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EDITORIAL

Multidisciplinary Considerations in the Implementation of the Findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 Study: A Practice-Changing Trial

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Surgical management of breast cancer has evolved from routine use of radical mastectomy to less disfiguring and extensive procedures, including breast-conserving approaches, for appropriately selected patients. Whereas this transition occurred over several decades, until recently axillary lymph node dissection (ALND) remained standard practice for patients with both node-positive and node-negative breast cancer. The introduction of sentinel lymph node dissection (SLND) was a major departure from ALND allowing for an alternative for nodal staging with less morbidity for the increasing population of patients presenting with clinically node-negative disease.[1,2] Although some early studies suggested a survival advantage for patients who undergo ALND compared with no axillary surgery, the likelihood that removing negative nodes could improve outcomes has been questioned.

SLND has become the standard of care for patients with clinically node-negative disease. With fewer nodes removed, pathologists can perform a more detailed examination. This allows for improved staging and increases the detection of small-volume metastases. As the population of patients with small burden nodal disease has increased, there has been a growing debate regarding the optimal treatment of node-positive disease. The consensus statement from the American Society of Clinical Oncology and the guidelines from the National Comprehensive Cancer Network recommend a completion ALND (cALND) when metastases are identified on SLND.[3,4] These recommendations are supported by data from a meta-analysis of 69 trials, which included 8,059 patients who underwent SLND and cALND, where 53% of the patients with a positive SLN were found to have additional disease in non-SLNs.[5] The cALND allows for assessment of the total number of nodes involved, which has prognostic and potentially therapeutic implications. The American Joint Committee on Cancer staging system includes designations for metastases in $\geq$10 lymph nodes (pN3), 4–9 lymph nodes (pN2), and 1–3 lymph nodes (pN1), as well as micrometastasis (pN1mi; $>$0.2–2.0 mm) and isolated tumor cells (pN0(i +); $\leq$0.2 mm).[6] The extent of nodal disease may have implications in terms of local-regional control as well as use of systemic therapy and regional and nodal irradiation.[7,8]

Although cALND has been standard practice when SLNs are involved with metastatic disease, many have

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questioned the need for cALND in patients with small-volume metastases. The meta-analysis previously discussed showed that 53% of patients had additional nodes with metastatic disease on cALND.[5] When considering patients with micrometastatic disease in the SLN(s), the rate of non-SLN involvement is as low as 20%; and for patients with isolated tumor cells the rate decreases to 12%.[9,10] These findings have prompted a trend toward omitting cALND in selected patients. In an analysis of the surveillance, epidemiology, and end results (SEER) data from 1998 to 2004, up to 16% of SLN-positive patients did not undergo cALND—a trend seen in older women with low-grade, estrogen receptor (ER)-positive tumors. Considering only patients with micrometastasis in the SLN, the proportion treated with SLND alone increased from 21 to 38%.[11] Similarly, a review of the National Cancer Data Base (NCDB) data from 1998 to 2005 revealed that 20.8% of patients with a positive SLN did not undergo cALND. To evaluate a more contemporary cohort, these authors analyzed data from patients diagnosed between 2004 and 2005 and found that the proportion of patients who underwent SLND alone increased in patients with micrometastases, whereas the proportion of patients who underwent SLND alone after macrometastases were identified in the SLN declined slightly during the same time period. At a median follow-up of just more than five years, there were no differences in axillary recurrence rates or survival for patients who underwent SLND alone versus SLND with cALND. This was true for patients with both micrometastases and macrometastases in the SLN.[12] These data suggest that many clinicians do not believe that cALND plays an important role in the management of patients with small-volume metastases in the SLN.

The American College of Surgeons Oncology Group (ACOSOG) recently reported the results of the Z0011 trial—a prospective, randomized trial designed to evaluate the impact of cALND on local-regional recurrence and survival in patients with early-stage breast cancer and a positive SLN. The purpose of this article is to review the results of the Z0011 trial and to discuss how these data can be implemented in multidisciplinary practice.

