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Sentinel Node Lymph Node Surgery After Neoadjuvant Therapy: Principles and Techniques

Jennifer M. Racz, MD, MBA[1], and Abigail S. Caudle, MD, MS[2]

[1]Department of Surgery, Mayo Clinic, Rochester, MN; [2]Department of Breast Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT Surgical management of the axilla in breast cancer has been a topic of great interest. While sentinel lymph node biopsy (SLNB) is an established approach for patients undergoing surgical treatment as the first element of their care, there is continued debate regarding surgical management of the axilla in patients receiving neoadjuvant chemotherapy (NAC). In clinically node-negative patients, it has been debated whether or not SLNB should be performed before chemotherapy to accurately determine the clinical stage, or after chemotherapy, thus prioritizing the response to therapy and potentially minimizing axillary surgery. Node-positive patients have undergone axillary lymph node dissection in the past, however this paradigm has been challenged in recent years. Thus, surgeons must understand the importance of accurate axillary information both before and after NAC, and its role in multidisciplinary planning. We present a summary of the data surrounding axillary management in patients receiving NAC, and recommendations for surgical technique.

Accurate assessment of the axilla has become an area of intense study recently. Given the importance of accurate nodal staging and the morbidity of extensive axillary surgery, the focus on clear data and optimization of technical aspects is vital. The ultimate goal is to get reliable information about nodal status while limiting the impact to a patient's quality of life. Surgeons must have a complete understanding of the impact of axillary surgery on multidisciplinary management. The goal of this summary is to outline the recommendations for surgical technique when performing sentinel lymph node biopsy (SLNB) for patients receiving neoadjuvant chemotherapy (NAC).

CLINICAL ASSESSMENT OF THE AXILLA

Nodal status is the most important prognostic factor for overall survival in breast cancer and is particularly important in patients receiving NAC as it often dictates multidisciplinary treatment decisions. While physical examination is important, it is unreliable, with a false negative rate (FNR) as high as 45%.[1] Ultrasound evaluation is recommended as it allows for histologic evaluation of abnormal nodes with needle biopsy in the same setting. Several studies have shown that axillary ultrasound with fine needle aspiration (FNA) of abnormal nodes has a sensitivity of 47.1–90%, specificity of 100%, and FNR of 7.7–23.7%.[2–5] The sensitivity is 44% when the largest focus is < 5 mm, but increases to 93% in patients with metastatic deposits measuring > 5 mm.[2]

CLINICALLY NODE-NEGATIVE PATIENTS

While node-positive disease is often the impetus for consideration of NAC, it can also be considered for node-negative patients, especially with high-risk tumor biology. The debate in these patients revolves around the optimal timing of SLNB. By performing SLNB at the completion of NAC, patients benefit from a single operation that allows for evaluation of response to therapy. Patients with residual disease after NAC may now be considered for adjuvant systemic therapy, making assessment after NAC critical.[6,7] Review of data from MD Anderson Cancer Center demonstrates that the SLN identification rate is slightly improved before NAC (98.7%) than after NAC (97.4%)

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A. S. Caudle, MD, MS
e-mail: ascaudle@mdanderson.org

[$p = 0.017$], with comparable FNRs (4.1% surgery first vs. 5.9% after NAC, $p = 0.4$).[8] In addition, patients with T2-3 tumors with SLNB performed after NAC had a lower probability of having a positive SLN (T2: 20.5% vs. 36.5%, $p < 0.0001$; T3: 30.4% vs. 51.4%, $p = 0.04$), thus sparing patients the morbidity of axillary lymph node dissection (ALND). The two cohorts had similar oncologic outcomes.[8] Evaluation of the Netherlands Cancer Registry also supports the use of SLNB after NAC, showing SLN identification rates of 98% when SLN biopsy was performed before NAC and 95% when performed after NAC. The probability of identifying a positive SLN was higher when performed before NAC (45% vs. 33%, $p = 0.006$).[9] Dual tracer mapping and surgeon experience improve SLN identification, while retrieval of two or more SLNs is associated with a decreased FNR.[8] The feasibility of performing SLNB after NAC can also be seen when comparing trials such as NSABP-B32, which reported an FNR of 9.8% for SLNB performed before NAC with an identification rate of 97.3%,[10] with trials assessing the use after NAC, such as NSABP B-27 and a meta-analysis of 27 studies that show similar rates, as summarized in Table 1.[10–12]

