Published in final edited form as:

Breast J. 2018 January ; 24(1): 28–34. doi:10.1111/tbj.12829.

Factors Impacting the Accuracy of Intra-operative Evaluation of Sentinel Lymph Nodes in Breast Cancer

Catherine L. Akay, MD¹, Constance Albarracin, MD², Tiffany Torstenson, DO³, Roland Bassett⁴, Elizabeth A. Mittendorf, MD, PhD¹, Min Yi, MD, PhD¹, Henry M. Kuerer, MD, PhD¹, Gildy V. Babiera, MD¹, Isabelle Bedrosian, MD¹, Kelly K. Hunt, MD¹, and Rosa F. Hwang, MD¹

¹Department of Surgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

²Department of Pathology, University of Texas M.D. Anderson Cancer Center, Houston, TX

³Department of Surgery, Mercy Medical Center, Des Moines, IA

⁴Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

Sentinel lymph node dissection (SLND) is a standard axillary staging technique in breast cancer and intraoperative sentinel lymph node (SLN) assessment is important for decision-making regarding additional treatment and reconstruction. This study was undertaken to investigate clinicopathologic factors impacting the accuracy of intraoperative sentinel lymph node (SLN) evaluation.

Records of patients with clinically node-negative, invasive breast cancer who underwent SLND with frozen section intraoperative pathologic evaluation from 2004–2007 were reviewed. Intraoperative SLN assessment results were compared to final pathology. Patients with positive SLNs that were initially reported as negative during intraoperative assessment were considered false negative (FN) events. Primary tumor histology, grade, receptor status, size, lymphovascular invasion (LVI), multifocality, neoadjuvant chemotherapy or hormonal therapy, number of SLNs retrieved, and SLN metastasis size were evaluated.

The study included 681 patients, of whom 262 (38%) received neoadjuvant therapy. There were 183 (27%) patients who had a positive SLN on final pathology, of whom 60 (33%) had FN events. On univariate analysis, lobular histology, favorable histology, absence of LVI and micrometastasis were associated with a higher FN rate. On multivariate analysis, favorable and lobular histology and micrometastasis were independent predictors of FN events whereas LVI and receipt of neoadjuvant therapy were not statistically significant predictors.

The accuracy of intraoperative SLN evaluation for breast cancer is affected by primary tumor histology and size of the SLN metastasis. There was no significant association between neoadjuvant therapy and the FN rate by intraoperative assessment. This information may be

helpful in counseling patients about their risk for a FN intraoperative SLN assessment and for planning for immediate breast reconstruction in patients undergoing mastectomy.

Keywords

breast cancer; sentinel lymph node biopsy; frozen section; neoadjuvant therapy; metastasis

Introduction

Sentinel lymph node dissection (SLND) is a standard technique for axillary staging in breast cancer(1, 2). A positive intraoperative sentinel lymph node (SLN) assessment may enable single-stage surgery in cases where axillary dissection is indicated and may help guide decisions regarding immediate breast reconstruction.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that completion axillary lymph node dissection (CLND) may be omitted in clinically node negative patients undergoing lumpectomy who are found to have fewer than three positive SLNs and who are planned for adjuvant whole breast radiotherapy (3). There were no differences in local control or survival between patients who underwent CLND compared to those who did not. As a result, assessment of SLNs in this cohort is now deferred to permanent section at many centers, including our own(4).

For those patients with a positive SLN who fall outside of the Z0011 selection criteria, however, further axillary surgery would typically still be recommended. Thus, intraoperative SLN assessment continues to be a valuable tool in intraoperative decision-making regarding additional axillary surgery. In particular, patients undergoing total mastectomy and those who receive neoadjuvant chemotherapy do not meet the Z0011 criteria and an intraoperative decision to perform CLND is often based on the results of immediate assessment of the SLNs. In addition to avoiding another surgery, the intraoperative results of the SLN can also be helpful for patients who desire immediate reconstruction following total mastectomy as the status of the axilla is a major determinant of post-mastectomy radiotherapy which can influence the options for reconstruction. As the indications for SLND continue to expand, knowledge of factors which affect the accuracy of intraoperative SLN assessment will be helpful, particularly in regard to intraoperative decision-making.

