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Landmark Trials Affecting the Surgical Management of Invasive Breast Cancer

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SYNOPSIS

Significant progress has been made in the surgical management of breast cancer. Historically, women with invasive breast cancer underwent a Halsted radical mastectomy; morbid procedure removing the breast, underlying muscle and regional lymph nodes. In contemporary practice, the majority of women diagnosed with early stage invasive breast cancer can now be managed with breast conserving therapy to include a segmental mastectomy followed by radiation. Axillary lymph nodes are routinely assessed by sentinel lymph node biopsy. Axillary lymph node dissection is reserved for patients with documented nodal metastasis, however, here too progress has been made as a population of low risk patients has been identified in whom a complete dissection is not required even in the setting of a positive sentinel lymph node. This chapter details the landmark clinical trials that have guided the surgical management of breast cancer.

Keywords

Breast cancer; clinical trials; breast conserving therapy; sentinel lymph node biopsy

INTRODUCTION

Large cooperative group trials have defined surgical management of breast cancer. Until the late 1890s, breast cancer was a fatal disease. William Stewart Halsted challenged that theory by performing aggressive surgery to achieve local control. [1] Termed the Halsted radical mastectomy, the procedure involved removal of the breast, the underlying pectoralis major and minor muscles, and the regional lymph nodes. This extensive resection addressed Halsted's premise that cancer spread from the breast to the pectoralis muscles and regional lymph nodes first and then to distant sites. By the late 1960s, however, investigators had begun to question this "contiguous spread" model and suggested instead that breast cancer

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was a systemic disease. [2–5] Around the same time, interest in using chemotherapy for a variety of malignancies increased. Thus, investigators also started to question the need to routinely perform a procedure as morbid as the radical mastectomy. Subsequently, large randomized clinical trials in the United States and Europe demonstrated that breast cancer could be successfully treated with less radical surgery combined with other modalities including systemic chemotherapy, endocrine therapy, and radiation. Advances from these trials resulted in personalized surgical management of breast cancer. This chapter will review the most recently published data from landmark randomized trials that have guided current practices in surgical management of invasive breast cancer.

FROM RADICAL MASTECTOMY TO BREAST CONSERVING THERAPY

National Surgical Adjuvant Breast and Bowel Project B-04: Radical Mastectomy to Total Mastectomy

Dissatisfaction with the significant morbidity of radical mastectomy along with new information regarding tumor biology and metastasis led to anecdotal reports of surgeons using less aggressive surgery to treat breast cancer. [2, 6–8] This led investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) to conduct the NSABP B-04 trial, which compared radical mastectomy to less extensive surgery. [9] The trial was set up as two parallel trials: one for patients with clinically node-negative disease and one for patients with node-positive disease (Figure 1). Between 1971 and 1974, 1079 patients with clinically node-negative disease were randomized to radical mastectomy (n=362), total mastectomy plus local-regional/axillary radiation (n=352), or total mastectomy alone without axillary treatment (n=365). During the same period, 586 patients with clinically node-positive disease were randomized to radical mastectomy (n=292) or total mastectomy and radiation (n=294). [9] Patients did not receive systemic therapy. The goal was to determine whether patients who received local-regional treatment other than radical mastectomy had similar outcomes to those undergoing radical mastectomy.

Initial reports from the NSABP B-04 trial at 3, 5, and 10 years showed no significant differences with respect to disease-free survival (DFS), distant-disease-free survival (DDFS), and overall survival (OS) among the three groups of patients with clinically node-negative disease or the two groups of patients with clinically node-positive disease. [2, 9, 10] The 25-year outcomes from the NSABP B-04 trial reported in 2002 also revealed no significant differences between groups with respect to any endpoint. [11] In the node-negative arm, patients who underwent total mastectomy plus radiation had a lower rate of local-regional recurrence (LRR; 5%) than did those who underwent radical mastectomy (9%) or total mastectomy alone (13%) (p=0.002). In the node-positive arm, the LRR rates were not significantly different: 16% in patients who underwent radical mastectomy versus 14% in patients who underwent total mastectomy plus radiation (p=0.67). When broken down by local versus regional recurrence, the rate of local recurrence was significantly different between those who underwent radical mastectomy (8%) and those who underwent total mastectomy plus radiation (3%); however, no significant differences in regional recurrence rates were found.

Of note, 40% of the patients with clinically node-negative disease who underwent radical mastectomy had lymph node involvement in their surgical specimens. [9] Thus, one can assume that 40% of patients with clinically node-negative disease who underwent total mastectomy also had nodal involvement. However, of the 365 patients with node-negative disease who underwent total mastectomy without radiation, only 68 (19%) subsequently developed nodal disease and underwent axillary lymph node dissection (ALND). [11] The median time from mastectomy to identification of axillary metastases was 15 months (range, 3–135 months), and the majority of cases were identified within 2 years of the initial

operation. These patients remained in the total mastectomy cohort for survival analyses, therefore, because there was no significant difference with respect to OS between the arms of the trial, these data suggest that routine ALND for patients with a clinically node negative axilla is unnecessary and omission of this procedure until there is clinically evident disease in the axilla will not have a significant negative impact on OS. This study also did not demonstrate an advantage of adding local-regional radiation to total mastectomy. Most importantly, the trial supported the paradigm shift to less radical surgery for breast cancer.

