Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0–T4, N1–N2) Who Receive Neoadjuvant Chemotherapy

Results From ACOSOG Z1071 (Alliance)

Judy C. Boughey, MD, Karla V. Ballman, PhD,† Huong T. Le-Petross, MD,‡ Linda M. McCall,§
Elizabeth A. Mittendorf, MD, PhD,¶ Gretchen M. Ahrendt, MD,‖ Lee G. Wilke, MD,**
Bret Taback, MD,†† Eric C. Feliberti, MD,‡‡ and Kelly K. Hunt, MD¶*

Background: The American College of Surgeons Oncology Group Z1071 trial reported a false-negative rate (FNR) of 12.6% with sentinel lymph node (SLN) surgery after neoadjuvant chemotherapy in women presenting with node-positive breast cancer. One proposed method to decrease the FNR is clip placement in the positive node at initial diagnosis with confirmation of clipped node resection at surgery.

Methods: Z1071 was a multi-institutional trial wherein women with clinical T0–T4,N1–N2,M0 breast cancer underwent SLN surgery and axillary dissection (ALND) after neoadjuvant chemotherapy. In cases with a clip placed in the node, the clip location at surgery (SLN or ALND) was evaluated.

Results: A clip was placed at initial node biopsy in 203 patients. In the 170 (83.7%) patients with cN1 disease and at least 2 SLNs resected, clip location was confirmed in 141 cases. In 107 (75.9%) patients where the clipped node was within the SLN specimen, the FNR was 6.8% (confidence interval [CI]: 1.9%–16.5%). In 34 (24.1%) cases where the clipped node was in the ALND specimen, the FNR was 19.0% (CI: 5.4%–41.9%). In cases without a clip placed (n = 355) and in those where clipped node location was not confirmed at surgery (n = 29), the FNR was 13.4% and 14.3%, respectively.

Conclusions: Clip placement at diagnosis of node-positive disease with removal of the clipped node during SLN surgery reduces the FNR of SLN surgery after neoadjuvant chemotherapy. Clip placement in the biopsy-proven node at diagnosis and evaluation of resected specimens for the clipped node should be considered when conducting SLN surgery in this setting.

Axillary ultrasound is frequently used to assess axillary nodes at the time of initial diagnosis of breast cancer. In cases with abnormal-appearing lymph nodes on ultrasound evaluation, percutaneous biopsy by either fine needle aspiration or core needle biopsy can be performed to confirm the presence of metastatic disease. The combined approach of axillary ultrasound with percutaneous biopsy has a sensitivity of 65% to 86% and specificity of 96% to 100%.[1–7]

The use of axillary ultrasound with percutaneous biopsy was initially used to determine clinical nodal stage to guide surgical staging and allow patients to proceed directly to axillary lymph node dissection (ALND) and avoid sentinel lymph node (SLN) surgery in cases with biopsy-proven nodal metastasis.[8–10] Patients with axillary nodal disease identified by ultrasound and confirmed by percutaneous biopsy at diagnosis have a higher burden of disease and are frequently considered for neoadjuvant chemotherapy.[11–13] In patients treated with neoadjuvant chemotherapy, resolution of all nodal metastasis to pathologically confirmed node-negative disease at surgical resection occurs in approximately 40%, with rates as high as 60% to 70% in human epidermal growth factor receptor 2 (HER2)-positive disease.[14,15] The high rate of nodal downstaging has prompted consideration of SLN surgery after neoadjuvant chemotherapy for axillary staging of the nodes for those patients who were found to be biopsy-proven node-positive at initial presentation and have a good clinical response to chemotherapy. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial evaluated the false-negative rate (FNR) of SLN surgery in patients with clinical T0–T4,N1–N2 disease treated with neoadjuvant chemotherapy and found that the FNR was 12.6% in cN1 patients with 2 or more sentinel nodes evaluated.[16] The ACOSOG is now part of the Alliance for Clinical Trials in Oncology.

