Evolution of Axillary Nodal Staging in Breast Cancer: Clinical Implications of the ACOSOG Z0011 Trial

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Background: Management of the axilla in breast cancer patients has evolved from routine axillary lymph node dissection (ALND) for all patients to a highly selective approach based on the assessment of the sentinel lymph nodes (SLNs) as well as tumor and patient characteristics. Although ALND continues to have an important role in staging and regional control for many breast cancer patients, recent trial results question the need for routine ALND in patients who have positive SLNs.

Methods: Not all axillary disease becomes clinically detectable or relevant with respect to recurrence and survival. Therefore, recent trends indicate that many surgeons have omitted ALND in subgroups of patients, particularly those with clinically node-negative, SLN-positive, early-stage breast cancer undergoing breast-conserving therapy with postoperative irradiation. This review explores trends in axillary management, focusing primarily on the clinical implications of the results from the American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized controlled trial.

Results: According to the results of the ACOSOG Z0011 trial, the use of SLN dissection alone did not result in inferior survival compared with ALND in patients with limited SLN disease treated with breast-conserving therapy. This subgroup of women was spared the morbidity associated with ALND. However, several points of debate, including the smaller than anticipated sample size, the older study population, and the length of follow-up, suggest caution when applying these findings to all women with breast cancer.

Conclusions: Although the findings of ACOSOG Z0011 are impressive, in clinical practice they are applicable to a limited number of women with breast cancer: those with T1-2 primary tumors with clinically negative axilla and 1 to 2 positive SLNs undergoing breast-conserving surgery and adjuvant whole-breast irradiation. The next generation of clinical trials may answer some of the remaining questions regarding how best to manage the axilla in additional subsets of patients undergoing treatment of breast cancer.

A Historical Surgical Perspective
Traditionally, surgical oncologic principles have been based on obtaining an R0 resection. This principle led to the development of Halsted's radical mastectomy for treatment of breast cancer.\(^1\) Radical mastectomy was predicated on the belief that disease spreads in an orderly fashion from the breast to the regional lymph nodes and then to distant sites. Thus, aggressive local tumor control might prevent systemic...
tumor spread and potentially prevent death from breast cancer.

Alternatively, the hypothesis by Fisher et al\textsuperscript{2-3} centered on the concept that breast cancer becomes systemic early in its course, although the systemic disease may remain subclinical. Thus, the presence of regional nodal involvement may be a manifestation of metastatic disease elsewhere, and aggressive local tumor control may not affect overall survival. This view represents a pivotal question in breast cancer management. In accepting the latter hypothesis, the surgical management of breast cancer has evolved to develop conservative (less extensive) approaches.

Although several groups have reported their experience with “partial mastectomy” or breast-conserving surgery, Fisher et al\textsuperscript{4} and Veronesi et al\textsuperscript{5} demonstrated that breast-conserving surgery followed by irradiation of the primary tumor was a feasible option for women with early-stage breast cancer in randomized prospective trials. These studies showed that breast-conserving surgery offered patients equivalent long-term survival as traditional mastectomy.\textsuperscript{6} Just as the surgical management of the primary tumor has evolved, management of the axilla has evolved as well.

\textbf{The Changing Role of Axillary Lymph Node Dissection}

In 1990, the National Institutes of Health Consensus Conference concluded that the treatment of potentially curable breast cancer should include levels I and II axillary lymph node dissection (ALND).\textsuperscript{6} The need for routine ALND was challenged by the introduction of the sentinel lymph node (SLN) biopsy. This concept had a tremendous effect on management of the axilla. In 1994, Giuliano et al\textsuperscript{7} demonstrated that the status of the SLN accurately reflected the status of the entire axillary basin draining a primary breast tumor.

Since these initial reports, the accuracy of SLN surgery has been validated by multiple groups, sparing patients with negative sentinel nodes an ALND and its associated morbidity.\textsuperscript{8,9} Although risks such as lymphedema are present with SLN surgery, the incidence of arm lymphedema is significantly less than with ALND (7% vs 25%).\textsuperscript{10-12} The false-negative rate of SLN biopsy has been demonstrated to be approximately 9.8%,\textsuperscript{13} and the rate of locoregional tumor recurrence in patients with negative SLNs who did not have ALND has ranged from 0.1% to 1.5%.\textsuperscript{14-17} Smidt et al\textsuperscript{14} evaluated a series of 439 patients with a negative SLN. After a median follow-up of 26 months, axillary tumor recurrence was detected in 2 of 439 patients (0.46%). In addition, a meta-analysis of 3,184 patients with a negative SLN from 13 studies was performed, with a median follow-up of 21 months. Axillary tumor recurrence was detected in 8 of these patients (0.25%).\textsuperscript{14}