NSABP B-06: Total Mastectomy versus Breast-Conserving Therapy

To further minimize the extent of surgery, several investigators evaluated breast-conserving surgery and reported encouraging results in small studies that included patients with small tumors. [12–14] To further evaluate this strategy, NSABP investigators conducted the NSABP B-06 study; a randomized prospective trial comparing lumpectomy and ALND with or without breast irradiation with total mastectomy and ALND (modified radical mastectomy) in patients with tumors 4 cm or less (Figure 2). [15] Patients could enroll regardless of clinical nodal status, and all patients underwent level I and II ALND. Radiation was administered to 50 Gy without a boost to the lumpectomy bed or radiation to the axilla. Patients with positive axillary lymph nodes received adjuvant systemic therapy with fluorouracil and melphalan. The aim of this trial, which enrolled and randomized 2163 patients from 1976 to 1984, was to determine rates of ipsilateral breast cancer recurrence, DFS, DDFS, and OS. Initial reports of the trial at 5, 8, and 12 years included 1843 evaluable patients and showed no significant differences for any endpoint among the groups. [15–17]

The most recent publication from this trial reported 20-year follow-up data, which also showed no significant differences in DFS, DDFS, or OS among groups. [18] They did however identify differences among the three arms with respect to local control. [18] Chest wall recurrences were reported in 10% of patients who underwent mastectomy. The cumulative incidence of ipsilateral breast tumor recurrence (IBTR) in patients with tumor-free margins was 39% in patients who underwent lumpectomy alone and 14% in patients who underwent lumpectomy and radiation ($p<0.001$). Patients who received radiation had fewer late recurrences; 73% of recurrences in the lumpectomy plus radiation group were within 5 years while 9% occurred after 10 years compared to the lumpectomy-only group in which 40% of the recurrences were within 5 years and 30% occurred after 10 years. Importantly, patients with positive margins in either lumpectomy group (approximately 10% of patients) who subsequently underwent total mastectomy were followed in their respective lumpectomy group for survival outcome analyses. [18] Similarly, per protocol definition, an IBTR after lumpectomy was not considered an event in the DFS analysis because women who underwent total mastectomy were not at risk. Instead, an IBTR after lumpectomy was considered a cosmetic failure, and such patients who subsequently underwent mastectomy continued in their assigned lumpectomy group for data analyses. [18] The NSABP B-06 trial was critical for establishing the concept of breast-conserving therapy (BCT) and confirmed the importance of radiation as a component of such treatment. These results were confirmed by other randomized clinical trials conducted by others, including the group from the Milan Cancer Institute. [19, 20]

More modern series have reported even lower rates of local-regional failure after BCT. We recently reported our experience at The University of Texas MD Anderson Cancer Center with a cohort of 2331 patients who underwent BCT including lumpectomy and whole-breast irradiation (WBI) between 1987 and 2005. After a median follow-up of 8 years, the 5-year LRR-free rate was 97% (95% confidence interval [CI]: 96%–98%), and the 10-year rate was 94% (95% CI: 93%–95%). [21] These results reflect improvements in imaging and pathologic evaluation; expanding indications for adjuvant therapy including systemic chemotherapy and endocrine therapy, which have been shown to decrease LRR rates in the

breast; and improvements in systemic agents. An appreciation for the need to obtain a clearly negative margin at the time of surgery has also increased. [22] Although there is no consensus on the optimal margin width, “no ink on tumor” was considered to be a negative margin in the NSABP B-06 trial.

Cancer and Leukemia Group B 9343: Radiation in Women 70 years and Older—Once studies demonstrated the feasibility of BCT, investigators began questioning whether radiation could be safely omitted in selected patients in whom the absolute risk of recurrence would be predicted to be low. One trial that investigated this was the Cancer and Leukemia Group B (CALGB) 9343, conducted between 1994 and 1999. [23, 24] The trial enrolled 636 women 70 years and older who had undergone lumpectomy for stage I, ER-positive breast cancer. A negative surgical margin, defined as no tumor on the inked margin was required. Patients were randomized to receive tamoxifen (n=319) or tamoxifen and radiation (n=317). ALND was discouraged but was performed in approximately 36% of patients in both groups.[23] The primary endpoints were time to local or regional recurrence, frequency of mastectomy for recurrence, DFS, time to distant metastasis, and OS.

Initial results from the study were published in 2004 after a median follow-up of 5 years. [23] The investigators found no significant differences between the groups in the rates of subsequent mastectomy, distant metastases, or OS. The rate of local or regional recurrence was 1% in the tamoxifen plus radiation group and 4% in the tamoxifen alone group, a difference that was statistically significant ($p<0.001$). In 2005, following the initial report of the CALGB 9343 results, the National Comprehensive Cancer Network (NCCN) amended their guidelines with a footnote that stated “Breast irradiation may be omitted in those 70 years of age or older with ER-positive, clinically node-negative T1 tumors who receive adjuvant hormonal therapy.” [25] Updated data from this trial were presented in 2010. [24] After a median follow-up of 10.5 years, the LRR rate remained significantly different between the two groups: 9% in the tamoxifen alone group and 2% in the tamoxifen plus radiation group. The difference was driven largely by a difference in IBTR: 8% in the tamoxifen alone group and 2% in the tamoxifen plus radiation group. DDFS, breast cancer-specific survival, OS, and the ability to undergo breast-conserving therapy remained comparable between the two groups. On the basis of these findings, the authors concluded that lumpectomy with endocrine therapy and without radiation is an appropriate treatment option for women 70 years or older with node-negative, ER-positive breast cancer.

