Implementation of the American College of Surgeons Oncology Group Z1071 Trial Data in Clinical Practice: Is There a Way Forward for Sentinel Lymph Node Dissection in Clinically Node-Positive Breast Cancer Patients Treated with Neoadjuvant Chemotherapy?

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ABSTRACT For clinically node-positive breast cancer patients receiving neoadjuvant chemotherapy, approximately 40 % will be found to be pathologically node negative. The American College of Surgeons Oncology Group Z1071 trial was therefore conducted to evaluate sentinel lymph node dissection (SLND) in these patients. The trial's primary end point was to determine the false-negative rate (FNR) among patients with clinical N1 disease in whom at least 2 sentinel lymph nodes (SLNs) were identified. The FNR was 12.6 %, which exceeded the prespecified end point of 10.0 %. After data publication, our multidisciplinary team discussed the trial results and how we may incorporate the findings into clinical practice. Patient selection and surgical technique are critical. As an example, when dual tracer technique was used, the FNR was 10.8 %. Data from the trial presented at the San Antonio Breast Cancer Symposium suggested that the FNR could be improved if a clip was placed in the biopsy-proven positive lymph node and removal of that node during

SLND was confirmed. Taking this into consideration, we have proposed an approach to surgical management of the axilla in clinically node-positive patients receiving neoadjuvant chemotherapy termed targeted axillary dissection (TAD). TAD involves placing a clip at the time a lymph node is determined to be positive. After completion of neoadjuvant chemotherapy, the clipped node is localized by using a wire or radioactive seed, and during the SLND procedure, all SLNs and the clipped node are removed. We are currently evaluating the efficacy of TAD in axillary staging after neoadjuvant chemotherapy.

Sentinel lymph node dissection (SLND) is the standard for axillary staging for clinically node-negative breast cancer patients. When the sentinel lymph node (SLN) is negative, axillary lymph node dissection (ALND) can be omitted without a negative effect on overall survival, disease-free survival, or local-regional control, sparing patients the morbidity associated with ALND.^{1,2}

The practice of performing SLND in clinically node-negative patients is supported by single-institution, multicenter, and prospective randomized trials. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial randomized 5,611 women to SLND plus ALND or SLND and ALND only if the SLN was positive. Ten-year follow-up data showed no difference in disease-free survival or overall survival between patients with

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SLN-negative disease who underwent ALND versus SLND alone.³ Local-regional recurrences were uncommon, occurring in approximately 4 % of patients in both arms of the trial. Axillary recurrences as a first event were rare, occurring in three (0.2 %) patients in the ALND arm and nine (0.4 %) in the SLND arm. SLND in clinically node-negative patients receiving neoadjuvant chemotherapy is supported by numerous retrospective studies showing a high SLN identification rate and false-negative rates (FNRs) comparable to those seen in patients undergoing SLND before chemotherapy.^{4,5} In a study from the MD Anderson Cancer Center that included 575 clinically node-negative patients undergoing SLND after neoadjuvant chemotherapy, investigators reported an SLN identification rate of 97.4 % and an FNR of 5.9 %.⁶ For patients with T2 and T3 tumors, there was a lower rate of positive SLNs in patients receiving neoadjuvant chemotherapy compared with those undergoing surgery first, resulting in fewer patients with clinical T2/T3 tumors requiring ALND after chemotherapy.

Given the benefits of SLND in patients presenting with clinically node-negative disease, clinicians have questioned whether the technique could be applied to patients presenting with node-positive disease who receive neoadjuvant chemotherapy. Up to 40 % of patients treated with neoadjuvant chemotherapy will have a complete response in the axillary nodes. This response rate is even higher in patients with estrogen receptor-negative disease or high-grade tumors and as high as 74 % in those with HER2-positive tumors treated with trastuzumab-based neoadjuvant chemotherapy.⁷⁻⁹ Removing lymph nodes with no residual tumor is unlikely to benefit these patients. Initial reports of small series where SLND was performed in patients with clinically node-positive disease who receive neoadjuvant chemotherapy reported FNRs of up to 25 %.¹⁰⁻¹³ Although it was not a primary or secondary end point of the trial, some surgeons performed SLND in addition to completion ALND in patients treated with neoadjuvant chemotherapy in the NSABP B-27 trial. Of 428 patients who had SLND performed, the FNR was 10.7 %.¹⁴ The cohort included both clinically node-positive and node-negative patients, and there was no significant difference between these groups with respect to the FNR. There was no requirement for biopsy to confirm node-positive disease prior to initiation of chemotherapy. To prospectively study the question of the accuracy of SLND in clinically node-positive patients receiving neoadjuvant chemotherapy, the American College of Surgeons Oncology Group (ACOSOG) completed the Z1071 trial, a phase II study designed to determine the FNR for SLND performed after neoadjuvant chemotherapy in breast cancer patients presenting with pathologically confirmed node-positive disease.