The correlation between the axillary lymph node identified on initial axillary ultrasound and the sentinel lymph nodes identified at surgery has not been fully evaluated. Nathanson and colleagues reported a correlation between the lymph node identified by percutaneous biopsy and the lymph node(s) resected at the time of SLN surgery of 78%.[17] This study, which was not restricted to patients with positive nodes, suggests that, in the majority of cases, the node(s) resected at SLN surgery include the node that is identified on initial axillary ultrasound. However, the concordance is not 100%

and, at times, the initial node identified by ultrasound is not one of the SLNs.

In the ACOSOG Z1071 trial, a subset of patients had a clip placed in the lymph node at the time of initial biopsy and confirmation of metastatic disease. We hypothesized that identification of the clipped lymph node within the SLNs at the time of surgery would result in a lower FNR in this patient population. Here, we evaluate how often the lymph node containing the clip placed at percutaneous biopsy before chemotherapy was found at surgery to be one of the SLNs, and how often it was found in the nodes retrieved at ALND. In addition, we report the impact of identification of the clipped node within the SLNs on the FNR of SLN surgery.

METHODS

ACOSOG Z1071 was a prospective clinical trial that enrolled women with histologically proven clinical stage T0–T4,N1–N2, M0, primary invasive breast cancer who had completed or were planned to undergo neoadjuvant chemotherapy. All patients had undergone axillary ultrasound with percutaneous biopsy of abnormal axillary lymph nodes by fine needle aspiration biopsy or core needle biopsy and had biopsy-proven node-positive disease. Some of the patients enrolled in the trial had a clip placed in the positive lymph node at the time of diagnosis. This was not required by protocol; however, the protocol recommended that, in cases wherein a clip was placed, the location of the clip be documented at surgery. The current analysis includes all patients who met protocol eligibility, completed neoadjuvant chemotherapy, and underwent SLN surgery and ALND, with a focus on the cases where a clip was placed in the lymph node at initial diagnosis. The institutional review boards of all participating institutions approved the study, and written informed consent was obtained from each patient before study entry. The approximated breast cancer subtype was derived from the estrogen and progesterone receptors and HER2 status and used to classify cases into the following: HER2 positive, triple negative (estrogen and progesterone and HER2 negative), and hormone receptor positive and HER2 negative.

In cases where a clip was placed in the lymph node at initial diagnosis, the protocol recommended specimen radiograph of the SLNs resected. In cases where the clip was not identified in the SLNs, radiography of the axillary dissection specimen was recommended. In some cases, the presence of the clip in the SLN or in the axillary dissection contents was documented in the pathology report. If there was no documentation of the clip location by radiograph or pathology, the case was categorized as "clip location unknown." The location of the clipped node was classified as being in the SLN or ALND specimens. The exact location of the clipped node within the ALND specimen was not known and, therefore, whether that node was positive or negative was not always available.

Statistical Analysis

The FNR was calculated as the number of patients with negative SLNs who had residual disease in the contents of the ALND divided by the total number of patients with residual disease (in either the SLN or the ALND, or both). In addition to the point estimate, 95% binomial confidence intervals (CIs) were calculated. FNR calculations are limited to those cases with cN1 disease at presentation with at least 2 SLNs resected, as per the primary endpoint of Z1071, unless otherwise noted.

The number of patients for whom the clipped node was found in the SLNs or axillary lymph nodes was summarized with counts and relative frequencies. A 2-sample *t* test or Wilcoxon rank sum test, as appropriate, was used to evaluate differences for continuous variables between groups. Fisher's exact test was used to evaluate differences between/among groups for categorical variables; this includes the comparison of the FNRs.

All tests were 2-sided and *P* values less than 0.05 were considered statistically significant. The analyses were done with SAS (version 9.3). Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. These analyses were based on data available on August 21, 2013.