ACOSOG Z0011 TRIAL DESIGN AND INITIAL RESULTS

The ACOSOG Z0011 trial (Fig. 1) enrolled patients with clinical T1 or T2N0M0 breast cancer treated with breast-conserving surgery who were found to have one or two positive SLNs on standard pathologic examination and hematoxylin and eosin (H&E) staining. Patients with SLN metastasis identified only by IHC were not eligible. Patients with three or more positive SLNs were also ineligible; however, intraoperative randomization was available and a small number of patients were randomized intraoperatively and were found to have three or more positive SLNs on final pathologic examination. Patients were required to have negative margins in the breast and to receive whole breast irradiation. Patients were randomized to undergo ALND or SLND alone without any specific axillary treatment (third-field nodal irradiation was not allowed). The trial opened in 1999 with a planned accrual of 1,900 patients, based on a one-sided level of significance of 0.05 to detect a hazard ratio for OS of 1.2 with 90% power. The trial closed in 2004 due to slow accrual and a lower than expected event rate with a total of 891 patients enrolled. At a median follow-up of 6.3 years, the local-regional recurrence and survival data were reported.[13,14]

A number of randomized patients did not complete their assigned treatment. Therefore, data were analyzed on both intent-to-treat and treatment-received basis, with similar results noted for both analyses. In the intent-to-treat analysis, there were 420 patients in the ALND arm and 436 in the SLND only arm. Similar patient and tumor characteristics were noted between the two groups except for number of lymph nodes removed and distribution of micrometastases. There was a median of two lymph nodes removed in the SLND alone group versus 17 in the ALND

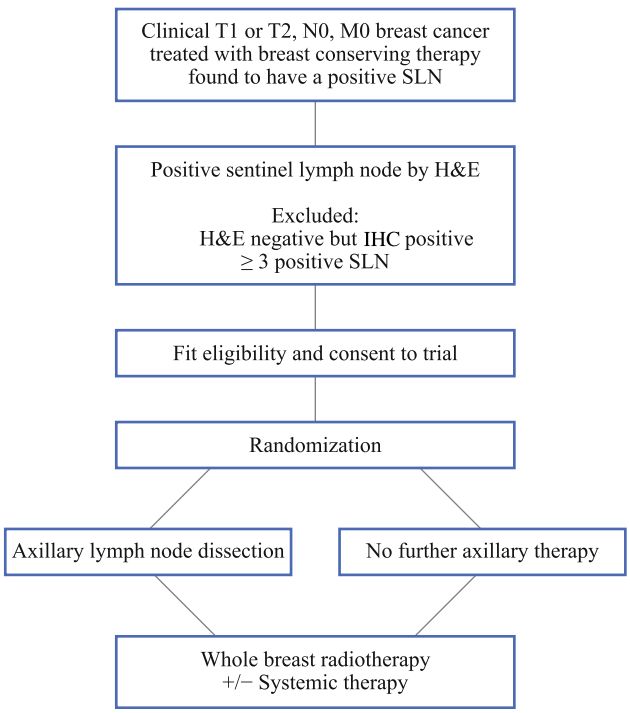

FIG. 1 ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer with a positive sentinel node

group. The median number of positive nodes in both groups was one; however, the ALND group had a greater percentage of patients having at least two positive nodes (40.8 vs. 21.9% in the SLND only group; $P < 0.001$). The SLND only group included 15 (3.6%) patients with at least three involved SLNs (identified after randomization) compared with 72 (21%) patients in the ALND group. Nodal metastases were found in non-SLNs in 27.3% of the ALND patients. Of the patients in this cohort who had a micrometastasis in their SLN, only 10% had positive non-SLNs.

Overall survival was the primary endpoint of the Z0011 trial with local-regional recurrence as a secondary endpoint. At a median follow-up of 6.3 years, local recurrence was reported in 3.6% ($n = 29$) of the ALND group versus 1.8% ($n = 8$) of the SLND-only group. Ipsilateral axillary recurrences were noted in 0.5% ($n = 2$) of patients after ALND versus 0.9% ($n = 4$) in the SLND-only arm. There were no differences in OS (ALND 91.9% vs. SLND-only 92.5%; $P = 0.24$) or disease-free survival (ALND 82.2% vs. SLND-only 83.8%; $P = 0.13$) at five years. The ACOSOG investigators concluded that routine use of ALND was not justified and that it may be safely omitted in selected patients with clinically node-negative disease who are found to have a positive SLN.

CONSIDERATIONS IN DATA INTERPRETATION

Despite the difficulty in accruing patients to the Z0011 trial, reports from the SEER and NCDB databases suggest that some surgeons are already omitting ALND in a percentage of patients with breast cancer, especially those with small-volume metastases. The ACOSOG investigators addressed this important clinical question with a randomized, prospective clinical trial. Because eligibility criteria were restricted and enrollment was limited to a homogenous group of patients, the data can be translated into clinical practice in a clearly defined population.