In cases of a positive SLN, standard treatment has been a completion ALND, as outlined by the consensus statement from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN).\textsuperscript{18,19} These guidelines stem from a meta-analysis of 69 trials including 8,059 patients who underwent SLN biopsy and subsequent ALND. The results demonstrated that 53% of patients with a positive SLN were found to have disease in non-SLNs.\textsuperscript{20}

The incidence of non-SLN involvement changes considerably with the extent of disease in the SLN. For patients whose SLN was involved by micrometastatic disease (tumor metastases greater than 2 mm), the incidence of non-SLN involvement is reported to be 40% to 58%.\textsuperscript{21} When the SLN is involved by micrometastatic disease (nodal metastasis 0.2 to 2 mm), the incidence of non-SLN involvement is 20%,\textsuperscript{22} and in the case of the SLN with isolated tumor cells (≤ 0.2 mm), the incidence decreases to 12%.\textsuperscript{23}

Factors that influence the degree of non-SLN involvement are tumor histology and grade, primary tumor size, multifocality, lymphovascular invasion, estrogen receptor (ER) status, and the ratio of positive SLNs to the total number of sentinel nodes removed.\textsuperscript{24-26} These findings have been important components in the developing trend of forgoing ALND in certain patients, particularly those thought to be at a lower likelihood of having additional disease in the non-SLNs. The American Society of Breast Surgeons issued a consensus statement in 2005 acknowledging this trend\textsuperscript{27}: “Outside of clinical trials, usual treatment for SLN-positive patients is a level I-II ALND. However, since axillary node metastases are limited to the SLN in more than half of SLN-positive individuals, there may be low-risk subsets for whom a completion ALND is not required. The decision to omit completion axillary dissection in such a case requires a balanced discussion between the surgeon and the patient regarding the risks of further surgery and any potential for improved outcome with more complete information and/or axillary clearance.”

The American College of Surgeons Oncology Group (ACOSOG) Z0011 study\textsuperscript{28,29} was a practice-changing trial that questioned the need for completion ALND in patients with early-stage disease undergoing breast conservation who were found to be SLN-positive. The study concept considered a number of factors, including the overall change in the extent of disease on initial presentation, the changes in the recommendations for adjuvant therapy based more heavily on primary tumor characteristics, and the demonstration of a low incidence of positive non-SLNs.\textsuperscript{29}

As previously discussed, the SLN has been demonstrated to be the only positive lymph node in many cases. Data from high-volume breast centers indicate that the SLN is the only site of nodal metastasis in 40% to 60% of axillary dissections.\textsuperscript{30} Veronesi et al\textsuperscript{31} reported on a series of 376 patients who underwent SLN surgery and subsequent ALND. In 73 of 168 patients with a positive SLN (44%), the SLN was the only site of metastatic disease. In a series of 443 patients
undergoing SLN and ALND, Krag et al\textsuperscript{32} noted a 97% accuracy in identifying the SLNs. In this group, 95 patients had 1 to 3 positive SLNs, and the SLN was the only positive node in 62% of cases. Similarly, Giuliano et al\textsuperscript{33} reported a study of 107 patients who underwent SLN surgery and subsequent axillary dissection. Forty-two patients were found to have positive SLNs, and in 67% of cases, the SLN was the only site of metastatic disease.

These findings may reflect a trend in identifying disease at an earlier stage and therefore at a lower nodal tumor burden. Expanded use of screening and increased awareness of breast cancers have led to a decreased size of primary tumors at presentation. Cady et al\textsuperscript{34} reported that the mean maximum diameter of breast cancers at diagnosis was 3 cm from 1979 to 1983 and 2 cm from 1989 to 1993. This downward trend in the size of tumors at presentation, coupled with the high incidence of SLN-only positive axillary disease, suggests that adequate local tumor control and staging in early-stage breast cancer may be accomplished by treating the primary tumor and removing the SLNs.

