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Internal Mammary Lymph Node Biopsy During Free-Flap Breast Reconstruction: Optimizing Adjuvant Breast Cancer Treatment Through Comprehensive Staging

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ABSTRACT

Background. Accurate breast cancer staging is essential for optimal management of adjuvant therapies. While breast lymphatic drainage involves both axillary and internal mammary (IM) lymph node (LN) basins, IM LN sampling is not routinely advocated. The current study analyzes the incidence of IM LN metastases sampled during free flap breast reconstruction and subsequent changes in adjuvant treatment.

Methods. A retrospective analysis of patients with positive IM LN biopsies during free flap breast reconstruction was performed. Pre-reconstruction surgical and adjuvant therapies as well as staging and prognostic data were recorded. Change in adjuvant therapies based solely on IM LN positivity was determined.

Results. IM LN metastases were found on 28 (1.3%) out of 2057 patients and comprised the study population. Mean age was 49 years with pre-reconstruction chemotherapy or radiation administered in 50 or 54% of cases, respectively. Five (18%) patients had previously undergone lumpectomy with axillary sampling. Mean tumor size was 3.1 cm with tumor location evenly distributed among all four quadrants. Ten (36%) patients had *isolated* IM LN metastases Patients with both axillary and IM disease had larger lesions, increased prevalence of pre-reconstruction chemotherapy and radiation. Based exclusively on positive IM LN disease, 17 (63%) patients had a change in adjuvant therapy.

Conclusion. Despite the low incidence of IM LN metastases, IM LN biopsy during free flap breast reconstruction is recommended. In 36% of cases, nodal metastases were isolated to the IM nodes. Identification of IM metastases influenced adjuvant therapies in a majority of cases.

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The clinical value of internal mammary (IM) lymph node (LN) biopsy for breast cancer patients remains controversial. Although the American Joint Committee on Cancer (AJCC) staging guidelines include both axillary and IM lymph nodes, lymphatic staging is limited to the axillary LN basins during routine surgical staging.[1–4] In fact, the IM LN chain, the second most common site for breast cancer node metastasis, is responsible for up to 30% of breast lymphatic drainage.[3,5,6]

Breast cancer metastasis to the IM LN basin represents significantly advanced disease and is associated with a worse prognosis than that for patients with only axillary LN involvement.[7,8] The factors limiting routine IM LN biopsy as part of breast cancer staging are (1) morbidity of IM LN access during routine extirpative procedures,[6] (2) the perception that lymphatic spread of breast cancer occurs in a stepwise fashion, with axillary LN metastases invariably preceding IM node involvement,[9] (3) historic data refuting the clinical benefit of IM LN dissection,[10] and (4) the perception that the presence of IM LN metastasis rarely alters adjuvant therapy.[11,12]

During free-flap breast reconstruction, the IM LN chain is routinely exposed as part of the recipient vessel dissection before pedicle anastomosis. In this setting, biopsy of IM LN can be performed easily under direct visualization without added morbidity. In our practice, IM LN biopsy is performed routinely for all breast cancer patients

undergoing free-flap breast reconstruction that uses the internal mammary vessels for anastomosis.

The current study aimed to determine the prevalence of IM LN metastases and to characterize the prognostic value of routine IM LN sampling for breast cancer patients undergoing free-flap breast reconstruction.

METHODS

After institutional review board (UT Health, San Antonio, TX, USA) approval, a retrospective review analyzed 2057 consecutive patients who underwent free-flap breast reconstruction in a delayed or immediate setting for breast cancer from September 2008 to December 2015. Patients without clinically positive axillary LN involvement underwent routine axillary sentinel LN biopsy with mapping of the lymphatic pathway using periareolar injection of technetium Tc 99 m-sulfur colloid before mastectomy. Preoperative imaging documenting the location of radioactivity uptake, whether in the axilla or elsewhere, was obtained at the discretion of the oncologic surgeon.

After mastectomy, IM LN biopsy was performed routinely for all patients who underwent free-flap breast reconstruction that used the internal mammary vessels for pedicle anastomosis. Patients with positive IM LN biopsies for metastatic disease comprised the study population ($n = 28$). Patients with negative IM LN biopsies were not included in the analysis. Patients undergoing reconstruction after prophylactic mastectomy and reconstruction in which internal mammary vessels were not exposed (thoracodorsal vessels used for anastomosis) were excluded from the study.