Summary and Future Directions: Management of the Primary Breast Tumor

Taken together, the randomized clinical trials discussed above have changed the paradigm of the surgical management of primary tumors of women with invasive breast cancer. As a result of these studies, most patients with early-stage breast cancer undergo BCT that includes segmental resection followed by radiation. Because BCT is now well established, ongoing cooperative group trials are attempting to evaluate other modalities for treating the primary tumor and to minimize radiation. There is interest in managing the primary tumor without surgery using one of several described modalities, including percutaneous ablation, radiofrequency ablation, or cryoablation. [26] For example, the American College of Surgeons Oncology Group (ACOSOG) is conducting the Z1072 trial, a phase II study exploring cryoablation for the treatment of invasive breast cancer less than 2 cm. [27] The trial is currently accruing patients, and the estimated completion date is March 2013.

The previously discussed trials describing BCT all evaluated WBI. Because most IBTRs occur near the lumpectomy cavity, investigators have begun exploring other methods of delivering radiation including accelerated partial-breast irradiation (APBI). APBI is associated with several purported benefits, including a shorter interval for treatment

completion, the potential for repeat breastconserving surgery when an in-breast event occurs outside the irradiated cavity, and an alternative for women who are reluctant to undergo WBI. APBI is being evaluated in a large trial by the NSABP and RTOG (NSABP B-39/ RTOG 0413). [28] The trial will enroll 4300 women with operable breast cancer treated with lumpectomy. Initial eligibility criteria included stage 0 DCIS or stage I or II invasive cancer that was 3 cm or smaller with fewer than three positive axillary lymph nodes. The trial opened in 2005 and after brisk accrual of low-risk patients (women older than 50 years with DCIS or node-negative and ER-positive invasive tumors), was closed to accrual of patients with these favorable characteristics. The trial continues to accrue higher-risk patients.

FROM AXILLARY LYMPH NODE DISSECTION TO SENTINEL LYMPH NODE DISSECTION

Axillary lymph node involvement has long been considered an important prognostic factor in breast cancer. To determine axillary status for staging purposes, to assist with adjuvant treatment recommendations, and to provide regional control, complete ALND was routinely performed. However, ALND is associated with potential morbidity, including lymphedema, shoulder dysfunction, pain, and paresthesias. [29, 30] In addition, in women presenting with clinically node-negative disease, the rate of nodal metastases is only 20–35%. [31–33] Removing healthy lymph nodes renders no benefit; therefore, sentinel lymph node dissection (SLND), a more selective approach to managing the axilla was developed. The concept of the sentinel lymph node (SLN) as the first draining lymph node was popularized in melanoma in the late 1980s and early 1990s.[34, 35] In 1994, Giuliano and colleagues published findings on the feasibility and accuracy of SLND for early-stage breast cancer in 114 patients and reported a 65% identification rate and 96% accuracy.[36] This report led to the design and conduct of larger trials evaluating SLND as a staging procedure for clinically node negative breast cancer.

Sentinel Lymph Node Dissection for Axillary Staging

NSABP B-32—To determine whether SLND renders the same survival benefit and regional control that ALND does but with fewer side effects in patients with clinically node-negative disease, NSABP investigators conducted the NSABP B-32 trial. Between 1999 and 2004, the trial enrolled 5611 patients and randomized them to undergo SLND plus ALND (group one) or SLND with ALND only if the SLN was positive (group two; Figure 3). The primary endpoints were OS, regional control, and morbidity. The secondary endpoints were accuracy and technical success. [37]

SLNs were defined as nodes that were radioactive, blue, or hard and highly suspicious for metastatic disease. Radioactive nodes were removed until the count in the axilla was less than 10% of the hottest *ex vivo* SLN. [31] Pathologic evaluation included sectioning at 2-mm intervals and staining with hematoxylin and eosin (H&E). Routine immunohistochemistry (IHC) was not allowed. The initial publication reported on technical success and accuracy in 5536 patients in whom data were available. [31] A SLN was identified in 5379 (97%). The SLN was positive in 26% of patients in both groups. In group one, the accuracy of SLND was 97%, and the false-negative rate was 9.8%. Factors associated with a higher false-negative rate included tumor location, the type of biopsy performed, and the number of SLNs removed. [31] Patient-reported outcomes and morbidity related to lymphedema, range of motion, sensory deficits, and pain have also been published and for all outcomes, morbidity was greater in patients who underwent ALND. [38, 39]

Data for the primary survival endpoints of the trial were published in 2010. [37] Per protocol, analysis included patients with a pathologically negative SLN in whom follow-up

information was available (n=3986). The two groups were well balanced with respect to age, clinical tumor size, and surgical treatment. The use of systemic therapy and radiation was similar between groups. The 5-year Kaplan-Meier estimates for OS were 97% and 95% for groups one and two, respectively, and the 8-year estimates were 92% and 90% respectively (p=0.12). Differences in DFS were also not statistically significant; the 8-year estimates of DFS were 82% in both groups. Rates of regional control were also similar. Eight regional nodal recurrences as first events, including two in the axilla, were reported in group one. Fourteen regional nodal recurrences as first events, including eight in the axilla, were reported in group two. Because the OS, DFS, and regional control rates between the treatment groups were statistically equivalent, the NSABP investigators concluded that when the SLN is negative, SLND alone without further ALND is appropriate for patients with clinically negative lymph nodes.