ALND has been associated with significant morbidity compared with SLN biopsy alone; the risk of lymphedema reported with SLN biopsy is 2% to 7% compared with a lifetime risk of lymphedema with ALND of 25%.\textsuperscript{10,35,36} Lucci et al\textsuperscript{12} compared the postoperative complication rate of women undergoing SLN vs SLN and ALND in the ACOSOG Z0011 study. They found that women in the ALND group had a significantly greater incidence of postoperative complications than did the SLN-only group (70% vs 25%). Complications included wound infection, axillary seromas, axillary paresthesias, brachial plexus injury, and lymphedema. As reported subjectively by study participants, the development of lymphedema was 13% at 1 year in the ALND group vs 2% in the SLN-only group.

**Trends to Omit ALND**

The use of completion ALND in patients with positive SLNs was decreasing prior to the presentation of the results of the ACOSOG Z0011 trial. This trend was evaluated retrospectively in a number of studies. Bilimoria et al\textsuperscript{37} reviewed patients from the National Cancer Data Base (NCDB) between 1998 and 2005. The 97,314 patients identified were clinically node-negative and found to have nodal metastasis on SLN biopsy. Approximately 20.8% of these node-positive patients underwent SLN biopsy alone without completion ALND. From 1998 to 2005, the proportion of patients who underwent SLN biopsy alone for macroscopic disease declined from 24.2% to 16.7%. However, the proportion of patients who underwent SLN biopsy alone for micrometastatic disease increased from 24.7% to 45.3%. Patients who underwent SLN biopsy alone were older (mean age, 58 vs 56 years), had lower-grade disease (58.8% grade I/II vs 32.5% grade III), had a smaller tumor size (1.8 vs 2.1 cm), and were undergoing breast-conserving surgery (81%). In this retrospective review, axillary recurrence and survival data were obtained for the cohort of patients diagnosed between 1998 and 2000. No significant difference was detected with respect to axillary tumor recurrence or survival between the patients undergoing SLN alone and those undergoing SLN and completion ALND, with a median follow-up of 63 months.

Yi et al\textsuperscript{38} reviewed patients from the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2004. A total of 26,986 patients with breast cancer underwent SLN biopsy and were found to have nodal metastasis. Of these patients with a positive SLN, 4,425 (16.4%) underwent SLN biopsy alone, and 22,561 (83.6%) underwent ALND. When the investigators evaluated the trend of patients undergoing SLN biopsy alone, there was a difference among patients who had micrometastatic vs macrometastatic disease. From 1998 to 2004, the proportion of patients with micrometastases who underwent SLN biopsy alone increased from 21% to 38%. However, in patients with macrometastasis, the proportion of patients who underwent SLN biopsy alone increased (5.7% to 13.1%) from 1998 to 2002 and then decreased slightly (13.1% to 10.6%) from 2002 to 2004.

Similar to the NCDB report, the cohort of patients who underwent SLN biopsy alone in the SEER report were older (59 vs 56 years of age), had a smaller tumor size (16 vs 20 mm), or had lower-grade tumors (21% grade I or II vs 13% grade III). Also, the majority of patients who had SLN biopsy alone underwent breast-conserving surgery (78.8%). This trend may reflect the increased comfort of physicians to forgo completion ALND in patients who are candidates for postoperative radiotherapy. The authors noted that patients with micrometastasis had no difference in ipsilateral regional events among the groups. Patients with macrometastasis who underwent SLN biopsy with ALND had a lower risk of ipsilateral regional events than did those who underwent SLN biopsy alone (0.08% vs 0.2%; \( P = .02 \)). However, no significant difference in survival was noted between the two groups at 50 months.

One of the factors that may have influenced the decrease in completion ALND for SLN-positive disease after the year 2000 may be the availability of online nomograms to predict non-SLN involvement. Currently, several nomograms have been developed to predict non-SLN involvement for patients with SLN-positive disease. The Memorial Sloan-Kettering Cancer Center (MSKCC) online nomogram,\textsuperscript{39} which has been externally validated, is one of the most commonly used.\textsuperscript{40,42} Other available nomograms have been developed at the Mayo Clinic, MD Anderson Cancer Center, and Stanford University.\textsuperscript{40,43,44} The MSKCC nomogram is an online calculator that provides a risk estimate of non-SLN metastasis based on 9 histopathological vari-
The trial recommended whole-breast radiation be administered to all patients; however, all patients did not undergo adjuvant radiation therapy. Whole-breast radiation was administered to 88.9% of patients in the ALND group vs 44.8% in the SLN-only group, with this difference being statistically significant (P = .05). This finding suggests that patients in the SLN-only group may have had a more favorable tumor burden. Comparison of the two groups at 6.3 years of follow-up revealed no difference in the rate of axillary tumor recurrence (0.5% vs 0.9% for arms 1 and 2, respectively), in-breast recurrence (3.6% vs 1.9%), or overall locoregional tumor recurrence (4.1% vs 2.8%). The 5-year disease-free survival rates were 82.2% in the ALND group and 83.9% in the SLN-only group, and 5-year overall survival rates were 91.8% and 92.5%, respectively.