Reported sensitivity rates of intraoperative SLN evaluation for breast cancer range from 58% to 72% (5–7). A number of clinicopathologic and technique-related factors such as tumor histology, size of the metastatic focus, number of SLNs retrieved and method of intraoperative assessment have been shown to affect the accuracy of intraoperative SLN evaluation (6, 8, 9). There are few reports on the accuracy of intraoperative SLN assessment after neoadjuvant therapy. The effects of chemotherapy-related cellular and stromal changes on intraoperative SLN analysis are not well understood.

This study was undertaken to evaluate the effects of various disease and treatment-related variables, including neoadjuvant therapy, on the accuracy of intraoperative SLN assessment in patients presenting with clinically node negative breast cancer.

Methods

Following approval from the MD Anderson Cancer Center institutional review board, a prospectively maintained database was queried for patients with clinically node-negative invasive breast cancer who underwent SLND with intraoperative frozen section evaluation from 2004–2007. Patient demographic data, disease and treatment-related variables including primary tumor histology, grade, hormone and Her2 receptor status, clinical size, presence of lymphovascular invasion (LVI), multifocality, type of surgery, neoadjuvant treatment received, number of SLNs retrieved and SLN metastasis size were analyzed. Metastatic foci $>0.2\text{mm}$ and $\leq 2\text{mm}$ were classified as micrometastases. Mucinous, tubular and papillary histologies were grouped together as “favorable.”

Axillary SLN mapping was performed using radiocolloid and/or isosulfan blue dye, according to surgeon preference. All identified SLNs were sent to pathology for detailed evaluation. Once a metastatic lymph node had been identified on intra-operative evaluation, remaining SLNs for that patient were processed by permanent section only. Intraoperative SLN evaluation was performed using frozen section analysis or touch preparation with frozen section analysis. Our group has previously reported superior sensitivity for SLN metastases with frozen section evaluation compared to touch imprint cytology and no longer routinely performs touch preparation alone(6). Therefore, patients whose SLNs were evaluated intraoperatively with only touch preparation were excluded. SLNs were bisected if they measured $<0.5\text{cm}$ in greatest diameter and sectioned at 2-mm intervals along the short axis if they measured $>0.5\text{cm}$. Touch imprints and/or frozen sections were prepared from both cut surfaces of lymph node sections and then stained with hematoxylin and eosin (H&E). For the permanent section analysis, paraffin blocks were sectioned at $5\text{ }\mu\text{m}$ intervals to produce two sections for H&E examination and one section for immunostaining for pancytokeratins if H&E sections were negative for metastases.

Results of the intraoperative evaluation were compared to results of the final pathologic evaluation of permanent sections. SLNs containing metastases that were $>0.2\text{mm}$ and identified by any method, including immunohistochemistry, were considered positive. However, SLNs containing only isolated tumor cells (metastasis measuring $\leq 0.2\text{mm}$, or <200 tumor cells per histologic cross section) were considered negative SLNs. Patients having any SLNs that were positive on permanent section analysis but initially reported as negative based on intraoperative assessment were counted as false negative (FN) events. FN rates for each variable were calculated using FN events in the numerator and the number of patients with positive SLNs in the denominator. Univariate logistic regression was used to assess the relationship between covariates of interest and the probability of having a FN event. P values were considered significant at the 5% level. Multivariate models were fit using all covariates that were statistically significant on univariate analysis as well as covariates felt to be of clinical significance. No model selection was performed and no statistical adjustment was made for the multiplicity of testing. The association between covariates of interest and neoadjuvant treatment category was assessed using Fisher’s exact test.

Results

A total of 681 patients who were clinically node negative and who underwent SLND with intraoperative frozen section analysis of their SLN(s) were identified. Of these, 262 (38%) received neoadjuvant therapy; the majority (n=247, 94%) received chemotherapy with or without endocrine therapy, while 15 (15, 6%) received endocrine therapy alone. Clinicopathologic characteristics of patients who did or did not receive neoadjuvant therapy are shown in Table 1.