The findings of the NSABP B-32 trial were confirmed by a single center randomized trial conducted at the European Institute of Oncology. This trial enrolled patients with primary tumors that were 2 cm or smaller who underwent BCT. Patients were randomized to SLND plus ALND (ALND arm; n=257) or SLND and ALND only if the SLN was positive for metastatic disease (SLND arm; n=259). [33, 40, 41] In 2010, the 10-year follow-up data from this trial were published. [41] The ALND and SLND groups were well matched with respect to clinicopathologic characteristics and adjuvant systemic therapy use. After a median follow-up of 102 months, no significant differences in OS were found. Taken together, the NSABP B-32 and EIO trials confirmed that SLND is effective for staging the axilla in patients with clinically node-negative breast cancer and that SLND alone is safe when the SLN is negative.

Role of Completion ALND in the Setting of a Positive SLN

Once SLND was shown to be safe in patients with clinically node-negative disease, omission of ALND in patients with a negative SLN became standard practice. For patients with a positive SLN, most consensus statements, including one from the American Society of Clinical Oncology (ASCO), and NCCN guidelines recommended completion ALND for patients with a positive SLN. [42, 43] However, recalling the results of the NSABP B-04 trial, a study that showed no survival advantage for patients who underwent ALND at the time of their initial surgery, and recognizing improvements in systemic therapy options and radiation delivery, the utility of completion ALND in all patients with a positive SLN was questioned.

To determine whether all patients with a positive SLN need an ALND, ACOSOG conducted the Z0011 trial which enrolled patients with clinical T1 or T2, N0, M0 breast cancer who underwent BCT and were found to have one or two positive SLNs by H&E evaluation. [44, 45] The patients were randomized to ALND or no further surgery. All patients received WBI (third-field axillary irradiation was not allowed), and recommendations for systemic adjuvant therapy were made at the discretion of the treating oncologist (Figure 4). The primary endpoint was OS and secondary endpoint was DFS. Local-regional control was not a pre-specified endpoint; however, because of concerns that the regional recurrence rates may be high without completion ALND, regional recurrences were monitored.

The trial, which was designed to enroll 1900 patients, began accrual in 1999. Because of slow accrual and a lower than anticipated event rate, the study was closed early in 2004 after 891 patients were randomized; 446 in the SLND alone arm and 445 in the SLND + ALND arm. Clinicopathologic characteristics were similar between the two groups and overall reflected a population of patients with favorable characteristics (Table 1). [45] Micrometastases were identified in the SLN of 38% of patients in the SLND alone arm and in the SLN of 45% of patients in the ALND arm (p=0.05). Additional positive lymph nodes

were identified in 27% of patients in the ALND arm.[44] Adjuvant systemic therapy was administered in 97% of patients in the SLND only arm, including chemotherapy in 58% and hormonal therapy in 47%. In the ALND arm, 96% of patients received adjuvant systemic therapy, including chemotherapy in 58% and hormonal therapy in 46%. [44]

After a median follow-up of 6.3 years, only 29 local-regional recurrences were reported in the entire population. The local recurrence rate was 2% in the SLND arm and 4% in the ALND arm. Ipsilateral axillary recurrences were uncommon, occurring in 4 (0.9%) patients in the SLND arm and 2 (0.5%) patients in the ALND arm. [44] The authors found no differences in DFS or OS between the two groups.[45] On the basis of these results, the ACOSOG investigators concluded that routine use of ALND is not justified and may be safely omitted in selected patients with clinically node-negative disease who have one or two positive SLNs. Importantly, the Z0011 trial did not include patients with T3 tumors or patients who had undergone mastectomy, those receiving neoadjuvant chemotherapy, APBI, or WBI administered in the prone position where the low axilla is not treated. Therefore, the ACOSOG investigators have cautioned against broad extrapolation of the data indicating that, in such patients, ALND remains the standard practice when a positive SLN is identified. [45]

When the Z0011 data were published, several questions were raised regarding the trial and whether the results of the study would change practice. [46] The most significant concern was that the planned sample size was not reached. One reason for early closure was that the increased acceptance of screening mammography and improvements in systemic therapy led to an event rate that was lower than anticipated at the time of study design. In addition, the study was designed to demonstrate the non-inferiority of SLND alone for OS with a p value of 0.008. Because the 95% CIs for the HR did not cross the predefined point at which the treatments would not be considered equal, the results would not be expected to change with a larger sample size. Finally, the endpoints of total local-regional recurrences, DFS, and OS all numerically favored the SLN group. [44–46]

The American Society of Breast Surgeons has issued a consensus statement on axillary management that incorporates the findings from the Z0011 trial. [47] Additionally, in the most recent version of its guidelines, the NCCN has changed their algorithm for the management of clinically node-negative disease in patients with a positive SLN to include the category 1 recommendation to consider no further surgery for patients who meet all of the following criteria: T1 or T2 tumor, one or two positive SLNs, undergoing BCT, planned to receive WBI, and did not receive neoadjuvant chemotherapy. [48] Emerging data confirm that the Z0011 data have been practice changing. [46, 49–51]

The International Breast Cancer Study Group (IBCSG 23–01) trial will provide additional data regarding the necessity of ALND in patients with a positive SLN. This trial enrolled patients with clinically node-negative breast cancer and a primary tumor that was 5 cm or smaller who were found to have a SLN micrometastasis that was 2 mm or smaller. Patients were randomized to ALND or no further axillary surgery. Unlike the Z0011 trial, which required patients to undergo BCT, patients in the IBCSG 23-01 trial could undergo mastectomy. The primary endpoint was DFS, and the secondary endpoints were OS and systemic DFS. The trial was designed to accrue 1960 patients. It opened in 2001 and closed early in 2010 after enrolling 934 patients. Similar to the Z0011 trial, reasons for early closure included slow accrual and a lower than anticipated event rate.