By intent-to-treat analysis, adjuvant systemic therapy was delivered to 403 patients in the ALND group (96%) and 423 in the SLN-only arm (97%). Hormonal therapy was given to 195 patients in the ALND group (46.4%) compared with 203 patients in the SLN-only arm (46.6%). Chemotherapy was administered to 243 patients in the ALND arm (57.9%) and 253 patients in the SLN-only arm (58%). Locoregional tumor recurrence was 3.4% in patients who received adjuvant systemic therapy and 3.3% in those who did not.

The trial recommended whole-breast radiation be administered to all patients; however, all patients did not undergo adjuvant radiation therapy. Whole-breast radiation was administered to 88.9% of patients in
the ALND group and 89.6% of patients in the SLN-only group. In the group of patients who underwent ALND, 27% had additional nodal metastasis identified on histopathological assessment of the axillary contents. Ten percent of patients with micrometastasis on SLN biopsy who underwent ALND had additional involved nodes removed. We may presume that a similar number of patients in the SLN-only arm had residual non-SLN metastasis. However, this conclusion may not be entirely accurate, as a greater percentage of the SLN-only cohort had micrometastasis and patients with micrometastasis had lower rates of additional nodal metastasis. Failure to stratify patients based on the size of SLN metastasis is a limitation of this trial. The axillary tumor recurrence rate for this arm was less than 1% at 6.3 years. Although subclinical disease may have been treated by adjuvant systemic therapy and irradiation, this finding suggests that not all non-SLN metastasis develops into clinically detectable disease. Removing additional involved nodes with an axillary dissection in this group of patients did not improve locoregional tumor recurrence or overall survival.

**Supporting Data From Other Clinical Trials**

The recently reported update by Galimberti et al. of the International Breast Cancer Study Group (IBCSG) trial 23-01 sheds light on the issue of ALND in patients with SLN micrometastasis. The study was a randomized, multicenter, phase III clinical trial comparing axillary dissection with no axillary dissection in patients with micrometastasis in the SLN. A total of 934 patients were randomized: about half to ALND and the other half to SLN only. Patients were clinically node-negative, had a primary tumor < 5 cm, and had a minimal (< 2 mm) tumor burden in 1 to 2 SLNs. The majority of patients (67%) had tumors < 2 cm, and 89% were ER+. Disease-free survival was the study's primary endpoint, and overall survival and systemic disease-free survival were secondary endpoints. The 5-year disease-free survival and overall survival rates in the ALND vs SLN-only groups were 87.3% vs 88.4% (P = .48) and 97.6% vs 98% (P = .35), respectively. Of note, 25% of patients included in this study underwent mastectomy. The fact that R0 resection to remove all positive lymph nodes may not be required and does not affect overall survival is not a new idea. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study provided insight into the natural progression of axillary disease and the clinical consequences of axillary nontreatment. In this study, clinically node-negative patients were randomized to undergo total mastectomy with ALND (n = 354), total mastectomy with regional irradiation (n = 282), or total mastectomy alone (no treatment to the axilla, n = 344). The total mastectomy-alone arm provides information on the consequences of no treatment to the axilla, neither surgery nor irradiation, and no systemic therapy. Of note, 40% of patients randomized to undergo total mastectomy with axillary dissection were found to have positive axillary lymph nodes on final pathology review. This finding indicates that the mastectomy-only arm also had a similarly high percentage of lymph-node positivity, even though they were clinically N0. Of the patients in the mastectomy-only arm, 18.6% presented with clinically palpable axillary nodes on follow-up and underwent delayed ALND. This study result is remarkable in that it is less than half the presumed number of patients with subclinical positive nodes. After assessing for these salvage axillary surgeries, no significant difference in the rates of uncontrolled regional tumor recurrence and overall survival among these clinically node-negative patients was demonstrated, with a 25-year follow-up. These results support Fisher's concept that the biology of breast cancer will dictate its disease progression, as opposed to the mere presence of nodal involvement.