RESULTS

There were 756 patients enrolled in the ACOSOG Z1071 from 136 institutions from July 2009 to June 2011. Of these, 687 met eligibility criteria and underwent SLN surgery and ALND. A total of 637 patients had at least 1 SLN identified and underwent ALND of which 203 had a clip placed in the positive node at initial diagnosis. There were 525 patients in the primary endpoint analysis, which was limited to patients with cN1 disease and 2 or more SLNs confirmed on pathology. Of these 525 patients, 170 had a clip placed in the positive lymph node at initial diagnosis. There were 63 of the 136 institutions (49%) where clips were placed in all or some of the patients at the time of initial node biopsy. No significant differences were identified between the 170 patients with a clip placed and the 355 patients without a clip placed at diagnosis (Table 1).

Impact of Clip Identification on SLN FNR in Patients With cN1 Disease With 2 or More SLNs Resected

In the 170 patients with a clip placed at diagnosis, the location of the clipped node at surgery was not documented by either specimen radiograph or pathology in 29 cases. Of the remaining 141 cases, the clipped node was documented to be one of the SLNs in 107 cases (75.9%) and documented to be in the ALND [ie, definitely not in the SLN(s)] in 34 cases (24.1%). In cases with 2 SLNs identified on pathology, the clipped node was in the SLN in 24 (65%) cases and in the ALND in 13 (35%) cases. In patients with 3 SLNs identified, the clipped node was an SLN in 31 (78%) cases and, in 9 (22%) cases, the clipped node was in the ALND. In patients with 4 or more SLNs, the clipped node was a SLN in 52 (81%) cases and was found in the ALND in 12 (19%) cases. In addition, when a dual mapping agent technique (blue dye and radiolabeled colloid) was utilized for SLN identification, the clipped node was found to be one of the SLNs in 78% of cases (101/130), compared to only 50% (1/2) of cases where blue dye alone was used and 55% (5/9) of cases where radiolabeled colloid alone was used ($P = 0.16$).

The FNR of SLN surgery was 6.8% (95% CI: 1.9%–16.5%) in the 107 cases where the clipped node was identified within the SLN specimen compared to 19.0% (95% CI: 5.4%–41.9%) in the 34 cases where the clipped node was in the ALND specimen and not in one of the SLNs ($P = 0.20$, Table 2). In the 29 cases where a clip was placed but the location of the clipped node at surgery was not documented, the FNR was 14.3%, which was similar to the 13.4% FNR in the 355 cases where a clip was not placed.

Comparison of the Pathologic Status of the Clipped Node and Overall Axillary Status in Patients With cN1 Disease and 2 or More SLNs Resected

In the 107 patients where the clipped node was found in one of the SLNs, the clipped SLN was positive in 51 cases, negative in 55 cases, and unknown in 1 case. In 21 of the 51 cases where the clipped SLN was positive, it was the only positive node in the axilla (41%). In the 55 cases where the clipped SLN was negative, the axilla was negative in 48 (87%) and positive in 7 (13%) cases. The clipped SLN reflected the overall nodal status in 99 (93%) cases.

In the 34 patients where the clipped node was found in the ALND specimen, 13 cases were node negative (38%) and 17 cases had a positive SLN identified (in 5, only the SLNs were positive and

TABLE 1. Patient and Treatment Characteristics Comparing Those Patients Where a Clip Was Placed and Those Without a Clip Placed for the 525 Patients With cN1 Disease and 2 or More SLNs Evaluated Included in the Calculation of the False-negative Rate