The median number of SLNs retrieved per patient was 3. One hundred eighty-three patients (27%) had at least one positive SLN on final pathology. The rate of SLN positivity was 22% and 30% ($p=0.02$) for the neoadjuvant therapy and no-neoadjuvant therapy groups, respectively. The diameter of the largest SLN metastasis was a macrometastasis in 66% (121/183) of patients and a micrometastasis in 34% (62/183). There were 60 patients with FN intraoperative assessments, yielding a FN rate of 33%. There were no false positive events. On univariate analysis, four variables were significantly associated with FN events: favorable histology, lobular histology, absence of LVI, and micrometastases. Patients whose tumors demonstrated favorable (OR=3.32, $p=0.005$) or invasive lobular (OR=4.8, $p=0.001$) phenotypes were more likely to have FN intraoperative SLN assessments compared to those with invasive ductal carcinoma. Larger SLN metastasis size was associated with a lower FN rate (OR per mm=0.71, $p<0.0001$), and SLNs containing a micrometastasis were associated with a higher FN rate (OR=8.44, $p<0.0001$) than SLNs containing a macrometastasis. Tumors with LVI (OR=0.37, $p=0.006$) were significantly less likely to be associated with a FN intraoperative assessment. There was no significant difference in FN rate between those patients who received neoadjuvant therapy versus those who did not (OR=1.82, $p=0.07$) (Table 2).

Factors significantly associated with FN events on univariate analysis as well as estrogen receptor status, triple negative receptor status, receipt of neoadjuvant therapy, multifocality and primary tumor size were included in a multivariate regression analysis. Favorable (OR=4.39, $p=0.02$) and lobular (OR=6.15, $p=0.006$) histology as well as micrometastasis (OR=7.29, $p<0.0001$) were independently associated with a higher FN rate (Table 3). Neoadjuvant treatment was not significant on multivariate analysis. Univariate (data not shown) and multivariate analyses (Table 4) of patient, disease and treatment-related variables among patients who received neoadjuvant therapy and had a FN intraoperative assessment were performed. The presence of micrometastasis was the only independent predictor of FN events among this subset (OR=7.87, $p=0.008$).

There were 18 patients with isolated tumor cell clusters (ITCs) in our cohort, and all were considered node-negative in the data analysis described above. Eleven of the 18 patients received neoadjuvant chemotherapy and 7 of them did not. Only one of the patients with ITCs had a FN intraoperative result, and this patient had not received neoadjuvant chemotherapy. Inclusion of the N0(i+) patients in the SLN positive group did not significantly impact results of the data analysis. Progesterone receptor-positive status became a predictor for FN result due to a change in p value from 0.07 to 0.05. Otherwise, there was no change in the predictive variables (Table 5).

Discussion

In this study, we have shown a 33% FN rate for intraoperative SLN evaluation. This is consistent with the 25–42% rate published elsewhere in the literature(5–7, 10). Analysis of clinicopathologic variables impacting the accuracy of intraoperative SLN assessment identified three factors that are independently associated with FN events: favorable histology, lobular histology and micrometastasis. The presence of LVI was associated with a lower FN event rate on univariate analysis, but this association did not persist on multivariate analysis.

Though the OR for a FN event after neoadjuvant therapy (OR= 1.8) is suggestive of an association, this factor did not reach statistical significance on either univariate or multivariate analysis. In other single-institution reports, accuracy rates for intraoperative SLN assessment after neoadjuvant therapy range from 72–100% and sensitivity ranges from 38–100%(11–14). The largest of these series by Gimbergues *et al*, prospectively evaluated the accuracy of intraoperative touch imprint cytology after neoadjuvant therapy in 80 patients who underwent SLND(15). In both our study and that by Gimbergues and colleagues, the sensitivity rate after neoadjuvant therapy was lower than that seen in patients who did not receive preoperative treatment, but this did not reach statistical significance.