ACOSOG Z1071

The ACOSOG Z1071 trial enrolled patients with clinical stage T0-4, N1-2, M0 breast cancer. Axillary disease was confirmed by fine-needle aspiration or core needle biopsy. Patients received neoadjuvant chemotherapy, after which they underwent SLND with ALND. The protocol specified that at least two SLNs be resected, and surgeons were encouraged to use a dual tracer technique with radioisotope and blue dye. SLNs were examined with hematoxylin and eosin, and a positive SLN was defined as metastasis larger than 0.2 mm. The primary aim was to determine the FNR of SLND after chemotherapy in the patients with clinical N1 disease when at least two SLNs were removed. The prespecified criteria for success was a FNR of 10 % or less, consistent with accepted FNRs in patients presenting with clinically negative nodes.⁷

Between July 2009 and June 2011, 756 patients were enrolled. Of these, 663 patients had clinical N1 disease, and 649 completed chemotherapy followed by SLND and ALND. The SLN identification rate was 92.9 %. One SLN was identified in 78 patients, leaving 525 patients with two or more SLNs identified for the primary end point analysis. Of these 525 patients, 215 (41 %) had a pathologic complete nodal response. In 39 patients, metastases were not identified in the SLN but were found in the ALND specimen; therefore, the FNR was 12.6 % (90 % Bayesian credible interval, 9.85-16.05 %).⁷ ACOSOG Z1071 investigators concluded that changes in approach and patient selection resulting in increased sensitivity would be required before the routine use of SLND as an alternative to ALND could be recommended in this patient population.

CONSIDERATIONS IN DATA INTERPRETATION

Because Z1071 did not meet the prespecified end point, it is fair to conclude that SLND after neoadjuvant chemotherapy is not yet ready for “prime time.” However, the question remains as to whether there is a way forward to be more selective in the axillary management in patients presenting with clinically node-positive disease.

In Z1071, the recommended technique for SLND was use of blue dye and radioisotope. A metaanalysis of studies evaluating SLND in early-stage breast cancer showed a higher SLN identification rate and lower FNR when dual tracers were used versus single-agent mapping.¹⁵ In the Z1071 trial, 79.1 % of patients had mapping performed with dual tracers, 16.8 % with radioisotope alone, and 4.1 % with blue dye alone. For patients with dual tracer mapping, the FNR was 10.8 %, versus 20.3 % when a single agent was used. The trial also specified that at least 2 SLNs be removed to ensure that surgeons do a complete

SLND before beginning the ALND portion of the procedure. When the FNR was evaluated by the number of SLNs excised, it was 31.5 % with one SLN removed (data presented at San Antonio Breast Cancer Symposium [SABCS] 2012), 21 % with two SLNs removed, and 9.1 % with three or more SLNs removed.⁷ Three or more SLNs were examined in 57.1 % of patients.

These data are consistent with two other trials evaluating SLND in clinically node-positive patients treated with neoadjuvant chemotherapy. The Sentinel NeoAdjuvant (SENTINA) trial was a four-arm, prospective, multicenter trial evaluating SLND and ALND in patients receiving neoadjuvant chemotherapy. Arm C included patients that were clinically node positive who converted to clinically node negative after chemotherapy. FNRs were 24.3 % when a single SLN was identified, 18.5 % when two SLNs were removed, and less than 10 % when three or more SLNs were removed.¹⁶ Similar to Z1071, the FNR was lower (8.6 %) for patients who underwent mapping with radioisotope and blue dye. The Sentinel Node biopsy Following NeoAdjuvant Chemotherapy in biopsy-proven node-positive breast cancer (SN FNAC study) was presented at the 2013 American Society of Clinical Oncology meeting.¹⁷ The trial included 145 evaluable clinical T0–3, N1–2 patients undergoing SLND and ALND after neoadjuvant chemotherapy, and the FNR was 8.4 %. In that trial, SLNs that were negative by hematoxylin and eosin were evaluated by immunohistochemistry, and those with isolated tumor cells (pN0i+) were considered positive. If the pN0i+ were classified as negative, the FNR was 13.3 %. Similar to the Z1071 and SENTINA trials, identifying more SLNs resulted in lower FNRs; the FNR was 18.2 % when one SLN was removed and 4.9 % when two or more were excised. Taken together, the data from these trials regarding tracer use and the number of SLNs removed suggest that surgical technique is critical in lowering the FNR in this setting. Surgeons considering the use of SLND in node-positive patients receiving neoadjuvant chemotherapy should discuss the possibility that an ALND may be required if there is failure to identify an SLN or when only one SLN is identified.