Characteristics	Clip Placed, N = 170	Clip Not Placed, N = 355	P
Age			0.61
Mean ± SD	50.4 ± 11.3	49.6 ± 10.2	
Median (min, max)	51 (26, 78)	49 (23, 75)	
Race/ethnicity	137 (80.6%)	285 (80.3%)	0.93
White	33 (19.4%)	70 (19.7%)	
Other			
Body mass index			0.62
Mean ± SD	29.3 ± 6.8	29.4 ± 6.4	
Median (min, max)	28.2 (17.6, 47.9)	28.7 (15.4, 64.1)	
ECOG Performance Score			0.99
0	138 (81.2%)	288 (81.1%)	
1	32 (18.8%)	67 (18.9%)	
2	0	0	
Clinical T category at diagnosis			0.63
T0/Tis	2 (1.2%)	2 (0.6%)	
T1	21 (12.4%)	44 (12.4%)	
T2	101 (59.4%)	208 (58.6%)	
T3	39 (22.9%)	92 (25.9%)	
T4	7 (4.1%)	9 (2.5%)	
Approximated tumor subtype			
HER2-positive	49 (28.8%)	107 (30.2%)	0.83
HR-positive and HER2-negative	75 (44.1%)	160 (45.2%)	
Triple receptor negative	46 (27.1%)	87 (24.6%)	
Unknown	0	1	
Tumor histology			0.33
IDC	151 (88.8%)	318 (89.6%)	
ILC	8 (4.7%)	20 (5.6%)	
Mixed	2 (1.2%)	8 (2.2%)	
Other	9 (5.3%)	9 (2.5%)	
Chemotherapy completed			0.54
Yes	156 (91.8%)	331 (93.2%)	
No	14 (8.2%)	24 (6.8%)	
Type of breast surgery			0.23
Partial mastectomy	78 (45.9%)	143 (40.4%)	
Total mastectomy	92 (54.1%)	211 (59.6%)	
Not available	0	1	
# SLNs removed			0.43
Mean ± SD	3.9 ± 2.1	3.7 ± 1.8	
Median (min, max)	3 (2, 13)	3 (2, 13)	
# ALNs removed			0.093
Mean ± SD	13.7 ± 7.2	14.9 ± 7.6	
Median (min, max)	12.5 (2, 54)	14 (2, 61)	
Pathologic N stage			0.94
pN0	69 (40.6%)	145 (41.0%)	
pN1+	101 (59.4%)	209 (59.0%)	

ALN indicates axillary lymph node; HR, hormone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SD, standard deviation.

12 had both positive SLNs and axillary nodes). There were only 4 cases where the SLNs were negative, but there was a positive node in the ALND specimen (ie, false-negative SLN). Overall, the axillary status was correctly identified by SLN surgery in 30 (88%) cases.

Patients With a Single SLN Resected

Patients with only one SLN evaluated (n = 86) were excluded from the primary endpoint analysis of Z1071. The FNR in these patients was 29.3% (95% CI: 18.1%−42.7%). A clip was placed in the lymph node at the time of initial diagnosis in 25 of the 86 patients with a single SLN resected. The FNR for these 25 cases was 35.0% (95% CI: 15.4%−59.2%). In those where the clipped node was the single SLN (n = 14), the FNR was 16.7% (95% CI: 2.1%−48.4%).

The location of the clipped node at surgery was the SLN in 13 cases, in the ALND in 5 cases, and was not reported (unknown) in 7 cases. Of the 13 cases where the clipped node was the SLN, it was positive in 9 cases and, in 4 of these cases, it was the only positive node. In the 4 cases where the clipped SLN was negative, the overall axilla was negative in 2 cases and positive in 2 cases. Of the 5 cases where the clipped node was found in the ALND specimen, 1 was node negative, 1 had a positive SLN, and 3 had positive axillary nodes (ie, 3 false-negative SLNs).

Patients With cN2 Disease

Patients with clinical N2 disease (n = 34) were excluded from the primary endpoint analysis. There were no false-negative events in this group. A clip was placed in the positive lymph node at the time of diagnosis in 14 of the 34 patients with cN2 disease. The location of