Incidence of pre-reconstruction adjuvant therapies, history of lumpectomy with axillary LN sampling, preoperative magnetic resonance imaging (MRI), and location of primary malignancies were recorded. Tumor size, axillary LN status, number of IM lymph nodes included in the biopsy specimen, and size of metastatic IM LN foci as well as prognostic factors for both the primary tumor and internal mammary nodal metastasis were obtained from final pathologic reports. Post-reconstruction alteration in adjuvant therapies (chemotherapy or external beam radiation) based solely on IM LN positivity was determined by multidisciplinary breast cancer committees and recorded appropriately. Medical oncologists were not specifically asked to describe the chemotherapy regimen planned before IM LN biopsy or the algorithm used to determine treatment recommendations.

Descriptive statistics were expressed as mean ± standard deviation or median (range), as appropriate, for continuous variables, and counts with percentages were reported for categorical variables. Patients with both positive axillary and IM nodal disease were compared with patients who had isolated IM node metastasis using Fisher's exact test for categorical variables and the Mann–Whitney test for continuously distributed outcomes. The significance of variation in prevalence in primary lesion location and genomic profile was assessed with Fisher's exact test. A one-way Chi square test for equal proportions was used to assess prevalence differences in primary lesion location and genomic profile. Correlations between proliferative rates of breast lesion and internal mammary node were assessed using the Spearman correlation coefficient. The significance of the association between previous lumpectomy and breast conservation surgery/axillary sampling status was assessed using logistic regression. All statistical testing was two-sided, with a significance level of 5% and SAS Version 9.4 (SAS Institute, Cary, NC, USA) used throughout.

RESULTS

Among 2057 consecutive patients who underwent IM LN biopsy during free-flap breast reconstruction, 28 (1.3%) were found to have IM LN metastasis. Internal mammary LN metastatic foci were classified as macroscopic ($\geq$ 2 mm) in 19 patients (67.9%), whereas the remainder (in 9 patients, 32.1%) were microscopic ($<$ 2 mm). The mean number of IM lymph nodes resected during biopsy was 2 (range 1–6).

The mean age of the patients with positive IM metastasis was 49 years (range 35–69 years) (Table 1). Pre-reconstruction chemotherapy was administered to 14 patients (50%) and external beam radiation to 15 patients (53.6%). Five of the patients (17.9%) who received pre-reconstruction radiation had previously undergone breast conservation therapy with axillary sampling before completion mastectomy and free-flap reconstruction for breast cancer recurrence.

Internal mammary LN metastases were discovered in 13 patients (46.4%) who underwent reconstruction in the immediate setting and in 15 patients (53.6%) after delayed reconstruction. None of the patients who underwent mastectomy and immediate reconstruction received neoadjuvant chemotherapy.

Before mastectomy, three patients (10.7%) in the study population underwent formal lymphoscinitigraphy, with imaging as part of sentinel LN biopsy. In the three patients who underwent lymphoscinitigraphy, radioactivity was limited to the axillary LN basins without localization to the IM LN chain. Of the 28 patients found to have IM LN metastasis, 18 (64.3%) had preoperative breast MRI as part of their workup. Of these 18 patients with preoperative MRI, 2 had radiologic findings suggestive of IM LN metastasis before biopsy (sensitivity, 11%).

TABLE 1 Patient demographics and pathologic staging ($n = 28$)

Variable	Mean (SD)	*n* (%)
Age	49 (8.1)	
Pre-reconstruction		
Radiation		15 (53.6)
Chemotherapy		14 (50)
Lumpectomy/Axillary sampling		5 (17.9)
Pre-operative MRI		18 (64.3)
Immediate reconstruction		13 (46.4)
Delayed reconstruction		15 (53.6)
Primary lesion		
Invasive ductal carcinoma		23 (82.1)
Invasive lobular carcinoma		7 (25)
Tumor stage		
1 (a–c)		7 (25.9)
2		9 (33.3)
3		11 (40.7)
Nuclear grade		
1		4 (14.8)
2		14 (51.9)
3		9 (33.3)
Lymphovascular invasion		8 (30.8)
Nodal stage		
1b		10 (35.7)
1c		11 (39.2)
3b		7 (25)

