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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role for Sentinel Lymph Node Dissection after Neoadjuvant Chemotherapy in Patients who Present with Node-Positive Breast Cancer

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ABSTRACT

Background. Sentinel lymph node (SLN) dissection has been investigated after neoadjuvant chemotherapy and has shown mixed results. Our objective was to evaluate SLN dissection in node-positive patients and to determine whether postchemotherapy ultrasound could select patients for this technique.

Methods. Between 1994 and 2010, 150 patients with biopsy proven axillary metastasis underwent SLN dissection after chemotherapy and 121 underwent axillary lymph node dissection (ALND). Clinicopathologic characteristics were analyzed before and after chemotherapy. Statistical analyses included Fisher's exact test for nodal response and multivariate logistic regression for factors associated with false-negative events.

Results. Median age was 52 years. Median tumor size at presentation was 2 cm. The SLN was identified in 93 % (139/150). In 111 patients in whom a SLN was identified and ALND performed, 15 patients had a false-negative SLN (20.8 %). In the 52 patients with normalized nodes on ultrasound, the false-negative rate decreased to 16.1 %. Multivariate analysis revealed smaller initial tumor size and fewer SLNs removed (<2) were associated with a false-negative SLN. There were 63 (42 %) patients with a pathologic complete response (pCR) in the nodes. Of those with normalized nodes on ultrasound, 38 (51 %) of 75 had a pCR. Only 25 (33 %) of 75 with persistent suspicious/malignant-appearing nodes had a pCR ($p = 0.047$).

Conclusions. Approximately 42 % of patients have a pCR in the nodes after chemotherapy. Normalized morphology on ultrasound correlates with a higher pCR rate. SLN dissection in these patients is associated with a false-negative rate of 20.8 %. Removing fewer than two SLNs is associated with a higher false-negative rate.

Axillary lymph node status is an important prognostic indicator for breast cancer patients. The introduction of sentinel lymph node (SLN) dissection provided surgeons a less morbid alternative to axillary lymph node dissection (ALND) for nodal staging.[1,2] Several large studies have confirmed its accuracy and decreased morbidity, and SLN dissection is now standard practice for axillary staging in clinically node-negative patients.[1,3–5]

Neoadjuvant chemotherapy has been used in the setting of locally advanced breast cancers, and targeted treatment strategies have resulted in an increasing rate of pathologic complete responses (pCR). This has led to increasing enthusiasm for using neoadjuvant chemotherapy in patients with operable and early-stage breast cancer who are planned for systemic therapy based on adverse factors and/or receptor status. As a result, some patients become candidates for breast-conserving surgery with outcomes equivalent to those undergoing mastectomy.[6]

Surgeons have embraced SLN dissection for staging patients with early-stage disease undergoing surgery first.

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Some have extended its application to clinically node-negative patients receiving neoadjuvant chemotherapy. Hunt et al.[7] showed that SLN dissection after neoadjuvant chemotherapy was accurate in this population and use of chemotherapy resulted in fewer positive SLNs, decreasing the need for ALND. Several investigators also have shown that SLN dissection after chemotherapy is an accurate tool for postchemotherapy staging.[3,8–10]

To date, it is unclear whether SLN dissection should be applied to patients who present with node-positive disease before neoadjuvant chemotherapy. Several small studies as well as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial and the French prospective multicentric study have evaluated this patient population.[11,12] Shen et al.[13] reported a false-negative rate of 25 % and concluded that SLN dissection could not be used to accurately stage the axilla. Kang et al.[14] correlated clinical complete response by ultrasound to pathologic response and found that the false-negative rate decreased from 17.1 to 10 % when ultrasound features were taken into account. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was designed to answer this question enrolling patients with biopsy proven node-positive disease and utilizing ultrasound and SLN dissection for nodal staging in patients planned for completion ALND. The study has completed accrual, but the results have not yet been reported.

In the current study, we evaluated patients with documented axillary node-positive disease who received neoadjuvant chemotherapy and subsequent SLN dissection. The objectives were to evaluate the accuracy of SLN dissection in this setting and to determine whether postchemotherapy ultrasound selects appropriate patients for this technique.

