN-positive patients. Further, the International Breast Cancer Study Group (IBCSG) 23-01 trial to investigate the necessity of ALND in SLN-positive

patients is currently ongoing. The eligibility criteria were as follows: clinically node negative, breast tumors $\leq$5 cm, and SLN micrometastasis ($\leq$2 mm). The patients were randomized into two groups: ALND or no further axillary surgery. Unlike the Z-0011 trial, patients who underwent mastectomy were eligible for enrollment. The primary endpoint was DFS, and the secondary endpoints were OS and systemic DFS. Although this trial was designed for 1960 patients, its enrollment began in 2001 and was closed early in 2010 after 934 patients were randomized. The reasons for early closure of the IBCSG 23-01 trial were the same as those for the Z-0011 trial. The initial results were presented in 2011, and after a median follow-up period of 49 months, the 4-year DFS rate was 91 %. The first comparison of outcomes between the two groups will be reported after a median follow-up of 5 years. Considering the low DFS event rate in the IBCSG 23-01 trial, ALND may be omitted in patients undergoing mastectomy with micrometastatic SLNs.

3.4 Summary

Surgical treatments for breast cancer have been developed through randomized clinical trials conducted over the past few decades, ranging from the Halsted radical mastectomy to more noninvasive surgeries. Currently, most patients are able to receive personalized surgical treatment with cosmetically acceptable outcomes as well as favorable oncological outcomes, although other modalities to treat a primary tumor in a more noninvasive way have also attracted attention, including percutaneous ablation, radiofrequency ablation, and cryoablation, which have been assessed in several clinical trials.

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