TABLE 2. False-negative Rate by Clip Location and Patient Group Analyzed

	N	Residual Disease Identified in SLNs or ALND, n (%)	FNR (%)	95% CI
Patients with ≥2 SLNs removed and cN1 disease				
Clip in SLN	107	59 (55.1)	6.8	1.9–16.5
Clip in ALND	34	21 (61.8)	19.0	5.4–41.9
Clip location unknown	29	21 (72.4)	14.3	3.0–36.3
Clip not placed	355	209 (59.0)	13.4	9.1–18.8
Patients with single SLN resected				
Clip in SLN	14	12 (85.7)	16.7	2.1–48.4
Clip in ALND	5	4 (80.0)	75.0	19.4–99.4
Clip location unknown	6	4 (66.7)	50.0	6.7–93.2
Clip not placed	61	39 (63.9)	26.3	13.4–43.1
Patients with cN2 disease				
Clip in SLN	8	4 (50.0)	0	
Clip in ALND	2	1 (50.0)	0	
Clip location unknown	4	1 (25.0)	0	
Clip not placed	20	12 (60.0)	0	
All patients with a clip placed				
Clip in SLN	127	73 (57.5)	7.2	2.7–15.1
Clip in ALND	40	26 (65.0)	26.9	11.6–47.8
Clip location unknown	36	25 (69.4)	20.0	6.8–40.7
Clip not placed	434	259 (59.8)	14.7	10.6–19.6

the clipped node at surgery was not reported in 4, was within the SLNs in 8, and in the axillary nodes in 2 cases. Of the 8 cases when the clipped node was within the SLN specimen, the clipped node was positive in 4 cases and, in 2 of these cases, was the only positive node. In the other 4 cases, the clipped node was negative and the overall axillary status was negative. In the 2 cases where the clipped node was in the ALND, 1 was node negative and 1 had a positive SLN with negative axillary nodes.

FNR in the Entire Cohort Where a Clip Was Placed

Across the entire cohort of 203 patients with a clip placed at diagnosis, there were 22 patients who had negative SLN(s), and the clipped node was identified in the ALND specimen. Of these cases, 15 were node negative and 7 had a negative SLN but a positive axillary node. The FNR in the 127 patients where the clipped node was in the SLN(s) was 7.2% (95% CI: 2.7–15.1%). The FNR was 26.9% (95% CI: 11.6–47.8%) in the cases where the clipped node was found in the ALND specimen ($P = 0.013$). The FNR in cases where the clipped node location was not reported was 20.0% and, in those where a clip was not placed, it was 14.7%.

DISCUSSION

With primary systemic therapy, axillary nodal disease can be eradicated with rates of complete nodal response increasing with improvements in targeted systemic therapies. SLN surgery after neoadjuvant chemotherapy can provide a less invasive method for staging residual axillary disease after chemotherapy but has been associated with higher FNRs. Placement of a clip in the biopsy-proven positive node is 1 method that can help ensure that the initially biopsy-proven positive node is removed at the time of surgery to be carefully evaluated for residual disease after chemotherapy. Placement of a clip at initial biopsy with confirmation of resection of the clipped node at SLN surgery results in an FNR of 6.8%.

It is not known how often the lymph node visualized and biopsied on axillary ultrasound is one of the lymph node(s) removed at SLN surgery. Which lymph node is biopsied under ultrasound guidance at presentation is dependent on sonographic visualization. The indication for biopsy is based on size and morphological features identified sonographically.[18] Lymph nodes removed at SLN surgery are identified by entirely different criteria with the use of lymphatic mapping agents, such as radiolabeled colloid and/or blue dye, injected in the breast to identify the draining lymph nodes. Exposure of the axilla during surgery allows for visualization of nodes and mapping agents and also permits palpation of the lymph nodes.

One previous study of patients who underwent surgery as their first treatment modality and included both lymph node-negative and lymph node-positive cases showed that the clipped lymph node was removed as part of the sentinel node procedure in 78% of cases.[17] In the Z1071 study, we found that the clipped lymph node was removed as part of SLN surgery in 76% of cases, similar to the findings of the previous study.[17] However, Z1071 included only cases with biopsy-proven positive lymph nodes and the SLN surgery was performed after neoadjuvant chemotherapy. A recent small series evaluating this question after neoadjuvant chemotherapy had similar results with the clipped node in the SLN specimen in 4 of 5 cases (80%).[19]

A clip was placed in only 32% of all patients enrolled in Z1071, which limits the power for detecting a statistically significant improvement in FNR associated with the identification of the clipped node as one of the nodes removed during SLN surgery. However, we did find differences in the SLN FNR between those cases when the clip was identified in the SLN versus those cases with the clip identified in the ALND specimen, and this difference may be clinically relevant.