METHODS

Following approval from our Institutional Review Board, we queried the Surgical Breast Oncology database for patients with a diagnosis of invasive breast cancer (T1–T4) and axillary node-positive disease (N1–N3) identified by ultrasound-guided, fine-needle aspiration who were treated with neoadjuvant chemotherapy between 1994 and 2010 and had surgery that included SLN dissection. The chemotherapy regimens utilized were at the discretion of the treating oncologists. Patients enrolled on ACOSOG Z1071 were excluded. We identified 150 patients, and of these, 121 underwent completion ALND. Clinical and pathologic characteristics were analyzed at diagnosis, after chemotherapy, and after surgery. An ultrasound of the regional lymph nodes was performed before and after chemotherapy. Nodal size, morphology, and clinical response were assessed by ultrasound.

Statistical Analyses

Fisher's exact test was used to assess correlation between clinical and pathologic response in the nodes after neoadjuvant chemotherapy. A false-negative event was defined as a negative SLN in a patient with metastasis detected in at least one non-SLN. Multivariate logistic regression was used to determine factors associated with a false-negative event. Lymph node size on ultrasound, before and after chemotherapy, was recorded and logistic regression performed to determine whether a decrease in size on ultrasound correlated to pathologic response.

RESULTS

Patient and Tumor Characteristics at Presentation

Table 1 illustrates patient and tumor characteristics prior to chemotherapy. Median patient age at diagnosis was 52 (range, 24–80) years. Most patients had T1 or T2 tumors (78.6 %) with a mean tumor size of 2.6 (range, 0.1–11) cm. The most common histology was invasive ductal (83.3 %); most were grade III (54.7 %) and estrogen receptor (ER) positive (58.7 %). A total of 101 (67.3 %) were HER-2 negative and 38 (25.3 %) had lymphovascular invasion. Mean lymph node size was 2 (range, 0.5–6) cm by ultrasound.

Tumor Characteristics after Neoadjuvant Chemotherapy

Tumor characteristics after neoadjuvant chemotherapy are illustrated in Table 2. A complete (20.7 %) or partial (60.7 %) response in the primary tumor by ultrasound occurred in 122 patients. A complete clinical response in the axilla was seen in 52.7 %, a partial response in 44 %, and minimal/no response in 3.3 %. In 132 (88 %) patients there was no palpable lymphadenopathy after chemotherapy, and 75 (50 %) were described as having normalized morphology on ultrasound. Thirty-nine (26 %) had a pCR in the primary tumor, and 63 (42 %) had a pCR in the axilla. Mean tumor size decreased to 1.7 cm.

Surgical Treatment

All 150 patients underwent SLN dissection at the time of surgical treatment (Table 3). In most cases (77.3 %), both radiocolloid and blue dye were used. Peritumoral injection was utilized in 130 (86.7 %) patients. SLN identification was successful in 139 (92.7 %) patients. In 8 of 11 unsuccessful mappings, a combination of radiocolloid and blue dye was used, and 6 of 11 patients were found to have

TABLE 1 Patient and tumor characteristics before chemotherapy

Characteristics	No. of patients ($N = 150$) (%)
Age at diagnosis, year	
Mean (median)	51.4 (52)
Range	24-80
Race	
White	91 (60.7)
Black	23 (15.3)
Other	36 (24.0)
Clinical T stage	
T1	26 (17.3)
T2	92 (61.3)
T3	20 (13.3)
T4	12 (8.1)
Tumor location	
UOQ	63 (42)
UIQ	16 (10.7)
LOQ	14 (9.3)
LIQ	5 (3.3)
Central	33 (22)
Multicentric	19 (12.7)
Clinical tumor size, cm	
Mean (median)	2.6 (2)
Range	0.1–11
Clinical N stage	
N1	119 (79.3)
N2	10 (6.7)
N3	21 (14)
Tumor grade	
I	11 (7.3)
II	52 (34.7)
III	82 (54.7)
Unknown	5 (3.3)
Histology of primary tumor	
Invasive ductal	125 (83.3)
Invasive lobular	13 (8.7)
Mixed ductal and lobular	11 (7.3)
Medullary	1 (0.7)
ER	
Positive	88 (58.7)
Negative	60 (40)
Unknown	2 (1.3)
PR	
Positive	73 (48.7)
Negative	75 (50)
Unknown	2 (1.3)
HER-2	
Positive	38 (25.3)
Negative	101 (67.3)
Unknown	11 (7.3)
Lymphvascular space invasion	
Absent	112 (74.7)
Present	38 (25.3)
Lymph node palpable	
Yes	93 (62)
No	57 (38)
Ultrasound description of lymph nodes	
Indeterminate	25 (16.7)
Suspicious	107 (71.3)
Malignant-appearing	18 (12)
Clinical AJCC stage	
IIA	28 (18.7)
IIB	66 (44)
IIIA	22 (14.7)
IIIB	11 (7.3)
IIIC	23 (15.3)
Clinical abnormal lymph node size, cm	
Mean (range)	2 (0.5–6)
Median	1.9