TABLE 2 Microscopic/macroscopic IM lymph node metastasis ($N = 28$) primary lesion location

Primary lesion	N (%)	*p*
Location		0.51
Upper outer quadrant	9 (32.1)	
Lower inner quadrant	6 (21.4)	
Lower outer quadrant	5 (17.9)	
Upper inner quadrant	3 (10.7)	
Multicentric	5 (17.9)	

The primary histology of breast malignancies was most commonly invasive ductal carcinoma (82.1%) at the final pathology (Table 1). The mean breast tumor size was 3.8 cm (range, 0.4–10 cm). Primary tumor stage classification, nuclear grade, presence of lymphovascular invasion, and final pathologic nodal stage are additionally presented in Table 1. No significant differences between multicentric and individual breast quadrant locations were found ($p = 0.51$; Table 2).

Comparison of receptor status and proliferative index (Ki-67) between primary breast lesions and IM node metastases was performed (Table 3). A strong association between the primary breast lesion and IM node receptor status was observed (all $p \leq 0.01$), and the Spearman correlation coefficient for proliferative index rates (Ki-67) was 0.71 ($p < 0.01$).

Internal mammary LN metastases were identified in 10 patients (35.7%) previously classified as pN0 before delayed reconstruction or found to have negative axillary staging at the time of mastectomy and immediate reconstruction. Patients with both positive axillary and internal mammary nodal disease ($n = 17$) were compared with patients who had isolated internal mammary node metastasis ($n = 10$) (Table 4). The patients with both axillary and internal mammary disease had larger lesions (4.4 vs. 2.5 cm; $p = 0.04$), increased prevalence of pre-reconstruction chemotherapy (65% vs. 20%; $p = 0.05$), and radiation (71% vs. 20%; $p = 0.02$). Multivariate logistic modelling did not identify any significant independent factors associated with isolated IM LN metastases. A numerically greater prevalence of previous lumpectomy and axillary node sampling (odds ratio [OR], 3.2; 95% confidence interval [CI], 0.4–23.8) was observed among the patients with isolated IM LN metastases. Based exclusively on the diagnosis of positive IM LN metastases, 17 patients (63%) had a change in their adjuvant therapy (additional chemotherapy or IM radiation therapy) after reconstruction (Table 5).

DISCUSSION

Accurate staging of patients with breast cancer is a critical component of comprehensive and effective multidisciplinary treatment.[13,14] Although the AJCC staging guidelines include both axillary and IM node basins,[13] the benefit of IM LN biopsy as a component of routine surgical staging is debated.[8,11,15–17] Various factors have been cited to support omitting routine surgical biopsy of IM lymph nodes. Among these factors is the low prevalence IM LN metastases reported in previous studies.[18–23] In addition, increased surgical morbidity traditionally associated with IM LN exposure [6] coupled with the perceived notion that IM LN metastases, if present, do not generally alter adjuvant treatment [11,12] has effectively deterred routine biopsy of IM lymph nodes.

In support of IM LN biopsy, previous studies have suggested that isolated IM LN metastasis imparts a prognosis similar to that for isolated axillary LN disease.[24] In addition, although patients with both axillary and IM nodal diseases have historically experienced a worse prognosis than patients with isolated axillary nodal

TABLE 3 Prognostic factors of primary lesion and IM lymph node ($n = 28$)

Prognostic factors	*n* (%)	Mean (SD)
Primary lesion		
Estrogen receptor (+)	20 (71.4)	
Progesterone receptor (+)	15 (55.6)	
Her-2 neu (+)	7 (28)	
Ki-67		43.8 (32.3)
IM lymph node		
Estrogen receptor (+)	17 (81)	
Progesterone receptor (+)	7 (33.3)	
Her-2 neu (+)	4 (19)	
Ki-67		22 (24.6)

IM internal mammary

metastasis,[10,14,25,26] recent studies have reported improved outcomes for patients with both axillary and IM nodal disease who received more contemporary adjuvant regimens.[11,24,27] These recent studies support the practical benefit of accurate upstaging based on positive IM LN biopsy and more appropriate adjuvant treatment.