Previous studies evaluating histologic findings after neoadjuvant therapy have shown chemotherapy-induced stromal and cellular changes such as fibrosis, histiocytic infiltrates, partial obliteration of tissue architecture, fat necrosis and cytoplasmic vacuolization of epithelial cells (16, 17). These histologic changes can make it challenging for pathologists to accurately identify metastatic deposits in lymph nodes on either frozen section or paraffin-embedded sections. Examples of the variable effects of neoadjuvant therapy on metastasis-containing SLNs are shown in Figure 1. Chemotherapy-induced histologic changes affect the nuclear and cytoplasmic features as well as the architecture of the tumor. The nuclear changes include enlargement of the nuclei with irregular borders, multinucleation and vesiculation of the chromatin. On the other hand, the nuclear features can have a lower nuclear grade than the original tumor, resulting in a low nuclear to cytoplasmic ratio and mimicking benign breast epithelium. These heterogeneous changes can occur within the same tumor and within the same field. The cytoplasm can be abundant, vacuolated and can have an eosinophilic or bluish gray tinge. The cytoplasmic changes are rather nonspecific as these can be seen in lobular carcinoma as well as in histiocytes in areas of fat necrosis and repair. The architecture is also affected by neoadjuvant chemotherapy and the residual tumor can present as isolated tumor cells, tumor clusters and even minute well defined glands with bland nuclei. When the pathologic response is good, the residual tumor can be sparse and difficult to identify.

Overall, the presence of micrometastases was associated with a greater than 8-fold higher FN rate on univariate analysis, a finding which persisted on multivariate analysis. Of the SLN-positive patients in our series, 39% in the neoadjuvant therapy group had micrometastases versus 32% in the no-neoadjuvant therapy group. When we looked specifically at the neoadjuvant therapy group, we performed a subset analysis to identify factors associated with FN events and only SLN metastasis size was found to be a significant

predictor. Other series showing lower sensitivity of both frozen section and touch imprint cytology for micrometastases in the non-neoadjuvant treatment population further support this(7, 10).

In so far as disease-related variables are concerned (favorable histology, lobular histology, micrometastasis), a higher index of suspicion by the pathologist may improve accuracy of intraoperative frozen section evaluation in these cases. The addition of intraoperative rapid cytokeratin analysis or closer interval sectioning of the SLN may also improve accuracy, but could result in unacceptable intraoperative delays.

Of the 681 patients in the overall study population, 60 (8.8%) had a FN intraoperative SLN assessment. For patients receiving NCT, 9% (24/262) had a FN intraoperative result. Considering the data in this way may be helpful for counseling patients preoperatively about their chances of needing a second operation for completion axillary dissection or for potentially being considered for post-mastectomy radiotherapy after immediate breast reconstruction. The association between neoadjuvant chemotherapy and FN rate did not reach statistical significance, and no preoperative variables were identified within the subset of NCT patients that could be used to identify those at increased risk for a FN assessment. Our data suggest that for clinically node negative patients receiving neoadjuvant chemotherapy, the accuracy of intraoperative assessment of the SLNs is not inferior to that seen in patients who are chemo-naïve.

One limitation of this study is that we did not include patients who present with node positive disease, a group for whom traditionally ALND has been routinely performed. Several recent and ongoing studies are exploring the role for more limited axillary surgery for staging these patients. The ACOSOG Z1071 study demonstrated that SLND could be performed in patients with clinically node positive breast cancer after neoadjuvant chemotherapy with an acceptable false negative rate when performed with proper technique(18). In addition, targeted axillary dissection has been proposed as a novel approach to accurately stage patients with node positive disease after neoadjuvant chemotherapy(19). Building on these results, two additional cooperative group trials are underway to examine whether additional axillary treatment is warranted for clinically node positive patients after neoadjuvant chemotherapy and sentinel lymph node biopsy. In the NSABP B-51/RTOG 1304 trial, patients who convert to a negative SLN are randomized to receive radiotherapy or no radiotherapy to the axilla (20). In the Alliance A11202 trial, patients with persistent SLN metastases are randomized to either CLND or no CLND but with nodal radiotherapy for all patients (21). Randomization for CLND may be based on either final pathology or intraoperative assessment of the SLN. These studies illustrate the recent trend towards minimizing axillary surgery for node-positive patients treated with neoadjuvant therapy. For these patients, immediate assessment of the SLN will be an essential tool for intraoperative decision making and is the focus of a future study.

Acknowledgments

This work was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant [CA016672].

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Figure 1.