axillary metastasis on pathology. The median number of SLNs was 2 (range, 1–7). The median number of non-SLNs was 15 (range, 4–35) in patients who had ALND.

Correlation of SLN Dissection Results with ALND

Of the 150 patients, 121 underwent completion ALND. Of 111 with successful SLN identification (Table 4), 72 (64.9 %) had metastasis on final pathology. SLN dissection successfully identified 39 (72.2 %) true-negatives. Fifteen patients were classified as having a false-negative SLN for an event rate of 20.8 % (15/72). Of 79 patients with a complete clinical response by ultrasound and physical examination, 62 had an ALND and 5 had no SLN identified. Of the remaining 57 patients, 32 had a positive lymph node and 6 of these had a false-negative event, for a false-negative event rate of 18.8 %.

In contrast, of 66 patients who had a partial clinical response by ultrasound and physical examination, 60 had an ALND and 4 had no SLN identified. Of the remaining 56 patients, 42 had a positive lymph node and 14 of these had a false-negative event, for an event rate of 33.3 %. In those who had a complete response by ultrasound ($n = 52$), the false-negative rate decreased to 16.1 % (5/31) but was 27.8 % (10/36) in those with persistently indeterminate morphology. In patients with HER-2 positive disease, the false-negative rate was 33.3 % versus 18 % in those with HER-2 negative disease. Of the 111 patients, 87

TABLE 2 Tumor characteristics after chemotherapy

Characteristics	No. of patients ($n = 150$) (%)
Clinical response in the primary tumor	
Complete	31 (20.7)
Partial (≥50 %)	91 (60.7)
Minimal (<50 %)	18 (12)
Stable disease	10 (6.6)
Pathologic response in the primary tumor	
Complete (no residual invasive tumor)/ ductal carcinoma in situ only	39 (26)
Residual infiltrating carcinoma ≤1 cm	35 (23.3)
Residual infiltrating carcinoma >1 cm	76 (50.7)
Clinical response in axillary lymph nodes	
Complete	79 (52.7)
Partial	66 (44)
Minimal/none	5 (3.3)
Pathologic response in axillary lymph nodes	
Partial	87 (58)
Complete	63 (42)
Pathologic tumor size (cm)	
Mean (range)	1.7(0–11)
Median	1
Palpable lymph nodes postchemotherapy	
Yes	18 (12)
No	132 (88)
Ultrasound description of lymph nodes postchemotherapy	
Normal	75 (50)
Indeterminate	64 (42.7)
Suspicious	7 (4.6)
Malignant-appearing	4 (2.7)

TABLE 3 Surgical treatment and details of SLN dissection

Characteristics	No. of patients ($n = 150$) (%)
SLN Identification rate (technical success)	
Yes	139 (92.7)
No	11 (7.3)
Surgical treatment	
Lumpectomy	87 (58)
Total mastectomy	63 (42)
SLN mapping method	
Radioactive colloid/Blue dye alone	34 (22.7)
Combination	116 (77.3)
Location of radiocolloid injection	
Peritumoral	130 (86.7)
Subareolar	20 (13.3)
Preoperative lymphoscintigraphy performed	
Yes	131 (87.3)
No	19 (12.7)
Median visualization time on lymphoscintigraphy [range], minutes	60 (8–360)
Number SLNs removed	
Mean (range)	2.6 (1–7)
Median	2
Positive SLN	
Yes	59 (42.5)
No	80 (57.5)
ALND	
No	29 (19.3)
Yes	121 (80.7)
Number of non-SLNs removed	
Mean (range)	14 (0–35)
Median	14
No. of non-SLNs removed, ALND patients ($N = 121$)	
Mean (range)	16.2 (4–35)
Median	15