TABLE 4 Clinical characteristics by in axillary + IM node mets and IM node mets only

Clinical characteristic	Axillary + IM node mets ($n = 17$)	IM node mets only ($n = 10$)	*p*
Age, mean (SD)	50.6 (7.3)	47.6 (8.4)	0.22
Pre-recon chemotherapy *n* (%)	11 (64.7)	2 (20)	0.05
Pre-recon radiation	12 (70.6)	2 (20)	0.02
BCS/axillary sampling	2 (11.8)	3 (30)	0.33
Lesion			
Invasive ductal carcinoma	15 (88.2)	7 (70)	0.33
Invasive lobular carcinoma	3 (17.6)	3 (30)	0.64
Lesion size, mean (SD)	4.4 (2.7)	2.5 (1.3)	0.04
Tumor stage			0.03
1 (a–c)	2 (12.5)	5 (50)	
2	5 (31.3)	4 (40)	
3	9 (56.3)	1 (10)	
Nuclear grade			
1	2 (12.5)	1 (10)	
2	8 (50)	6 (60)	
3	6 (37.5)	3 (30)	
Lymphovascular invasion	7 (43.8)	1 (10)	0.18
Location of primary lesion			
Upper outer quadrant	6 (35.3)	2 (20)	0.67
Upper inner quadrant	1 (5.9)	2 (20)	0.54
Lower outer quadrant	3 (17.6)	2 (20)	1
Lower inner quadrant	3 (17.6)	3 (30)	0.64
Multicentric	4 (23.5)	1 (10)	0.62

BCS breast conservation surgery

Routine biopsy of IM lymph nodes during extirpative procedures has been associated with increased morbidity.[6] During free-flap breast reconstruction after mastectomy, however, IM LN biopsy can be easily and safely performed under direct visualization without increased operative time or added morbidity. This is made possible due to the wide exposure of the internal mammary vessels required for free-flap pedicle anastomosis. The internal mammary vessels are routinely exposed by partial medial (3rd or 4th) rib resection in the parasternal area. After resection of the perichondrium and limited adjacent intercostal musculature, wide exposure of the IM LN is simultaneously achieved under direct visualization, enabling excisional biopsy of all lymphatic tissue and more accurate lymphatic staging. This biopsy, however, is not guided by any imaging, such as lymphoscintigraphy, but rather by the optimal location for free-flap vessel anastomosis. Thus, clinically occult nodes may reside above or below the exposed area. Coincidentally, nonetheless, previous studies have reported that the IM lymph nodes at the third and fourth intercostal spaces are the most common sites of breast lymphatic drainage and IM LN metastasis.[28,29] In this setting, if exposure of the internal mammary vessels is required for free-flap breast reconstruction at the most common level of LN metastasis, a biopsy of any lymph nodes encountered can be performed without detriment and can only increase staging accuracy. This is in direct contrast to alloplastic reconstruction or alternative autologous methods, such as pedicled latissimus dorsi or pedicled transverse rectus abdominus myocutaneous (TRAM) flap reconstruction, in which the internal mammary vessels are not exposed.

Previous studies have reported possible risk factors for IM nodal involvement including larger lesions, medial tumor location, and axillary metastases.[30,31] The current study findings, however, suggest that IM LN metastases are associated with high primary breast lesion variability regarding location and size. Whereas previous studies have reported a higher prevalence of IM LN metastases from lesions located in the medial half of the breast,[31] our data suggest that IM LN metastases may originate from breast lesions located in each of the four breast quadrants with similar prevalence (Table 2). Similarly, although primary breast lesion size is a recognized predictor of axillary LN involvement, we found that IM LN metastases are associated with a wide range of primary breast lesion sizes (0.4–10 cm). Indeed, similar distributions of patients within each T stage classification were found to have IM LN metastases (Table 1).