**Controversies Surrounding the ACOSOG Z0011 Trial**

Several points of debate about the ACOSOG Z0011 trial have been explored: the smaller than anticipated sample size and the low event rate; the older (> 50 years) study population (raising the question of applicability to younger women); the largely ER+ study population (again raising the question of applicability to women with ER– or HER-2+ tumors); the applicability to invasive lobular carcinoma, which comprised a minority of the study cohort; and the length of follow-up.

The planned target accrual for the ACOSOG Z0011 trial was 1,900 patients, as previously mentioned. This number was calculated using a prediction of overall survival rate of 80% at 5 years for women with optimally treated node-positive breast cancer, and clinical noninferiority was defined as the SLN-only group having a 5-year survival rate of less than 75% of that observed in the ALND group. An estimated 500 deaths were needed for the study to have 90% power to confirm noninferiority of SLN alone compared with ALND.

The first patient was enrolled in May 1999. Due to the slow mortality rate observed, the ACOSOG Data and Safety Monitoring Committee closed the study to new patients in December 2004. Even if the trial had accrued the target 1,900 patients, it would have taken more than 20 years of follow-up to observe 500 deaths due to the slower-than-predicted event rate. No preliminary analysis had been performed at the time of closure of the study.

It could be argued that the information obtained from the study is limited, based on a smaller sample size than anticipated and a low event rate. At a median follow-up of 6.3 years, there were 94 deaths: 42 in the SLN-alone group and 52 in the ALND group. Despite the low event rate and significantly lower number of patients enrolled than expected, the study authors maintain that the predefined statistical analy-
The majority of women in the ACOSOG Z0011 study were older than 50 years. In the multivariate analysis, tumor grade and patient age were associated with locoregional tumor recurrence in either arm. Upon closer evaluation, the majority of locoregional tumor recurrences in young women were in-breast recurrences as opposed to nodal recurrences. In patients younger than age 50, the SLN-only group experienced 5 locoregional recurrence events: 4 in the breast and 1 nodal. The ALND group had 11 locoregional recurrence events: 9 in the breast and 2 nodal.

The tendency of young women to have a higher rate of in-breast tumor recurrence has been demonstrated in previous reports. One retrospective review evaluating 3,064 patients who underwent breast-conserving therapy demonstrated that age < 40 years was an independent risk factor for local tumor recurrence. Based on the fact that the observed locoregional tumor recurrences in women younger than age 50 were primarily breast recurrences as opposed to nodal recurrences, the authors of ACOSOG Z0011 maintain that the study does not provide evidence that young women have a higher rate of nodal tumor recurrence. However, as the majority of women enrolled in the study were older than age 50, the findings may not be widely applicable to younger women.

Another question raised about the ACOSOG Z0011 data is their applicability to subgroups of patients with tumors who are ER− or HER-2/neu+. The development and use of targeted adjuvant endocrine therapy have been demonstrated to significantly reduce the rate of locoregional tumor recurrence as well as improve the rates of disease-free survival and overall survival in women with ER+ tumors. The remarkably low locoregional tumor recurrence rate reported in the ACOSOG Z0011 trial is in part due to the use of targeted adjuvant therapy, which likely treats subclinical disease in the axillary nodal basin. According to the multivariate analysis in the ACOSOG Z0011 trial, there was no difference in the rate of locoregional tumor recurrence in patients who had ER− vs ER+ tumors. However, only 16% of patients in each arm were ER−, which raises the question of whether these results can be extrapolated to patients with ER− disease.

Information with respect to HER-2 status was not included within the study design. When the trial opened in 1999, routine testing of HER-2 was not uniformly practiced. Tumors that express HER-2 tend to be more aggressive. However, patients with HER-2+ tumors may benefit from the use of targeted adjuvant therapy such as trastuzumab (Herceptin). In randomized controlled trials, the use of adjuvant trastuzumab has been demonstrated to improve the disease-free and overall survival rates in patients with HER-2+ breast cancer. Thus, HER-2 positivity may not be a reason to omit or proceed with ALND but rather must be weighed along with the rest of the data available for a patient. The findings of ACOSOG Z0011 may not apply to patients who have not had the benefit of targeted adjuvant therapy, such as those with triple-negative disease. However, the authors suggest that although the prognosis of patients with triple-negative breast cancer is poor, these tumors are less likely to metastasize to lymph nodes, and thus their prognosis may not rely on a heavy nodal burden.