Photomicrographs of lymph nodes containing breast cancer metastases. A large metastatic focus of invasive ductal carcinoma may be readily detected on routine H&E staining, shown at 4 $\times$ (A) and 20 $\times$ (B) magnification. Neoadjuvant chemotherapy may decrease the size of the metastasis and cause histopathologic changes that make assessment more challenging. Nests of invasive ductal carcinoma after treatment, demonstrated on H&E staining at 20 $\times$ magnification (C), may be more apparent with immunostaining for cytokeratin (D). The tumor cells of metastatic lobular carcinoma have abundant cytoplasm and bland nuclear features. Detection of a small subcapsular focus of invasive lobular carcinoma (E, arrow) may be aided by immunostaining for cytokeratin (F).

Clinicopathologic variables for the entire cohort, neoadjuvant therapy and no-neoadjuvant therapy groups.

Table 1

Variable	Entire Cohort n=681 (%)	Neoadjuvant Therapy n=262 (%)	No Neoadjuvant therapy n=419 (%)	p value
Age, years	average	55	55	0.12
	range	23–90	27–83	
Histology	IDC	417 (61)	110 (42)	307 (73)
	Favorable	125 (18)	101 (39)	24 (6)
	IDC/ILC	60 (9)	26 (10)	34 (8)
	ILC	66 (10)	20 (8)	46 (11)
	Other	13 (2)	5 (2)	8 (2)
Grade	1	89 (13)	36 (14)	53 (13)
	2	322 (47)	107 (41)	215 (51)
	3	259 (38)	110 (42)	149 (36)
	Unknown	11 (2)	9 (3)	2 (0)
				NS
ER	Negative	154 (23)	67 (26)	87 (21)
	Positive	519 (76)	193 (74)	326 (78)
	Unknown	8 (1)	2 (1)	6 (1)
PR	Negative	256 (38)	109 (42)	147 (35)
	Positive	417 (61)	151 (58)	266 (63)
	Unknown	8 (1)	0 (0)	8 (2)
				NS
HER2	Negative	564 (83)	212 (81)	352 (84)
	Positive	96 (14)	39 (15)	57 (14)
	Unknown	21 (3)	11 (4)	3 (1)
Triple Negative	No	553 (81)	208 (79)	345 (82)
	Yes	106 (16)	43 (16)	63 (15)
	Unknown	22 (3)	11 (4)	11 (3)
				NS
LVI	No	501 (74)	204 (78)	297 (71)
	Yes	139 (20)	51 (19)	88 (21)
	Unknown	41 (6)	7 (3)	34 (8)
Multifocal	No	557 (82)	203 (77)	354 (84)
				0.02

Variable	Entire Cohort n=681 (%)	Neoadjuvant Therapy n=262 (%)	No Neoadjuvant therapy n=419 (%)	p value
	Yes	59 (23)	65 (16)	
Surgery	BCT	352 (52)	116 (44)	0.003
	Mastectomy	329 (48)	146 (56)	
#SLNs Retrieved	1	149 (22)	55 (21)	94 (22)
	2	176 (26)	75 (29)	101 (24)
	>2	356 (52)	132 (50)	224 (53)
	Average	2.4	3.02	2.04
Primary Tumor Size(cm)	Range	0.1–14	0.1–14	0.1–13
	Micromet	62 (9)	22 (8)	40 (10)
SLN Metastasis Size	Macromet	121 (18)	35 (13)	86 (21)
	Average(mm)	4.8	4.5	5.0
	Range	0.2–40	0.2–25	0.2–40
				NS
<0.0001				

Univariate analysis of factors associated with false negative results of intraoperative SLN assessment.

Table 2

Variable		Pos SLN n=183	# FN	OR	p value
Histology	IDC	108	25	----	----
	Favorable	30	15	3.32	0.005
	IDC/ILC	18	5	1.28	NS
	ILC	22	13	4.80	0.001
Grade	Other	5	2	2.21	NS
	1	23	9	----	----
	2	94	35	0.92	NS
	3	65	15	0.47	NS
	Unknown	1	1	----	----
ER	Negative	28	6	----	----
	Positive	153	53	1.94	NS
	Unknown	2	1	----	----
PR	Negative	56	13	----	----
	Positive	125	46	1.93	NS
	Unknown	2	1	----	----
HER2	Negative	150	52	----	----
	Positive	29	5	0.39	NS
	Unknown	4	3	----	----
Triple Negative	No	161	54	---	---
	Yes	18	3	0.40	NS
	Unknown	4	3	----	----
LVI	No	107	44	----	----
	Yes	68	14	0.37	0.006
	Unknown	8	2	----	----
Noadjuvant Treatment	No	126	36	----	----
	Yes	57	24	1.82	NS
Multifocal	No	133	45	----	----