The multicenter SENTinel NeoAdjuvant (SENTINA) cohort study also provides further insight into the feasibility and accuracy of SLNB. This study was designed to evaluate the timing of a standardized SLNB procedure in patients receiving NAC, with two arms focusing on clinically node-negative patients. Arm A included patients undergoing SLNB prior to NAC, while Arm B included patients with a positive SLN prior to chemotherapy who underwent a second (repeat) SLNB after NAC. Most striking in this Arm B was the low SLN identification rate (60.8%) and the high FNR (51.6%) when a second (repeat) SLNB was attempted, reflecting that this is a suboptimal approach.[13]

While these studies outline the feasibility and accuracy of SLNB, there are also studies showing oncologic outcomes of this approach. For instance, the GANEA 2 (GAnglion sentinal apres chimiotherapie NEoAdjuvante) trial, the first to look at this prospectively, enrolled 419 cN0 patients who had SLNB after NAC. Only one axillary recurrence at a median 3-year follow-up was reported, along with a 3-year event-free survival of 97.8%. This is similar to the retrospective data from MD Anderson Cancer Center, which reported a 1.2% regional recurrence rate for the cohort undergoing SLNB after NAC compared with 0.9% for those who underwent SLNB first at a median of 47 months.[8] A study from Japan also showed low recurrence rates when evaluating 183 patients who underwent SLNB before NAC, with no axillary recurrences seen at a median of 51 months compared with 0.8% in the 996 patients who underwent SLNB first.[14]

CLINICALLY NODE-POSITIVE PATIENTS

ALND remains the standard of care for patients who present with clinically node-positive disease, although recent trials have explored the use of minimally invasive approaches. With effective systemic therapy options, NAC can eradicate nodal disease in a significant proportion of patients, which has led investigators to examine the possibility of less extensive axillary surgery.[15] Single-institution, mostly retrospective reports addressing the use of SLNB have shown FNRs ranging from 5 to 20%.[16–19] Three multi-institutional, prospective, registry studies have been published evaluating the use of SLNB in clinically

TABLE 1 Overview of studies evaluating sentinel lymph node biopsy before and after chemotherapy in node-negative patients with breast cancer

	SLNB prior to NAC		SLNB after NAC	
	MDACC[8] ($N = 3171$)	Netherlands[9] ($N = 980$)	MDACC[8] ($N = 575$)	Netherlands[9] ($N = 203$)
Single-institution studies				
Identification rate (%)	98.7	98	97.4	95
False negative rate (%)	4.1	–	5.9	–
	NSABP B-32[10] ($N = 2619$)		NSABP B-27[a11] ($N = 326$)	Meta-analysis[a,b12] ($N = 266$)
Multi-institution studies				
Identification rate (%)	97.3		84.4	92.7
False negative rate (%)	9.8		12.4	15.8

SLNB sentinel lymph node biopsy, *NAC* neoadjuvant chemotherapy, *MDACC* MD Anderson Cancer Center

[a]cN0 patients only

[b]Only five studies included cN0 patients (27 studies were included in the meta-analysis)

node-positive patients treated with NAC: the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, the European SENTINA trial, and the Canadian Sentinel Node biopsy Following NeoAdjuvant Chemotherapy (SN FNAC) trial. The trials enrolled patients with clinical T1-4, N1-2, M0 breast cancer who received NAC, and had similar trial designs. After completion of chemotherapy, subjects underwent SLNB followed by ALND in order to determine the FNR of SLNB[13,20,21] (summarized in Table 2).

The three trials showed similar FNRs of 12.6–14.2%, and all highlighted the importance of surgical technique. In all three trials, the use of the dual tracer technique reduced the FNR significantly (although this was not significant in multivariate analysis for the SENTINA trial).[13,20,21] In addition, all three trials showed that removing a higher number of SLNs reduced the FNR, which was also seen in the GANEA 2 study.[13,20–22] The SN-FNAC trial highlighted the benefit of immunohistochemistry (IHC) for evaluation of SLNs. In this trial, an FNR of 16.9% (14/83) when only macrometastases were considered as pathologically positive; however, this decreased to 13.3% (11/83) when micrometastases were also considered positive, and further reduced to 8.4% (7/83) if isolated tumor cells (ITCs) were included as a positive result.[21] The ACOSOG Z1071 trial also showed a reduction in FNR to 8.7% when IHC was incorporated.[23]