Initial results from this trial were presented in 2011. [52] The mean age of enrolled patients was 54 years (range, 26–81 years), and 56% were postmenopausal. The majority (67%) had tumors that were smaller than 2 cm; 89% had tumors that were ER positive, and 74% had

grade 1 or 2 disease. Breast-conserving surgery was performed in 75%. In 85% of patients, one or two SLNs were identified. The SLN metastasis was 1.0 mm or smaller in approximately 70% of patients and 1.1–2.0 mm in approximately 30%. After a median follow-up of 49 months, the investigators reported 88 total DFS events, including 66 that were breast cancer related (8 local, 6 regional, 42 distant, and 10 contralateral breast). 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. The overall low event rate in the IBCSG 23-01 trial supports the findings from the Z0011 trial suggesting that ALND can be safely omitted in selected patients with clinically node-negative early-stage breast cancer who have a positive SLN.

Sentinel Lymph Node Micrometastases

One purported benefit of SLND is that it allows more rigorous pathologic evaluation of fewer lymph nodes that are at greatest risk for harboring disease. Whereas lymph nodes obtained during ALND are bi-valved and subjected to H&E staining, SLNs routinely undergo serial sectioning with or without IHC. Using these techniques, pathologists can identify small-volume metastases down to the level of isolated tumor cells (ITCs). The clinical relevance of this small-volume disease has been the subject of considerable debate. [53–55]

NSABP B-32—The NSABP B-32 trial, discussed in detail above, provided an opportunity to investigate the clinical significance of occult metastatic disease. Tissue blocks from patients with negative SLNs at the local site were sent for central evaluation. Additional sections deeper in each block were evaluated via H&E staining and IHC to identify occult metastases. [56] For the analysis, patients who underwent SLNB plus ALND and those who underwent SLND alone were grouped together and classified according to whether occult metastasis were detected. The primary outcomes were OS, DFS, and DDFS. [57] Because central analysis results were blinded, no clinical decisions regarding adjuvant therapy were made on the basis of the knowledge of whether occult metastases were present.

Pathologic material was available for 3887 (97%) patients who were determined at local sites to have a negative SLN. Occult metastases were detected in approximately 16%; 11% had ITCs, 4.4% had micrometastases, and 0.4% had macrometastases. The median duration of study enrollment was 95 months. There were significant differences in OS (p=0.03), DFS (p=0.02), and DDFS (p=0.04) between patients with and without occult metastases. The 5-year OS estimates for patients with and without occult metastases were 94.6% and 95.8% respectively. Although occult metastases were associated with a statistically significant detriment in OS, the small degree of absolute difference led investigators to conclude that the additional evaluation of initially negative SLNs using IHC yielded no clinical benefit. [57]

ACOSOG Z0010—The Z0010 trial was designed specifically to evaluate the incidence and significance of SLN and bone marrow micrometastases in patients with early-stage breast cancer who underwent breast-conserving surgery and WBI. [32] Briefly, patients with clinical T1 or T2, N0, M0 breast cancer were enrolled and underwent breast-conserving surgery that included lumpectomy and SLND as well as bilateral anterior iliac crest bone marrow aspiration biopsies (Figure 5). Bone marrow aspiration was initially an optional procedure; however, it was subsequently integrated as a mandatory trial component. Bone marrow aspirates and SLNs that were negative via H&E evaluation at local sites were submitted to a central laboratory for immunocytochemistry (to detect bone marrow micrometasasis) or IHC (to detect SLN micrometastasis). Treating physicians were blinded

to the immunochemical status of bone marrow and SLN specimens. The primary endpoint was OS, and the secondary endpoint was DFS.

The Z0010 trial began enrolling patients in 1999 with an accrual goal of 5300. The study completed accrual in 2003 with 5538 patients, 5210 of whom were eligible. Of these, 5119 (98%) had a SLN identified, 3904 (76%) of which were negative via H&E staining. Of those that were negative via H&E staining, 3326 (85%) were available to be assessed centrally via IHC, and 349 (11%) of those contained occult metastases. [32] The ages and tumor characteristics of patients with SLNs examined via IHC are shown in Table 2. At a median follow-up of 6.3 years, the investigators found no significant association between IHC-detected occult metastases and OS or DFS. [32] The 5-year OS rates for patients with IHC-positive and negative SLNs were 95% and 96%, respectively (p=0.64). The 5-year DFS rates in these patients were 90% and 92%, respectively (p=.82). IHC-positive SLN metastases were not associated with decreased OS on either univariate or multivariate analysis. Occult metastases were identified in 104 (3%) of 3413 patients who underwent bone marrow biopsy. No concordance between the presence of SLNs and bone marrow occult metastases was found. Bone marrow metastases were associated with decreased OS (unadjusted HR for mortality = 1.94; 95% CI: 1.02 – 3.67, p=0.04); however this association was not significant on multivariate analysis. The only factors found on multivariate analysis to be associated with decreased OS were age greater than 50 years and tumor size larger than 1 cm. Bone marrow metastases were not associated with increased recurrence. [32]