TARGETED AXILLARY DISSECTION

After presentation of the Z1071 trial results, our breast surgical oncology group convened to discuss the data to determine how it should affect our practice. Although we recognize that the 12.6 % FNR is high and that the clinical effect of a false-negative event in this population is unknown, we remain optimistic that there is a way forward to personalize axillary management in these node-positive patients, particularly those who have a good clinical response to neoadjuvant chemotherapy.

Data from Z1071 presented at the SABCS but not yet published suggested utility in placing a clip in the biopsy-proven positive lymph node at diagnosis and then ensuring that the clipped node is removed as an SLN during the SLND procedure. In 96 patients in whom a clip was placed and documented to be one of the SLNs removed, the FNR was 7.4 % (95 % confidence interval, 2.0–17.4 %). Taking this into consideration, we have proposed an approach to surgical management of the axilla in these clinically node-positive patients receiving neoadjuvant chemotherapy termed targeted axillary dissection (TAD).

Briefly, TAD involves a multidisciplinary approach to axillary staging after neoadjuvant chemotherapy based on the finding that confirmation that one of the SLNs removed during SLND was the clipped node (i.e., the node with biopsy-proven metastasis) improved the FNR in Z1071. At the time of diagnosis, patients undergo an ultrasound examination of the breast and regional lymph nodes, and suspicious lymph nodes are subjected to fine-needle aspiration biopsy.¹⁸ For patients in whom only axillary nodes are abnormal in appearance, the most suspicious node is biopsied, and a clip is placed to mark that node so that it can later be targeted for removal. For patients with matted adenopathy (clinical N2) or disease identified in the internal mammary (clinical N2 if in the absence of clinical axillary disease or clinical N3 with clinically evident axillary disease), infraclavicular, or supraclavicular lymph nodes (clinical N3), no clip is placed, because these patients are either not eligible (clinical N3) or not included (clinical N2) in the primary analysis of Z1071, and they require ALND after completion of neoadjuvant chemotherapy. After completion of neoadjuvant chemotherapy, the patient undergoes SLND. In addition, we have the opportunity to localize the node with confirmed metastasis which contains a clip by using a wire or a I^{125} radioactive seed (Fig. 1), thereby enabling us to ensure removal of the clipped node. We have completed a pilot study showing that this technique is feasible and are currently evaluating efficacy in axillary staging after chemotherapy under an institutional review board–approved protocol. In addition to removing all SLNs and the clipped node, we are currently performing completion ALND. This will allow us to determine the rate of correlation between the SLN(s) and the clipped node and the FNR of TAD.

MULTIDISCIPLINARY CONSIDERATIONS

We have also discussed the Z1071 data in a multidisciplinary forum involving clinicians from surgical oncology, medical oncology, radiation oncology, radiology, and pathology. As a group, we agreed that optimizing axillary management for clinically node-positive patients is

FIG. 1 Localization of a clipped lymph node with an I^{125} radioactive seed. At the time of breast cancer diagnosis, all patients undergo an ultrasound of the breast and regional nodal basins. Suspicious-appearing lymph nodes are subjected to fine-needle aspiration biopsy, and immediate assessment for specimen adequacy is performed by cytopathologists. A clip is placed in the biopsied lymph node. At the time of surgery, the clipped lymph node can be localized with a radioactive seed (a). When the seed-containing lymph node is removed during surgery, it is radiographed in the pathology suite to document the presence of the marker clip and radioactive seed (b)

an important goal. For medical oncologists, the implication of Z1071 data is that in 12.6 % of patients whom we declare to have a nodal pathologic complete response (pCR), there will be residual nodal disease. This may have prognostic implications but will not alter current therapeutic recommendations; patients with HER2-positive disease will complete 1 year of trastuzumab, and patients with hormone receptor (HR)-positive disease will receive endocrine therapy.