The trials revealed that while ultrasound is beneficial before initiating NAC, its use for assessing axillary response may be limited. Central review of post-chemotherapy ultrasounds in the ACOSOG Z1071 trial were performed to determine if ultrasonography alone could predict nodal response. In patients who had normalized nodes on ultrasound after NAC, 56.5% had residual disease. In contrast, 28.2% (51/181) of patients with abnormal-looking nodes on ultrasound after NAC had a nodal pathological complete response (pCR).[24] The authors conclude that ultrasound alone cannot assess axillary response. Ultrasound of patients in the SENTINA trial had a sensitivity of only 23.9%.[25]

An hypothesis-generating finding from ACOSOG Z1071 was that placement of a clip in nodes with biopsy-proven metastases may be beneficial. In that study, a clip was placed in the lymph node with metastases in 170 patients. The FNR was 6.8% in the 107 patients where the clipped node was retrieved as an SLN.[26] This has prompted several institutions to look at the utility of placing clips in nodes with biopsy-confirmed disease, and ensuring removal and evaluation of this node. A prospective registry study from MD Anderson Cancer Center showed evaluation of the clipped node alone had an FNR of 4.2% (5/120).[27] A study from Turkey also demonstrated an FNR of 4.2% (1/24) if the clipped node was retrieved as an SLN, compared with 16.7% (1/6) if it was not an SLN.[28] One reason that specific evaluation of the clipped node improves axillary staging over SLNB alone is that the clipped node will not be retrieved as an SLN in 20–25% of cases.[26–31] Thus, focusing on SLNs alone would miss evaluation of the node known to harbor disease at presentation.

A recent meta-analysis showed that axillary staging using a combination of SLNB and removal of the marked node was more accurate than either approach alone.[32] Targeted axillary dissection (TAD) has been proposed as an approach to ensure evaluation of the lymph node with known disease (the clipped node) in addition to the nodes most likely to harbor disease (SLNs).[27,33] The technique involves placing a clip in a node when biopsy confirms metastasis. At the time of surgery, the clipped node is localized to facilitate selective removal in addition to

TABLE 2 Trials evaluating sentinel lymph node biopsy in clinically node-positive patients who received neoadjuvant chemotherapy

	ACOSOG Z1071[20,23]	SENTINA (Arm C)[13]	SN FNAC[21]
No. of patients	cN1 = 603 cN2 = 34	592	153
SLN identification rate (%)	92.7	87.8	87.6
Overall FNR (%)	12.6	14.2	13.4
FNR based on mapping agents (%)			
One agent	20.3	16	16
Dual agent	10.8	8.6	5.2
FNR by number of SLNs (%)			
1 SLN	31	24.3	18.2
2 SLNs	21.1	18.5	4.9 (≥ 2 SLNs)
≥ 3 SLNs	9.1	4.9	
FNR with IHC (%)	8.7	NA	8.4%

SLN sentinel lymph node, *FNR* false negative rate, *IHC* immunohistochemistry, *NA* not available

removal of the SLNs. One approach to localization uses radioactive seeds placed under ultrasound guidance in order to identify the clipped node. The FNR of this approach is reported as low as 2%.[27] While the removal of more than two nodes lowers the FNR when sentinel lymph node dissection is performed alone, ensured removal of the clipped node with the SLNs may make this technical aspect less important. Many groups have now published on TAD as well as other methods for identifying and removing the marked node.[29,31,34–36] The MARI technique (Marking Axillary lymph nodes with Radioactive Iodine Seeds) is used in The Nethrlands, in which a radioactive seed is placed at the time of biopsy and left in place throughout chemotherapy.[37] They are now conducting a trial that will add SLNB to removal of the marked node (RISAS trial).[38] Furthermore, prospective, multi-institutional trials assessing TAD, including the German SenTa trial[39] and the French GANEA-3 trial, are ongoing.[40] Other groups have explored the use of black or charcoal tattoo to mark the biopsied node instead of placing a clip. While the initial series are small, they all show successful retrieval of the marked node at surgery.[34–36] The prospective Pre-ATNEC trial will further evaluate the use of tattooing.[41] Early reports using wires for nodal localization show technical challenges. A German feasibility study reported that the clipped node was only retrieved in 70.8% (17/24) of cases with wire localization, with investigators noting that wire localization was impacted by patient movements as well as surgical dissection, with the potential for displacement of the wire. These investigators concluded that the challenges of clip identification and the use of wires for localization limited the use of this technique; however, they also noted that the small sample size may impact the results, and acknowledge that these may improve with experience.[42]