The findings from the Z0010 trial therefore support the conclusion that routine use of IHC to detect occult micrometastases in SLNs negative by H&E staining has no clinical benefit. This conclusion is consistent with guidelines from the College of American Pathologists and ASCO, which do not recommend the routine use of IHC for SLN evaluation. [42, 58] Interestingly, the investigators found no correlation between bone marrow metastases and SLN occult metastases, thereby suggesting that the status of the bone marrow may be a distinct prognostic factor. However, the proportion of patients in the ACOSOG Z0010 trial with bone marrow metastases was low; thus, further investigation is needed before consideration can be given to recommending the incorporation of bone marrow aspiration biopsy into practice for patients with early-stage breast cancer.

Summary and Future Directions: Management of the Axilla

Randomized clinical trials have been instrumental in guiding the surgical management of breast cancer to include using SLND to determine the axillary status of patients with clinically node-negative disease. The status of the SLN accurately reflects the status of the entire nodal basin, therefore SLND permits accurate staging of the axilla. For patients with a negative SLN, no further axillary surgery is indicated; therefore, patients without axillary metastases are spared the morbidity of ALND. For patients with a positive SLN, standard practice had been completion ALND; however, data from the recently reported Z0011 trial suggests that ALND may be safely omitted in selected patients undergoing BCT that includes WBI. [44, 45] Data yet to be reported from the IBCSG 23-01 trial will determine whether selected patients who have undergone mastectomy can also avoid ALND after the finding of a micrometastasis in the SLN. Considering early data from that trial and data from the NSABP B-32 and Z0010 trials showing that occult metastases detected via IHC do not have clinical relevance, one would anticipate that the IBCSG 23-01 trial will confirm that ALND can safely be omitted in patients with micrometastasis in their SLN. However, final results of this trial are not yet known and on the basis of currently available data, standard practice for patients with a positive SLN who have undergone mastectomy is completion ALND.

Because ALND is associated with significant morbidity in a substantial proportion of patients, ongoing work is focused on investigating alternative strategies for axillary management in patients with a positive SLN. As has been discussed in detail, the Z0011 data support omitting ALND in a select group of patients undergoing BCT that includes WBI. Although WBI is designed to treat the breast, a portion of the lower axilla is naturally included in the treatment field. Therefore, among patients enrolled in the Z0011 trial, WBI likely had a therapeutic effect on a portion of the axilla, although data documenting the amount of the axilla that may have treated are not currently available. This raises the question however of whether axillary radiation is a less invasive alternative to ALND for patients with a positive SLN. In the NSABP B-04 trial, described in detail above, patients with clinically node-negative disease were randomized to radical mastectomy, total mastectomy, or total mastectomy with axillary radiation; the rate of axillary recurrence in the total mastectomy with axillary radiation arm was 4% after 25 years. [11] To further investigate whether axillary radiation is an appropriate alternative to ALND, investigators from the European Organization for Research and Treatment of Cancer are conducting the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial. AMAROS is a phase III study comparing ALND with axillary radiation in clinically node negative patients with tumors smaller than 3 cm who have a positive SLN. The primary objective is to prove that axillary radiation yields equivalent locoregional control and reduced morbidity when compared with ALND. Between 2001 and 2010, the trial accrued 4827 patients. [59] An initial publication from this trial reported the technical outcomes for the first 2000 patients. The SLN identification rate was 97%, and the SLN was positive in 647 (34%), including macrometastases in 409 (63%), micrometastases in 161 (25%), and ITCs in 77 (12%). For patients randomized to undergo ALND, additional nodal involvement was identified in 41% of patients with SLN macrometastases, 18% of patients with micrometastases, and 18% of patients with ITCs. [60] Because the extent of nodal involvement may have implications on adjuvant therapy, the investigators also evaluated the administration of adjuvant therapy in these first 2000 patients. In the ALND and axillary radiation arms, 58% and 61% of patients, respectively, received chemotherapy. Multivariate analysis showed that age, tumor grade, multifocality, and SLN metastasis size significantly affected decisions regarding the use of chemotherapy. Treatment arm was not a significant factor in the decision to administer systemic therapy. [61] Primary outcome data from the trial are not yet available.

Future trials will likely investigate whether there are populations of patients in whom any surgical intervention in the axilla, including SLND, can be safely omitted. A trial randomizing patients to SLND or no surgery seems reasonable in a population of patients with very favorable clinicopathologic characteristics, including postmenopausal women with clinical T1 N0, low to intermediate grade, ER-positive tumors. Because of the overall favorable DFS and OS for this population, such a trial may be difficult to conduct in light of the number of patients and length of follow-up time required. Because decisions regarding the use of adjuvant systemic therapy are now made largely on the basis of characteristics other than the nodal status, including patient age and pathologic features of the primary tumor, another potential trial could enroll patients in whom chemotherapy would be administered regardless of nodal status (e.g., patients with triple-negative breast cancer or HER2-positive breast cancer) and randomize them to SLND or no surgery. Such a trial is currently being discussed within the newly established Alliance for Clinical Trials in Oncology cooperative group (personal communication AE Giuliano and KK Hunt).