The implications of the FNR on adjuvant radiation therapy are more significant. For patients undergoing upfront surgery, recommendations for postmastectomy radiation therapy or regional nodal irradiation after breast-conserving surgery are well defined. According to the National Comprehensive Cancer Network guidelines, nodal irradiation should be given for patients with 4 or more positive nodes and strongly considered for patients with 1–3 positive nodes.¹⁹ These recommendations are based on multiple randomized trials evaluating patients treated with upfront surgery. For patients receiving neoadjuvant chemotherapy, there are no randomized trial data to guide decisions regarding nodal irradiation; therefore, the indications are less clear.^{20,21} At MD Anderson, we routinely administer nodal irradiation after neoadjuvant chemotherapy to patients with clinical stage III disease and to most patients with residual positive nodes after chemotherapy. Regional nodal radiation is considered for select patients with clinical stage II disease, including those with high-risk features such as young age, estrogen receptor-negative disease, lymphovascular invasion, and poor response to chemotherapy.²⁰ The possibility of a false-negative event therefore has significant implications for

FIG. 2 Schema for the NSABP B-51/RTOG 1304 trial

patients with clinical stage II disease in whom our current practice at MD Anderson is to omit regional nodal radiation if they had no residual nodal disease identified in an ALND specimen. For patients with clinical stage II disease in whom only an SLND is performed and the SLN is found to be negative, our radiation oncologists would take into consideration the 12.6 % FNR identified in Z1071 and the possibility of residual disease left behind when considering

FIG. 3 Schema for the Alliance A11202 trial

recommendations regarding regional nodal radiation. As will be discussed further below, optimal radiation for patients responding to neoadjuvant chemotherapy will be addressed in the ongoing NSABP/Radiation Therapy Oncology Group (RTOG) trial.

CLINICAL TRIALS

As the Z1071, SENTINA, and SN FNAC trials suggest, there is significant interest in determining optimal axillary management in patients presenting with clinically node-positive disease treated with neoadjuvant chemotherapy. This will be further addressed by two cooperative group trials, the NSABP B-51/RTOG1304 trial and the Alliance A11202 trial. The NSABP/RTOG trial randomizes clinically node-positive patients that convert to pathologically node-negative disease documented by SLND or ALND, to regional nodal irradiation or no regional nodal irradiation (Fig. 2).²² The primary aim is to evaluate whether the addition of regional nodal irradiation will significantly reduce the invasive breast cancer recurrence-free interval. The Alliance trial (Fig. 3) is randomizing patients with a positive SLN to ALND or axillary radiation. In addition to this axillary-specific treatment, all patients will receive nodal radiation targeting the supraclavicular and internal mammary lymph nodes in the first 3 intercostal spaces.²³ The primary aim is to evaluate whether axillary radiation alone is not inferior to axillary radiation plus ALND in terms of invasive breast cancer recurrence-free survival.

CONCLUSION

The Z1071 trial failed to meet its prespecified threshold of an FNR <10 %; however, important data from the study suggest a way forward for SLND in clinically node-positive patients receiving neoadjuvant chemotherapy. Surgical technique is critical, with the best results using dual tracers and ensuring all SLNs are removed. Experienced surgeons must assess the quality of the mapping procedure and determine whether SLND is appropriate in a given patient or whether ALND is warranted. TAD ensures that the node proven to be positive at diagnosis is clipped and removed at SLND and may help to minimize the FNR.

Selection of appropriate patients will also be important. Patients enrolled on Z1071 had an axillary ultrasound performed before and after chemotherapy, and those data are being analyzed to determine whether ultrasound can help select patients for SLND. Breast cancer subtype may also help guide patient selection. In the NeoSphere trial, there was a pCR rate of 45.8 % in HER2-positive breast cancer patients treated with docetaxel, trastuzumab, and pertuzumab, with a 26.0 % pCR rate in HR-positive patients and 63.2 % in HR-negative patients.²⁴ Similarly, in the ACOSOG Z1041 trial that investigated the effect of the timing of trastuzumab administration with anthracycline and taxane neoadjuvant chemotherapy in HER2-positive patients, more than 70 % of HR-negative, HER2-positive patients experienced a pCR.²⁵ Although these rates reflect pCR in the breast and the axilla, it is likely that nodal pCR rates are comparable.

As continued improvements in systemic therapy lead to increased pCR rates, there will be further incentive to optimize local-regional management. SLND in patients with clinically node-positive disease receiving neoadjuvant chemotherapy should not be abandoned on the basis of the results of the Z1071 trial; rather, the data should guide future efforts to optimize local-regional management for these patients.

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