ALND axillary lymph node dissection, *SLN* sentinel lymph node

had N1 disease. Of these, 14 had a false-negative SLN for an event rate of 23.7 % (14/59). Nine had N2 disease and there were no false-negative events in this group. The remaining 15 had N3 disease; 1 patient had a false-negative SLN for an event rate of 7.7 % (1/13). Multivariate logistic regression analysis revealed that smaller tumor size (<2 cm) at presentation and fewer SLNs removed (<2) at surgery were associated with having a false-negative SLN ($P = 0.008$ and $P = 0.035$, respectively). All other variables in Table 1 were not associated with a false-negative SLN.

Correlation of Ultrasound with Pathologic Results

Pathologic response in the axilla did not correlate with lack of palpable lymphadenopathy on physical examination (Table 5). Although the percentage of lymph nodes with residual metastasis was higher in the palpable group (66.7 % vs. 56.8 %), this difference was not statistically significant ($P = 0.4$). Postchemotherapy nodal morphology by ultrasound correlated with pCR. In patients with normal-appearing nodes on ultrasound, 50.7 % (38/75) had a pCR compared with a pCR rate of 33.3 % (25/75) in those with persistent indeterminate/suspicious or malignant-appearing nodes ($P = 0.047$). A change in nodal size on ultrasound also was assessed. Patients with a larger change in nodal size before and after chemotherapy were less likely to have residual infiltrating carcinoma >1 cm in the primary tumor (odds ratio (OR), 0.38; $P = 0.024$).

DISCUSSION

Axillary lymph node dissection is an important component of the surgical management of breast cancer

TABLE 4 Pathologic status of sentinel and axillary lymph nodes ($N = 111$)

SLNs	Axillary LN positive	Axillary LN negative	Total
Positive	42 (73.7)	15 (26.3)	57
Negative	15 (27.8) [FN]	39 (72.2) [TN]	54
Total	57	54	111
False-negative rate: FN/(TP + FN) = 15/72 = 20.8 %			
N1 ($n = 87$)			
Positive	31 (68.9)	14 (31.1)	45
Negative	14 (33.3) [FN]	28 (66.7) [TN]	42
Total	45	42	87
False-negative rate: FN/(TP + FN) = 14/59 = 23.7 %			
N2 (n = 9)			
Positive	5 (83.3)	1 (16.7)	6
Negative	0 (0) [FN]	3 (100) [TN]	3
Total	5	4	9
False-negative rate: FN/(TP + FN) = 0/6 = 0 %			
N3 ($n = 15$)			
Positive	6 (100)	0 (0)	6
Negative	1 (11.1) [FN]	8 (88.9) [TN]	9
Total	7	8	15
False-negative rate: FN/(TP + FN) = 1/7 = 14.3 %			
N2/N3 ($n = 24$)			
Positive	11 (91.7)	1 (8.3)	12
Negative	1 (8.3) [FN]	11 (91.7) [TN]	12
Total	12	12	24
False-negative rate: FN/(TP + FN) = 1/13 = 7.7 %			
Her-2+ ($n = 30$)			
Positive	7 (58.3)	5 (41.7)	12
Negative	6 (33.3) [FN]	12 (33.3) [TN]	18
Total	13	17	30
False-negative rate: FN/(TP + FN) = 6/18 = 33.3 %			
Her-2− ($n = 73$)			
Positive	31 (75.6)	10 (24.4)	41
Negative	9 (28.1) [FN]	23 (71.9) [TN]	32
Total	40	33	73
False-negative rate: FN/(TP + FN) = 9/50 = 18 %			
Normal ultrasound features before chemo ($N = 19$)			
Positive	6 (66.7)	3 (33.3)	9
Negative	2 (20) [FN]	8 (80) [TN]	10
Total	8	11	19
False-negative rate: FN/(TP + FN) = 2/11 = 18.2 %			
Indeterminate ultrasound features before chemo ($N = 79$)			
Positive	30 (76.9)	9 (23.1)	39
Negative	13 (32.5) [FN]	27 (67.5) [TN]	40
Total	43	36	79
False-negative rate: FN/(TP + FN) = 13/52 = 25 %			
Suspicious or malignant ultrasound features before chemo ($N = 13$)			
Positive	6 (66.7)	3 (33.3)	9
Negative	0 (0) [FN]	4 (100) [TN]	4
Total	6	7	13
False-negative rate: FN/(TP + FN) = 0/9 = 0 %			
Normal ultrasound features after chemo ($N = 52$)			
Positive	17 (65.4)	9 (34.6)	26
Negative	5 (19.2) [FN]	21 (80.8) [TN]	26
Total	22	30	52
False-negative rate: FN/(TP + FN) = 5/31 = 16.1 %			
Indeterminate ultrasound features after chemo ($N = 52$)			
Positive	22 (84.6)	4 (14.4)	26
Negative	10 (38.5) [FN]	16 (61.5) [TN]	26
Total	32	20	52
False-negative rate: FN/(TP + FN) = 10/36 = 27.8 %			
Suspicious, or malignant ultrasound features after chemo ($N = 7$)			
Positive	3 (60)	2 (40)	5
Negative	0 (0) [FN]	2 (100) [TN]	2
Total	3	4	7
False-negative rate: FN/(TP + FN) = 0/5 = 0 %			