CONCLUSION

Randomized clinical trials have been critical in guiding the surgical management of breast cancer. Breast cancer is no longer a fatal disease or one that necessitates radical surgery with significant associated morbidity. Today, largely because of the efforts of surgeons

conducting these trials, the majority of patients receive personalized surgical management of their disease, including BCT with lumpectomy, SLND, and radiation.

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The authors acknowledge that this article only highlights notable trials that have guided the surgical management of breast cancer. Other trials have contributed to the advancement of breast surgical care however due to space limitations, are not included in this review.

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KEY POINTS

- Large randomized trials have demonstrated no OS difference between mastectomy and breast conserving therapy.
- SLND has replaced ALND as the recommended procedure for axillary staging of clinically node negative breast cancer patients.
- Select patients with 1–2 positive SLNs undergoing BCT can be spared ALND with no impact on local-regional recurrence or OS.
- Current cooperative group trials evaluating new radiation approaches, tumor ablative techniques, and systemic treatments along with the development of assays assessing tumor biology will continue to advance personalized local regional treatment plans for individual patients.

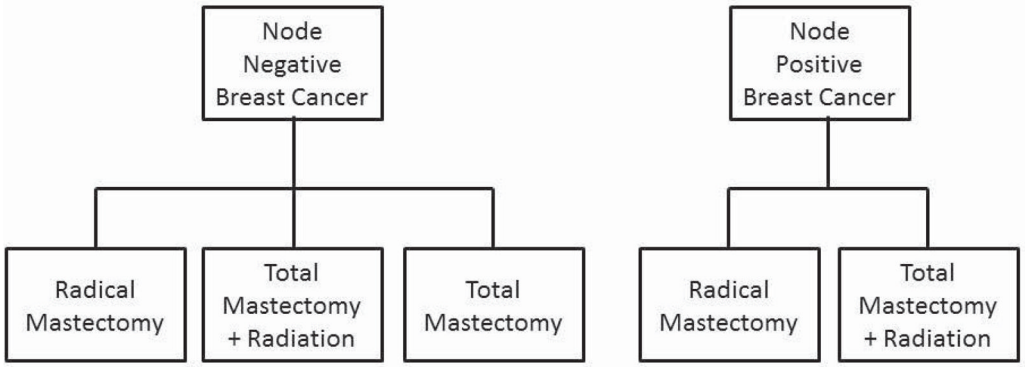

Figure 1.
Schema for NSABP B-04 trial.

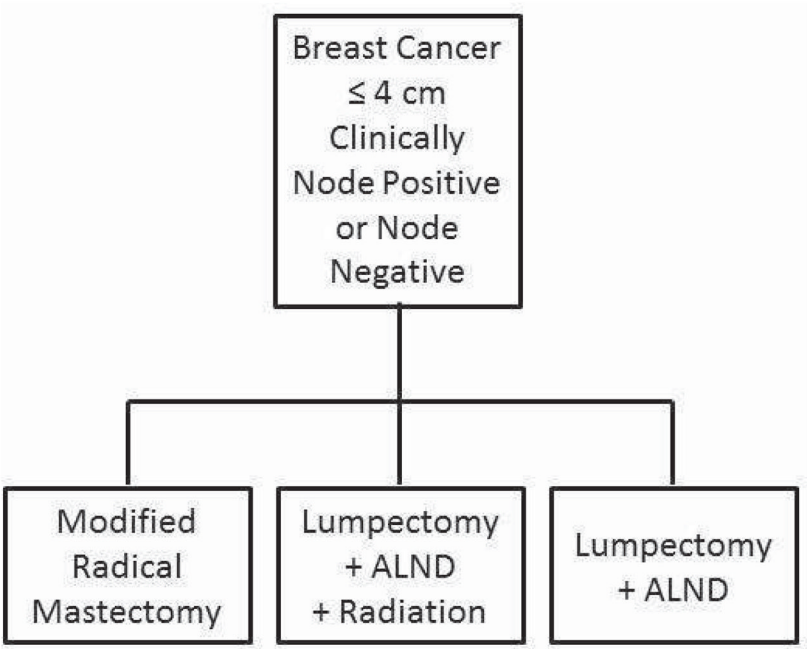

Figure 2.
Schema for NSABP B-06 trial. (ALND = axillary lymph node dissection)

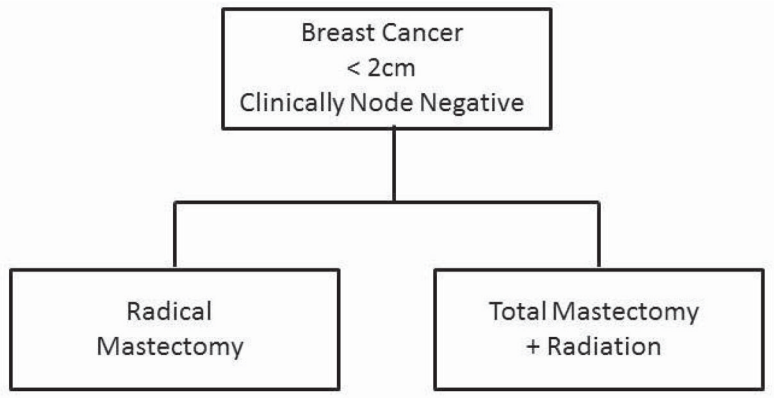

Figure 3.
Schema for NSABP B-32 trial.