A subset of patients not clearly defined in the ACOSOG Z0011 study consists of those with invasive lobular carcinoma. These patients represented only 7% of the trial population. The concern with evaluation of SLNs in patients with lobular histology is that these tumors are more likely to have multiple smaller foci of disease and isolated tumor cells in the SLN, which may not be detected by standard H&E analysis. These nodal metastases may require IHC for detection. Although isolated tumor cells represent a low tumor burden, they may have clinical relevance undetected in this study. This factor must be taken into consideration when evaluating patients with invasive lobular carcinoma with respect to performing ALND.

Routine IHC analysis of SLNs has not been supported by ASCO or the College of American Pathologists and was abandoned by many institutions after the data from ACOSOG Z0010 and NSABP B-32 were reported. The ACOSOG Z0010 observational study sought to determine the association between metastases detected by IHC staining of SLNs and bone marrow specimens from patients with early-stage breast cancer and survival. Of the 3,326 SLN specimens that were negative by H&E staining, 10.5% were found to be positive for metastasis on IHC. There was no significant difference in overall survival between patients with IHC-negative disease compared with IHC-positive disease (95.7% vs 95.1%; P = .64). NSABP B-32, which randomized clinically node-negative breast cancer patients to receive SLN alone or SLN plus ALND, identified lymph node metastases by IHC in 15.9% of patients who were SLN-negative on H&E staining. The absolute difference in overall survival between IHC-positive and IHC-negative patients was 1.2% (94.6% vs 95.8%; P = .03).

Another issue regarding the validity of the data from ACOSOG Z0011 is related to the length of follow-up for the enrolled patients and whether it is adequate for assessing recurrence and survival. We looked at previous studies to answer this question. In NSABP B-04, the median time to axillary tumor recurrence was 14.8 months in clinically node-negative women who did not undergo ALND. At 5 years, the rate of tumor recurrence was 16.2% (55 of 344 patients). On 10-year follow-up evaluation, 75% of patients who remained free of disease at the end of 5 years continued to be free of disease. Similarly, with respect to overall survival, about 75% of patients with negative nodes who were alive at 5 years remained alive at 10 years.

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years. Additionally, there was no significant difference between overall survival among the 3 node-negative groups over the entire follow-up. At 10 years, overall survival was 58% for the radical mastectomy group, 59% for patients treated with total mastectomy plus irradiation, and 54% for those undergoing total mastectomy alone. Furthermore, there was no difference in disease-free, distant relapse-free, or overall survival rates among these groups at 25 years.

Greco et al69 evaluated a series of 401 breast cancer patients prospectively. Patients had tumors up to 3 cm and clinically negative axilla. A total of 383 patients underwent quadrantectomy with no axillary dissection. Of these patients, 67% received postoperative adjuvant radiation therapy. The median time to axillary tumor recurrence was 30.6 months.

Martelli et al60 reported on a group of 671 patients over the age of 70 with clinically node-negative axilla who underwent breast-conserving therapy with or without axillary dissection (172 patients vs 499 patients). All patients received adjuvant tamoxifen therapy for at least 2 years. The median time from primary surgery to axillary tumor recurrence was 33 months. Upon 15-year follow-up, 90% of patients who developed axillary disease did so within 6 years of surgery. With respect to survival, there was no advantage to axillary dissection in terms of breast cancer mortality.

Grills et al61 demonstrated that in a group of 568 node-positive, ER+ patients treated with breast-conserving therapy or axillary dissection, with or without nodal irradiation, the incidence of nodal tumor recurrence increased only slightly after 5 years. Thus, based on data available from reported studies, the ACOSOG investigators maintain that a follow-up of 6.3 years is sufficient to capture the majority of axillary tumor recurrences.46

Whole-Breast Radiation Fields and Management of the Axilla

The ACOSOG Z0011 trial recommended whole-breast radiation therapy without the addition of a third field to treat the axilla. The standard technique of whole-breast radiation therapy applied to breast cancer patients following breast-conserving therapy is the two-portal opposed tangential approach. In addition to radiating all the breast tissue, this technique applies radiation to some extent to the low-lying axillary lymph nodes. When treating high-risk patients, some radiation oncologists advocate the use of “high tangential fields” to improve axillary coverage.62

Data from Reznik et al62 demonstrated that the average doses of radiation delivered to axillary levels 1, 2, and 3 with tangential fields are 66%, 44%, and 31% of the prescribed dose, respectively. With these normal tangents, 51% of level 1 and 26% of level 2 axillary nodes receive 95% of the prescribed dose. With minor variation in the field design, radiation can be delivered via high tangential fields. This technique achieves almost complete axillary coverage by field edge at least extending the superior field border to within 2 cm of the humeral head and by setting the deep field edge at least 2 cm posterior to the lung/chest wall interface.63 In this scenario, 79%, 51%, and 49% of levels I, II, and III receive 95% of the therapeutic dose, respectively.