TAD requires extra procedures, such as the placement of a clip at the time of biopsy and placement of a seed before surgery. In order to avoid these additional interventions, groups have looked at other methods to ensure evaluation of the nodes known to contain disease before initiation of NAC. In one study, treatment effect seen in nodes on pathologic evaluation was used as an indication of evaluation of the impacted nodes. This study showed that treatment effect could be identified in 88% of cases where at least three SLNs were retrieved.[43] The use of fine needle biopsy of the clipped node after chemotherapy has also been evaluated as an approach to avoid TAD in patients with confirmed residual disease; however, this was found to be unreliable, with an FNR of 53% (19/32).[44] It is possible that sampling a larger amount of tissue using a core biopsy might improve sensitivity.

As with implementation of any new technique, there is an associated learning curve. In this case, that curve involves radiologists and surgeons, thus multidisciplinary discussion and feedback is important for success. One of the critical aspects is placement of the clip so that it can be identified on subsequent imaging studies as the node becomes smaller. An inability to visualize the clip after completion of NAC has been reported as an issue in up to 20% of cases in early reports from the Mayo Clinic.[30] A prospective feasibility trial from Germany assessing wire localization of clipped nodes highlighted these technical challenges as the clipped node could only be identified on ultrasound in 83% (25/30) of cases, with wire localization only possible in 24 of the 30 patients enrolled. First, care must be made to position the clip within the node and not in the perinodal tissue as the node will likely shrink during therapy. In addition, the clip should be placed within the hypoechoic cortex instead of within the fatty hilum to improve visibility. Careful documentation of the location of the clipped node in the transverse and longitudinal planes, as well as recording the depth of the node and relation to other anatomic structures, can help.[45] The choice of clip may also impact the ease of identification after chemotherapy.[45,46]

While evolving surgical techniques have made identification of patients who convert to pathologic node-negative status more accurate, the question of what impact omission of ALND has on oncologic outcomes remains unanswered. This lack of data should be fully disclosed to patients in whom omission of ALND is being considered. In addition, discussion with both radiation and medical oncologists is also important because the decision to limit axillary surgery may impact adjuvant planning. While avoiding ALND in select patients may be appropriate, axillary clearance is still required if a positive node is identified after chemotherapy (unless in the setting of a clinical trial), even if the metastatic deposit is classified as a micrometastasis or ITC. In one study, 17% of patients with ITCs and 64% of patients with micrometastases found on SLNB after NAC had additional positive nodes at ALND.[47]

Two multicenter, randomized controlled trials are currently enrolling to further explore the management of clinically node-positive patients who receive NAC. The main goal of the NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 trial is to evaluate the benefit of nodal radiation in patients who achieve a nodal pCR after NAC. The trial randomizes patients to no dedicated nodal radiation versus regional nodal irradiation. In contrast, the Alliance A11202 trial is evaluating clinically node-positive patients who are found to have residual nodal disease after NAC. Patients are randomized to ALND versus no further axillary surgery, with all patients receiving regional nodal irradiation. The primary endpoint of these studies are recurrence, with secondary outcomes including survival, toxicity, quality of life, lymphedema development, adequacy of radiation fields, and residual cancer burden.

In summary, evaluation of axillary nodes after NAC offers critical prognostic information in patients presenting with both clinically node-negative and clinically node-positive disease. As the field transitions to minimally invasive approaches to assess the axilla, surgical technique is increasingly important. In clinically node-negative patients, SLNB assessment after NAC is a reasonable approach when adequate radiologic staging has been performed. The use of SLNB in patients presenting with clinically node-positive disease is evolving and may be an option; however, the lack of data related to oncologic outcomes must be acknowledged. When it is considered, use of the dual tracer mapping technique and removal of two or more nodes is essential. Furthermore, the use of IHC and the practice of placing a clip in biopsied-positive nodes with ensured removal improves the accuracy of axillary staging. Future studies will help further delineate the interactions of these aspects and guide adjuvant management decisions.

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