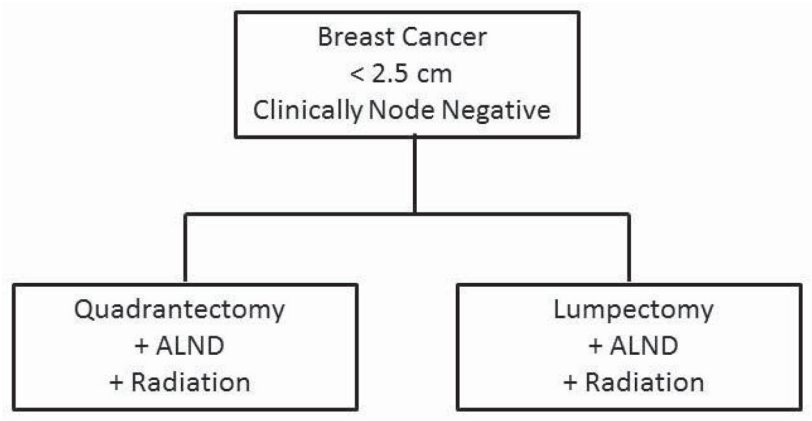

Figure 4.
Schema for ACOSOG Z0011 trial.

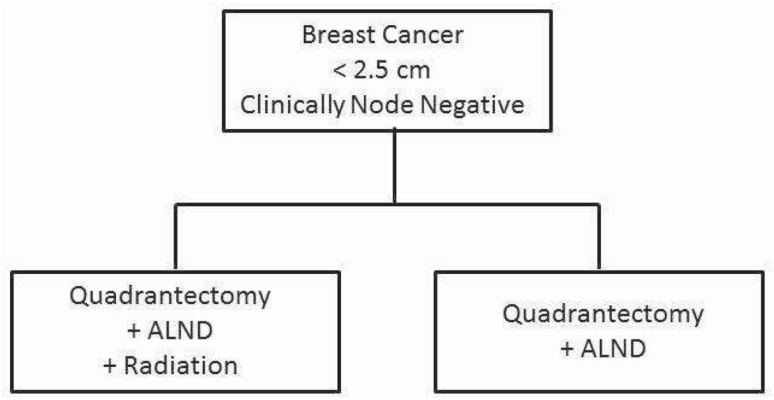

Figure 5.
Schema for ACOSOG Z0010 trial.

Table 1

Baseline patient and tumor characteristics of patients enrolled on the American College of Surgeons Oncology Group Z0011 trial. (Data from Giuliano AE, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis. JAMA 2011;305:569–75.)

Characteristic	ALND (n=420)	SLND alone (n=436)
Age in years, median (range)	56 (24–92)	54 (25–90)
Clinical T stage		
T1	284 (68%)	303 (71%)
T2	134 (32%)	126 (29%)
missing	2	7
Tumor size, median (range), cm	1.7 (0.4–7.0)	1.6 (0.0–5.0)
ER positive	317 (83%)	324 (83%)
LVI		
Present	129 (41%)	113 (35%)
Absent	189 (59%)	208 (65%)
Missing	102	115
Grade*		
1	71 (22%)	81 (26%)
2	158 (49%)	148 (47%)
3	94 (29%)	87 (27%)
Missing	97	120
Histology		
Infiltrating ductal	344 (83%)	356 (84%)
Infiltrating lobular	27 (6%)	36 (8.5%)
Other	45 (11%)	32 (7.5%)
Missing	4	12
Lymph node metastases		
0	4 (1%)	29 (7%)
1	199 (58%)	295 (71%)
2	68 (20%)	76 (18%)
3	25 (7%)	11 (3%)
≥ 4	47 (14%)	4 (1%)
Missing	77	21

ER = estrogen receptor

LVI = lymphovascular invasion

ALND = axillary lymph node dissection

SLND = sentinel lymph node dissection

* Grade was determined using the modified Bloom-Richardson score

Table 2

Age and tumor characteristics of patients in the American College of Surgeons Oncology Group Z0010 trial who had a negative SLN via H&E staining that was subsequently evaluated via IHC. (Data from: Giuliano AE, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA 2011;306:385–93.)

Variable	Negative via IHC (n=2977)	Positive via IHC (n=349)	P value
Age in years, median (range)	57 (23–95)	54 (27–87)	
Tumor size, cm			<.001
≤ 1.0	1260 (45%)	101 (31%)	
1.1 – 2.0	1202 (43%)	161 (49%)	
> 2.0	330 (12%)	67 (20%)	
Missing, number	185	20	
Histology			.002
Ductal	2387 (80%)	262 (75%)	
Lobular	226 (8%)	45 (13%)	
Both	77 (2%)	14 (4%)	
Other	284 (10%)	28 (8%)	
Missing	3	0	
ER status			.3
Positive	2225 (81%)	268 (84%)	
Negative	518 (19%)	53 (16%)	
Missing	234	28	
LVI			<.001
Absent	1921 (90%)	217 (83%)	
Present	205 (10%)	44 (17%)	
Missing	851	88	

IHC = immunohistochemistry

ER = estrogen receptor

LVI = lymphovascular invasion