LN lymph node, *SLN* sentinel lymph node, *FN* false-negative, *TN* true-negative

121 patients underwent a completion axillary LN dissection (minus 10 patients who did not have SLNs identified = 111 evaluable patients)

patients, providing staging information and removing metastatic disease within the axilla. However, ALND is associated with morbidity, including lymphedema, nerve injury, decreased range of motion, and chronic pain. SLN dissection has decreased morbidity and is now routinely utilized in patients with a clinically node-negative axilla. The purpose of this study was to determine clinical, radiographic, and pathologic characteristics that may aide in selection for SLN dissection in patients with node-positive disease at presentation treated with neoadjuvant chemotherapy. Overall, we found a false-negative rate of 20.8 %. Factors associated with a false-negative event were smaller primary tumor size at presentation and removing fewer than two SLNs at surgery. Normalization of nodal morphology on ultrasound correlated with a pCR and a lower false-negative rate.

In our study, 42 % of patients had a pCR in the axilla and potentially could have been spared the morbidity of a completion ALND if there were a reliable, less invasive method for staging the axilla. SLN dissection has been applied to patients with clinically node-negative disease before chemotherapy with acceptable false-negative rates. In the NSABP B-27 study, the investigators did not find a difference in false-negative rates among those patients with clinically node-positive disease or clinically node-negative disease at presentation, but they did not require a biopsy of the regional nodes to prove which patients had metastasis before chemotherapy.[11] In the French multicenter trial,

TABLE 5 Clinical and pathologic correlation in the lymph nodes after preoperative chemotherapy

Variable	No. residual axillary disease (%)	No. complete pathologic response (%)	*P* value
Lymph nodes palpable			0.4*
Yes	12 (66.7)	6 (33.3)	
No	75 (56.8)	57 (43.2)	
Ultrasound description of lymph nodes			0.1*
Normal	37 (49.3)	38 (50.7)	
Indeterminate	43 (67.2)	21 (32.8)	
Suspicious/ malignant	7 (63.6)	4 (36.4)	
Ultrasound description of lymph nodes			0.047*
Normal	37 (49.3)	38 (50.7)	
Indeterminate/ suspicious/ malignant	50 (66.7)	25 (33.3)	
Her-2 status			0.4*,[a]
Positive	18 (47.4)	20 (52.6)	
Negative	39 (38.6)	62 (61.4)	
Unknown	5	5	

[a] Excluded unknown category

* Fisher's exact test

they reported a higher false-negative rate (15 %) in those with proven node-positive disease at presentation compared with those who were clinically node-negative (9.4 %).[12] We found a false-negative rate of 20.8 % in our study, a rate higher than most clinicians would accept as a reliable test of axillary status after chemotherapy. We found that normalization of nodal morphology on ultrasound was associated with a higher pCR rate and a slightly lower false-negative rate (16.1 %). Kang et al.[14] also reported a lower false-negative rate when evidence of response by ultrasound was taken into account. The association between nodal morphology and pCR rates may be clinically useful but needs further study.