One important consideration in implementing the data into clinical practice is the definition of breast-conserving therapy. Study participants were required to complete whole breast irradiation without the addition of a third field to the treatment plan. The intent was to use the two-portal opposed tangential irradiation technique, which is expected to irradiate all breast tissue. Although this technique is designed to treat the entire breast, it is known that it also includes a significant portion of the lower axilla in the treatment field. Based on published data, the average doses delivered to levels I, II, and III are 66, 44, and 31% of the prescribed dose, respectively. Using these normal tangents, 51% of level I and 26% of level II axillary nodes receive 95% of the prescribed dose.[15] However, minor variations in the tangent field design can permit the majority of the level I/II axilla to receive a therapeutic dose.[16] Data concerning features of the field design were not captured for patients enrolled on the Z0011 trial; however, all patients were treated with standard whole breast irradiation, therefore, they received some radiation to the level I/II axilla and this may have prevented axillary recurrence in the SLN-only arm.

Another factor to consider is potential bias related to patient selection. Leitch et al. evaluated factors that influenced participation and reported that 69% of patients with node-positive disease who did not enroll in the Z0011 trial were treated with cALND.[17] Of those who enrolled, approximately 70% of patients had T1 tumors, 83% had ER-positive disease, and 35% had only micrometastases in the SLN. These data demonstrate that surgeons selected patients with very early-stage breast cancer with favorable characteristics for randomization with an expected low volume of axillary disease. These considerations are important in interpreting the Z0011 data and implementing these data into practice.

MD ANDERSON IMPLEMENTATION OF THE Z0011 DATA

Surgical Considerations

The Z0011 trial results are compelling and will influence clinical practice. Our goal is to safely apply these findings to the treatment of our patients. At The University of Texas MD Anderson Cancer Center, the results of the Z0011 trial were discussed in a multidisciplinary forum involving clinicians from the Departments of Surgical Oncology, Radiation Oncology, Medical Oncology, Radiology, and Pathology. As a group, we formulated general guidelines for implementation of these data. We agreed that patients in whom we could safely omit ALND are those who meet the eligibility criteria for the Z0011 trial: women with T1 or T2, clinically node-negative breast cancer who undergo breast-conserving surgery and whole breast irradiation that have 1 or 2 positive SLNs. Patients who undergo mastectomy and those who undergo breast-conserving surgery who are planned for accelerated partial-breast irradiation (APBI) are not eligible. Those patients planned for APBI who have a positive SLN should be considered for enrollment in the ongoing NSABP B-39/RTOG 0413 phase III clinical trial evaluating APBI versus whole breast irradiation. This trial requires patients with a positive SLN to undergo ALND or sampling with a minimum of six evaluated nodes. If the patient is not eligible for the NSABP B-39/RTOG 0413 trial, they should be treated with whole breast

irradiation and can avoid cALND. The Z0011 trial did not include patients treated with neoadjuvant systemic therapy; therefore, patients who have a positive SLN after neoadjuvant chemotherapy or endocrine therapy are counseled to undergo cALND.

Although these broad criteria are relatively straightforward, there are considerations with respect to clinical and pathologic subtypes that are less clearly defined in the trial. For example, patients with lobular histology represented only 7% of the trial population, limiting an accurate analysis of patients with this histologic subtype. Invasive lobular tumors are more likely to have isolated tumor cells in the SLN, a reflection of the noncohesive cellular characteristics that often require IHC for detection.[18] Small-volume nodal disease may have clinical relevance in this patient population different from those patients with invasive ductal histology. Consideration is therefore given to this difference in biology when we are counseling patients with invasive lobular carcinoma and a positive SLN with respect to performing cALND.

Hormone receptor (HR) status was reported on Z0011 participants with 83% of patients having ER-positive tumors and 65% having PR-positive tumors. Hormone receptor status was significant on univariate analysis for local-regional recurrence; however, when other factors, including receipt of systemic therapy, were assessed on multivariable analysis, HR status was no longer significant. We, therefore, would not use HR status as the determining factor in deciding to omit cALND; rather, we consider HR status in the context of all other data available for a given patient. There are limited data from the Z0011 trial with respect to HER2 status. The trial opened in 1999 when routine testing for HER2 was not performed and before the effectiveness of trastuzumab in the adjuvant setting was demonstrated. It is known that HER2-overexpressing tumors are more aggressive and are associated with increased rates of axillary lymph node metastases as well as higher rates of local-regional recurrence.[19–21] However, trastuzumab therapy has altered the natural history of HER2-overexpressing disease, resulting in improved disease-free survival with HER2-directed therapy.[22,23] Therefore, like HR status, HER2 status by itself should not determine whether a patient undergoes or can avoid cALND.