For patients with biopsy-proven node-positive disease at presentation, in most cases, only a single lymph node is biopsied percutaneously and the total number of involved lymph nodes at presentation is not known. How the involved lymph nodes respond to systemic therapy may not be uniform across all involved nodes. Removing the lymph node that was biopsied confirms that one of the lymph nodes that were positive at the outset was removed as part of the surgical axillary staging procedure. However, other nodes beyond

the clipped node may have residual disease. The clipped node could be negative and other nodes positive; therefore, the SLN FNR is not 0% in these patients. However, confirming removal of the clipped node does provide confirmation that the initially biopsy-proven positive node was removed and, therefore, allows evaluation for response to neoadjuvant chemotherapy in that specific node. This strategy of documenting that the clipped node is removed is 1 method along with the other techniques of SLN surgery and axillary evaluation to help refine SLN surgery in these patients.

Introducing the routine clipping of axillary lymph nodes at initial percutaneous biopsy requires a change in the workup of patients. Clips can either be placed routinely at the time of percutaneous lymph node biopsy or may require a second procedure at a later date. If the clip is placed routinely at the time of all percutaneous biopsies, clips will also be placed in negative lymph nodes. This is similar to the current standard of placing a clip at the site of percutaneous breast biopsies, resulting in clipping of benign lesions. If nodes are found to be benign, then the clipped node would not necessarily require removal at axillary surgery. The alternative approach of placing a clip only in cases once the results of the percutaneous biopsy results are positive for metastatic disease may require a second percutaneous procedure for clip placement. One potential strategy is placing clips at the time of percutaneous biopsy in cases with markedly abnormal nodes and, for the less suspicious nodes that still warrant percutaneous biopsy, one could await pathology results before placing a clip.

With incorporation of clip placement in lymph nodes at diagnosis, it is important to document the location of the clip at surgical excision, similar to the routine approach to radiography to confirm that a breast lesion has been excised. The clip can be documented by specimen radiograph, by the pathologist identifying the clip in the node, or both.

In Z1071, which exact lymph node contained the clip in cases with several SLNs within 1 specimen or when the clip was within the ALND specimen was not routinely reported, limiting the ability to always correlate whether the clipped node had residual disease in it or not. Working with the multidisciplinary team, in particular radiologists and pathologists, and making certain the surgeon is aware of the need to evaluate the specimen for the clip at surgery is important when introducing clip placement into clinical practice.

Placement of a clip also presents a challenge when the SLN does not contain the clip. Alternative strategies to ensure resection of the clipped node may be considered. These include preoperative localization of the clipped node with a wire, needle, radioactive seed, or intraoperative ultrasound to identify the clipped node.[20] Another proposal is to tattoo the lymph node at the time of biopsy and visualize the tattoo ink at surgery.[21]

As the data on whether the clipped node was positive or negative in the cases where the clipped node was part of the axillary dissection contents were unknown in approximately half of the cases, we were not able to assess the FNR with a strategy of SLN surgery plus resection of the clipped node. This is a method that is being evaluated in a prospective study of targeted axillary dissection at MD Anderson Cancer Center.[19,22]

CONCLUSIONS

Percutaneous placement of a clip in the axillary lymph node at the time of diagnosis of node-positive breast cancer is a potentially useful tool for those patients receiving neoadjuvant chemotherapy. Ensuring resection of the clipped node at the time of SLN surgery after completion of neoadjuvant chemotherapy may help to further decrease the FNR of SLN surgery in this patient population. The National Comprehensive Cancer Network (NCCN) guidelines have incorporated into their guidelines a comment that marking biopsied lymph nodes to document their removal is 1 method to decrease the FNR of SLN in this setting.[23]

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