A change in size of axillary nodes before and after chemotherapy has not been examined previously as a predictor of pCR in this patient population. We found that a greater decrease in size of the lymph nodes by ultrasound correlated with the response in the breast (residual infiltrating carcinoma <1 cm). However, decrease in size greater than 1 cm in the nodes was not a reliable indicator of pCR in the axillary nodes. This may be explained by a larger tumor burden at presentation. This is consistent with studies that have attempted SLN dissection after chemotherapy for patients with inflammatory breast cancer who often have a greater burden of disease, especially in the regional nodes.[15] Change in size of the lymph nodes, by ultrasound, deserves further study in a larger patient population to determine whether this could be a useful variable in surgical planning.

Brown et al.[16] previously showed that the absence of treatment effect in the sentinel nodes, such as fibrosis or fat necrosis, was associated with a false-negative event in patients who present with node-positive disease. Although we did not examine this variable, this type of histologic correlate may provide an additional tool in determining which patients might be appropriate candidates for SLN dissection alone, reserving ALND for those in whom the SLN fails to show any treatment effect. The French, multicenter study published by Classe et al.[12] (overall false-negative rate of 11.5 %; false-negative rate in node-positive patients at presentation 15 %) did not find a correlation between a false-negative event and lack of treatment effect in the axillary nodes using Sataloff grading, suggesting that there is a lack of consensus and that this variable requires further investigation. In our study, there was a high rate of nodal positivity in patients in whom a SLN was not identified: (6/11) 54.5 %. This may be a result of lymphatic obstruction from tumor emboli and/or chemotherapy effect. Others have found similar rates of nodal positivity in patients with failed identification of the SLN, concluding that ALND should be performed in these patients.[17,18]

In our study, a false-negative SLN was more likely in cases of smaller primary tumor size. Martin et al.[19] also found that tumor size <2.5 cm was associated with an increased false-negative rate. They suggest this may be because larger tumors are more likely to have multiple positive axillary nodes, leading to a higher likelihood of identifying a positive SLN, decreasing the false-negative rate. We also found that a false-negative SLN was more likely if fewer than two SLNs were removed at surgery. Although this variable may not always be controlled, every attempt should be made to remove all blue, hot, or palpable nodes to obtain accurate staging of the axilla. In a study that evaluated clinically node-negative patients receiving neoadjuvant chemotherapy, Hunt et al.[7] found that a false-negative event was more likely if fewer than two SLNs were removed. Investigators from the NSABP B-32 trial showed similar results in a cohort of clinically node-negative patients who underwent surgery first.[20] They reported a false-negative rate of 10 % when two nodes were removed and 17.7 % when only one was removed.

As with any retrospective review, there are limitations to our study. Not all patients consented to completion ALND and therefore could not be used in the analysis of the false-negative rate, decreasing our evaluable cohort. These

patients could not be used in correlating pCR to ultrasound findings. Additionally, we did not specify the surgical technique of the SLN dissection or the pathologic assessment of the SLNs. Therefore, there was the potential that not all hot and/or blue nodes were examined as SLNs, but rather were simply included in the entire ALND specimen. One strength of our study is that it is one of the largest cohorts in the literature specifically evaluating the use of SLN dissection after neoadjuvant chemotherapy in node-positive patients with some correlation to ultrasound findings before and after chemotherapy. Previous studies, with the exception of the French trial, included at most a cohort of 80 patients.[12–14,21,22] The imaging data and surgical parameters in our database were collected prospectively. Our radiologists have a standardized protocol for the use of ultrasound before and after chemotherapy and included cytologic documentation of nodal metastasis before treatment. This has been a well-studied technique for diagnosis of node-positive breast cancer and has been found to be reliable and sensitive by several groups.[5,23–25]

Current recommendations are for completion ALND in patients with node-positive disease.[26] The results of ACOSOG Z1071, "A phase II study of sentinel lymph node surgery and axillary lymph node dissection following neoadjuvant chemotherapy in women with stage II–IIIB node-positive breast cancer," are expected soon and should provide further data to help guide the management of this patient population. Our study provides important variables that should be considered in further selecting appropriate patients for this technique, including nodal morphology on ultrasound and the total number of SLNs removed at surgery. However, our data do not support the omission of completion ALND in this patient population.

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