A limitation of the ACOSOG Z0011 trial is that data concerning features of the field design were not captured for patients enrolled in the study. In addition, all patients did not undergo whole-breast radiation therapy as planned. As previously discussed, 88.9% of patients in the ALND group and 89.6% of patients in the SLN-alone group underwent adjuvant radiation therapy. Due to the potentially therapeutic effect of tangential field radiation on the axilla, the fact that this was not standardized among patients enrolled raises questions regarding the radiation fields for these patients. Therefore, when incorporating ACOSOG Z0011 results into clinical practice, radiation oncologists may question whether tangents should be raised to direct radiation to the axilla.

The delivery of radiation to the axilla for treatment of nodal disease is not novel. Gadd et al64 evaluated the outcome of patients with a positive SLN who underwent axillary radiation therapy in lieu of ALND. The study included 73 patients with clinically T1-2 N0 disease who underwent breast-conserving therapy with a finding of a positive SLN. These patients underwent adjuvant axillary radiation therapy as well as systemic therapy. Of the 73 patients, 1.4% developed an axillary tumor recurrence, with a median follow-up of 32 months. Although this study did not compare ALND and axillary radiation therapy, it does suggest that radiation therapy may be an acceptable alternative to ALND in a subset of patients with early-stage disease. However, the data from this study have been published only in abstract format.

This topic is being addressed further in a prospective randomized study by the European Organisation for Research and Treatment of Cancer (EORTC) in the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial.65 The AMAROS trial is a phase III study comparing ALND with axillary radiation therapy in patients with proven axillary metastasis by SLN biopsy. The main objective of the trial is to prove equivalent locoregional tumor control and reduced morbidity for axillary radiation therapy. This study will evaluate the axillary recurrence rate as the primary outcome measure. Secondary outcome measures include axillary recurrence-free survival, disease-free survival, overall survival, and quality-of-life measures.

The recently reported results from the NCIC-CTG MA.20 intergroup trial of regional nodal irradiation in early breast cancer have raised the question of additional nodal radiation therapy for high-risk patients undergoing breast-conserving therapy and whole-breast irradiation.66,67 The hypothesis for this trial
was that adding regional nodal radiation therapy may improve survival compared with breast-alone irradiation after breast-conserving therapy and systemic therapy. The concern with extending the radiation volume is that it may increase the risk of adverse side effects, such as pneumonitis, lymphedema, and cardiac disease (particularly after anthracycline-based chemotherapy). This study included patients who underwent breast-conserving therapy with ALND. Patients were eligible for additional nodal radiation therapy if they had involved nodes. If the nodes were negative, they were eligible if the primary tumor was > 2 cm, if they had < 10 nodes retrieved during ALND, or if they had either grade 3 histology, an ER– tumor, or the presence of lymphovascular tumor invasion.

The 1,832 women were randomized to receive either whole-breast and regional nodal radiation therapy or standard whole-breast irradiation. The whole-breast and regional nodal radiation group experienced improved isolated locoregional disease-free survival (96.8% vs 94.5%; \( P = .02 \)), improved distant disease-free survival (92.4% vs 87.0%; \( P = .002 \)), and a trend toward improved overall survival (92.3% vs 90.7%; \( P = .07 \)) at 5 years. The whole-breast and regional nodal radiation group also experienced an increase in pneumonitis (1.3% vs 0.2%; \( P = .01 \)) and lymphedema (7.3% vs 4.1%; \( P = .004 \)) over the standard whole-breast radiation group.

**Conclusions**

Management of the axilla in breast cancer patients has evolved over the past several decades. We have transitioned from the era of performing routine axillary lymph node dissection (ALND) on all breast cancer patients to identifying patients who need ALND based on results from sentinel lymph node (SLN) biopsy (Table). In doing so, many patients have been spared the morbidity associated with ALND. Currently, the approach to the axilla has become even more selective, as the choice of ALND may be based not only on the SLN result but also on tumor and patient characteristics. Evaluation of the SLN has also evolved, as data from recent trials support abandoning the routine use of IHC to identify occult metastasis.