Variable	Pos SLN n=183	# FN	OR	p value
	Yes	15	0.84	NS
Surgery	BCT	31	-----	-----
	Mastectomy	102	0.64	NS
#SLNs Retrieved	1	32	12	-----
	2	47	18	1.03
	>2	104	30	0.68
	per SLN	183	60	0.92
				NS
Primary Tumor Size	per cm	183	60	0.98
				NS
	per mm	183	60	0.71
SLN Metastasis Size				<0.0001
	Micromet	62	39	8.44
	Macromet	121	21	-----

Table 3

Multivariate analysis of factors associated with false negative results of intraoperative SLN assessment.

Variable		OR	95% CI	p value
Histology	IDC	----	----	----
	Favorable	4.39	1.23, 15.8	0.02
	IDC/ILC	1.82	0.46, 7.16	NS
	ILC	6.15	1.68, 22.5	0.006
	Other	4.63	0.30, 71.2	NS
ER	Negative	----	----	----
	Positive	0.80	0.17, 3.79	NS
Triple Negative	No	----	----	----
	Yes	0.50	0.07, 3.73	NS
LVI	No	----	----	----
	Yes	0.59	0.26, 1.35	NS
Neoadjuvant Treatment	No	----	----	----
	Yes	0.67	0.23, 1.92	NS
Multifocal	No	----	----	----
	Yes	0.85	0.34, 2.08	NS
Primary Tumor Size (per cm)	per cm	0.94	0.75, 1.17	NS
SLN Metastasis Size	Macromet	----	----	----
	Micromet	7.29	3.26, 16.28	<0.0001

Multivariate analysis of factors associated with false negative intraoperative SLN assessment in patients who received neoadjuvant therapy.

Table 4

Variable		# FN n= 24	OR	95% CI	p value
Histology	IDC	4			
	Favorable	12	2.19	0.43, 11.17	NS
	IDC/ILC	2	1.3	0.14, 12.05	NS
	ILC	5	4.07	0.4, 42	NS
	Other	1	3.19	0.06, 180	NS
LVI	No	20			
	Yes	4	0.4	0.09, 1.85	NS
	No	17			
Multifocal	Yes	7	1.65	0.34, 8.05	NS
	per cm	24	0.99	0.74, 1.32	NS
SLN Metastasis Size	Macromet	8			
	Micromet	16	7.87	1.71, 36.25	0.008

Univariate analysis of factors associated with false negative results of intraoperative SLN assessment when SLNs containing ITCs are considered positive lymph nodes

Table 5

Variable	Pos SLN n=201	# FN n=61	OR	P-value
Histology	IDC	26		***
	Favorable	15	2.60	0.02
	IDC/ILC	5	1.02	NS
	ILC	13	4.50	0.002
Grade	Other	2	2.31	NS
	1	24	9	***
	2	102	35	0.87 NS
	3	74	16	0.46 NS
	Unknown	1	**	**
ER	Negative	33	6	***
	Positive	166	54	2.17 NS
	Unknown	2	1	**
PR	Negative	63	13	***
	Positive	136	47	2.03 0.05
	Unknown	2	1	**
HER2	Negative	164	53	***
	Positive	32	5	0.39 NS
	Unknown	5	3	**
Triple Negative	No	175	55	***
	Yes	21	3	0.36 NS
	Unknown	5	3	**
LVI	No	122	45	***
	Yes	71	14	0.42 0.01
	Unknown	8	2	**
Neoadjuvant Treatment	None	133	37	***
	Received	68	24	1.42 NS

Variable	Pos SLN n=201	# FN n=61	OR	P-value
Multifocal	No	46		----
	Yes	57	0.76	NS
Surgery	BCT	31		-----
	MX	113	0.66	NS
# of SLNs Retrieved	Per SLN found	201	0.93	NS
Primary Tumor Size	Per cm	201	0.98	NS
SLN Max Met Size	Per unit	184	0.70	<0.0001