Another factor that is important in treatment decisions is patient age. Patients older than 18 years of age were eligible to enroll on Z0011; however, the median age of study participants was 54 years in the SLND group and 56 years in the ALND group with more than 62% of patients in each group being older than age 50 years. Patient age >50 years was one of only two factors (higher Bloom Richardson grade) associated with local-regional recurrence on multivariable analysis. There might have been reluctance by surgeons to randomize younger patients with node-positive disease to the SLND-only group and, therefore, there were fewer such patients in the study population. Menopausal status was not explicitly analyzed in the Z0011 trial and although it may impact systemic adjuvant therapy decisions, it is unclear how it should be used to determine local-regional therapy decisions.

An important factor that our group considers in treatment decisions is the nodal burden, as determined by the ratio of positive SLNs to the total number of SLNs harvested. The nodal ratio has been shown to be an important determinant for predicting additional nodal disease as established by several mathematical models.[24,25] A patient who has four SLNs removed with only one positive node may be at lower risk for additional disease than a patient with only two SLNs, both of which are positive. The Z0011 analysis did not find that the number of positive nodes, broken down as one, two, and three or more, was predictive of recurrence, suggesting that one would be justified in omitting cALND in patients with positive SLNs, regardless of the number of SLNs removed. However, only 20% of the ALND cohort in Z0011 had three or more total positive nodes and fewer than 15% had four or more total positive nodes, attributable to the overall relatively favorable characteristics of the population enrolled. We consider the nodal ratio in the context of all available data and believe nomograms are valuable in guiding decision-making. We have developed an MD Anderson nomogram incorporating nodal ratio and size of the SLN metastasis as a continuous variable to help guide decision-making (available at: http://www3.mdanderson.org/app/medcalc/bc_nomogram2). [26]

Incorporation of the Z0011 data into clinical practice has implications not only for the operative procedure but also for the decision to employ intraoperative pathologic assessment. It has been our practice to consent patients for ALND at the time of initial surgery and perform intraoperative assessment of the SLN. Patients were counseled that a cALND would be performed during the same operation if nodal metastases were identified. The Z0011 data have changed this practice, affecting preoperative discussions with patients and eliminating the need for routine intraoperative SLN assessment in selected patients. For patients meeting Z0011 eligibility criteria, we no longer routinely perform intraoperative analysis of the SLN.

Adjuvant Therapy Considerations

Because the decision to administer systemic chemotherapy or endocrine therapy is dictated largely by tumor biology, not the absolute numbers of positive lymph nodes, the results of the Z0011 trial have not changed

adjuvant systemic therapy recommendations by our breast medical oncology group. However, the decision to omit cALND in a select group of patients has affected treatment recommendations made by our radiation oncology group. As discussed above, the Z0011 trial design required that patients receive opposing tangential field whole breast radiation and stipulated that no third field would be added. Our radiation oncologists intend to modify the opposing tangential whole breast radiation fields for women who do not undergo cALND. The modified radiation fields, called high tangents, increase axillary coverage. Our group has previously published data about the use of high tangents and demonstrated that by extending the cranial border of the radiation field to 2-cm below the humeral head and 2-cm deep to the chest wall-lung interface, more than 80% of the level I/II axilla are covered in the treatment field.[16] Three-dimensional computed tomography treatment planning is used and the level I/II axilla is contoured. The cranial radiation field edge is raised and is nondivergent. Forward planning with subfields designed with multileaf collimators that improve the dose distribution within the three-dimensional treatment volume is used to assure adequate dose delivery to the axillary contents within the tangential field. The impact of extending the fields in this way on morbidity associated with irradiation has not been fully studied but is likely less than the addition of the third field that includes the supraclavicular fossa.

CONCLUSIONS

ACOSOG Z0011 is an important, practice-changing trial that supports what has become a trend in breast cancer care. As reflected by publications using the SEER and NCDB databases, the omission of cALND in selected patients has become part of the national practice pattern. The results from ACOSOG Z0011 support this trend and provide guidance for identifying patients in whom performing SLND alone is appropriate. At MD Anderson, we now counsel the majority of women with clinical T1/T2, N0 tumors with a positive SLN who are undergoing breast-conserving surgery with whole breast irradiation that they may forgo cALND with no significant impact on their rate of local-regional recurrence or OS.

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