The findings from the ACOSOG Z0011 trial are practice-changing, and they evoke the principle demonstrated in NSABP B-04: not all axillary disease becomes clinically detectable or relevant with respect to recurrence and survival. The recurrence and survival rates demonstrated in ACOSOG Z0011 are far superior to those in NSABP B-04, representing the evolution of breast cancer care received by contemporary women. These improved outcomes can be explained by improvements in screening and imaging, which have led to more women presenting with earlier-stage disease. In addition, improved pathological analysis, targeted adjuvant systemic therapy, and radiation therapy have improved locoregional tumor recurrence and overall survival.

Although the findings of ACOSOG Z0011 are impressive, in practice we must remember that the data are applicable to a limited number of cancer patients: those with T1-2 primary tumors with clinically negative axilla and 1 to 2 positive SLN(s) who underwent breast-conserving surgery and adjuvant whole-breast irradiation. The majority of patients were older and had invasive ductal carcinoma, ER+ disease, and a low nodal tumor volume. This patient cohort does not represent the breadth of patients who present with breast cancer. Surgeons must use discretion when applying these data to younger patients or to those with invasive lobular carcinoma, ER+, and HER-2+ disease. The trial did not address (and therefore should not be translated to) patients with early-stage disease who elect mastectomy, patients undergoing neoadjuvant chemotherapy, or patients who may be receiving partial-breast radiation therapy, intraoperative radiation therapy, or whole-breast irradiation in the prone position. Additionally, these data cannot be extrapolated to advise axillary radiation therapy in lieu of ALND. For patients with known positive lymph node metastasis preoperatively, those with palpable adenopathy, and those with more than 2 positive SLNs or lymph nodes with extracapsular tumor extension, ALND should be recommended.

Although nodal staging has become less invasive for more women, ALND still plays an important role for regional tumor control and staging for many breast cancer patients. We have transitioned from the era of performing routine axillary lymph node dissection (ALND) on all breast cancer patients to identifying patients who need ALND based on results from sentinel lymph node (SLN) biopsy (Table). In doing so, many patients have been spared the morbidity associated with ALND. Currently, the approach to the axilla has become even more selective, as the choice of ALND may be based not only on the SLN result but also on tumor and patient characteristics. Evaluation of the SLN has also evolved, as data from recent trials support abandoning the routine use of IHC to identify occult metastasis.

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**Table. — Guidelines for Management of Sentinel Lymph Node Findings**

<table>
<thead>
<tr>
<th>Biopsy Results</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative sentinel lymph node(s)</td>
<td>No further axillary surgery required. ALND may be omitted.</td>
</tr>
<tr>
<td>Positive lymph node at presentation</td>
<td>ALND should be performed.</td>
</tr>
<tr>
<td>(proven by FNA or core needle biopsy)</td>
<td></td>
</tr>
<tr>
<td>Positive sentinel lymph node(s)</td>
<td>ALND may be omitted if:</td>
</tr>
<tr>
<td>1 or 2 positive sentinel lymph nodes</td>
<td>• Primary tumor ≤ 5 cm</td>
</tr>
<tr>
<td></td>
<td>• Clinically negative axilla</td>
</tr>
<tr>
<td></td>
<td>• Successful breast conservation</td>
</tr>
<tr>
<td></td>
<td>• Will receive whole-breast radiation therapy and likely systemic therapy</td>
</tr>
<tr>
<td></td>
<td>ACOSOG Z0011 data do not apply to the following patients:</td>
</tr>
<tr>
<td></td>
<td>• Those undergoing mastectomy</td>
</tr>
<tr>
<td></td>
<td>• Those receiving neoadjuvant chemotherapy</td>
</tr>
<tr>
<td></td>
<td>• Those receiving partial-breast radiation therapy or radiation therapy in the prone position</td>
</tr>
<tr>
<td>3 or more positive sentinel lymph nodes</td>
<td>Completion ALND should be performed.</td>
</tr>
</tbody>
</table>

ALND = axillary lymph node dissection, FNA = fine-needle aspiration.
cancer patients. As the understanding of breast cancer biology deepens and adjuvant therapies become more effective, more individualized treatment via a multidisciplinary approach is possible. Important questions with regard to management of the axilla in additional subsets of patients may be answered in the future, with the next generation of trials. These trials may include patients undergoing mastectomy, neoadjuvant chemotherapy, axillary radiation therapy, or partial-breast irradiation.

References


64. Gadd M, Harris J, Taghian A. Prospective study of axillary radiation without axillary dissection for breast cancer patients with a positive sentinel node. 28th Annual San Antonio Breast Cancer Symposium; December 8-11, 2005; San Antonio, Texas.