TABLE 5 Patients with change in adjuvant therapy based exclusively on IM node positivity

Patient	Age	Malig side	Chemo	XRT	Prev lump/ Ax Sampl	Timing of recon	Primary lesion	Lesion size (cm)	Grade	Number positive axillary nodes	Estrogen receptor	Progest receptor	Her-2 ampl	Ki-67 index	Genomic profile	Alteration in therapy
Isolated internal mammary nodes																
1	45	R	no	no	no	Immediate	IDC	3.1	2	0	Pos	Neg	Neg	13	A	Chemotherapy change
2	37	L	yes	yes	yes	Immediate	IDC	1.5	3	0	Neg	Neg	Neg	19	T	IM XRT
3	47	R	no	no	yes	Immediate	IDC	3.5	3	0	Neg	Neg	Pos	52	H	IM XRT
4	48	L	no	no	no	Immediate	ILC	2.0	2	0	Pos	Pos	Neg	43	B	Chemotherapy change
5	46	L	yes	no	no	Delayed	IDC	1.3	1	0	Pos	Pos	Neg	6	A	IM XRT
6	41	L	no	no	no	Immediate	IDC	2.9	3	0	Neg	Neg	Pos	61	H	Chemotherapy change/IM XRT
7	54	R	no	no	no	Delayed	IDC	1.5	2	0	Pos	Neg	Neg	65	B	IM XRT
8	68	R	no	yes	yes	Immediate	ILC	1.7	2	0	Pos	Pos	Neg	33	B	IM XRT
Limited axillary lymph node disease (N1)																
9	54	L	no	no	no	Immediate	IDC	3.0	3	1	Neg	Neg	Pos	89	H	Chemotherapy change
10	55	R	no	yes	yes	Immediate	IDC	0.4	2	1	Pos	Pos	Neg	47	B	Chemotherapy change
11	48	R	yes	yes	yes	Delayed	IDC			1	Pos	Pos	Neg	11	A	IM XRT
12	52	L	yes	yes	no	Delayed	IDC	0.6	3	2	Neg	Neg	Pos	99	H	Chemotherapy change
13	62	R	no	no	no	Immediate	IDC	3.8	3	1	Pos	Pos	Neg	32	B	IM XRT
14	50	L	no	no	no	Immediate	IDC	2.4	1	1	Pos	Pos	Neg	7	A	Chemotherapy change
Locally advanced disease by tumor size																
15	53	R	yes	yes	no	Delayed	IDC	9.5	2	8	Pos	Pos	Neg	2	A	IM XRT
16	41	L	yes	yes	no	Delayed	IDC	5.5	3	4	Neg	Neg	Neg	45	T	IM XRT
17	40	L	yes	yes	no	Delayed	IDC	6.0	2	6	Pos	Neg	Neg	23	B	IM XRT

Chemo chemotherapy, *XRT* radiation Therapy, *IDC* invasive ductal carcinoma, *ILC* invasive ductal carcinoma *A* luminal A, *B* luminal B, *H* herceptin over-expression, *T* triple negative

Of the 28 patients found to have IM LN metastases, 10 (37%) had no axillary LN involvement. Patients such as these, with isolated IM LN metastases, are a unique subgroup previously identified [3,4] without prior characterization. We compared the characteristics of patients with both axillary and IM LN metastases and the characteristics of those with isolated IM LN involvement. The patients with isolated IM LN involvement demonstrated a lower T stage as well as a lower incidence of pre-reconstruction chemotherapy and radiation than the patients with both axillary and IM LN metastases (Table 4).

Using multivariate analysis, the study did not identify statistically significant independent risk factors for isolated IM LN involvement. A numerically greater prevalence of previous breast-conservation surgery (OR, 3.2; 95% CI, 0.4–23.8)) among patients with isolated IM LN metastases is possibly explained by increased lymphatic flow toward internal mammary LN basins and away from axillary lymph nodes due to disturbance of axillary-directed lymphatic channels from previous axillary staging. Naturally, this theory is strictly speculation and requires further studies to determine its validity.

Consistent with previous reports,[2,20–23,32] the current study identified IM LN metastases in 1.3% of the patients, characterized by three unique subgroups: (1) patients with isolated IM LN involvement in the setting of mastectomy and immediate reconstruction, (2) patients with IM LN involvement and limited axillary disease (N1) in the setting of mastectomy and immediate reconstruction, and (3) patients with previous mastectomy found to have IM LN involvement at the time of delayed reconstruction. Table 5 further characterizes these unique subgroups and their respective changes in adjuvant therapy.

Findings of IM LN metastases led to a change in post-reconstruction adjuvant therapy for 17 patients (63%) in the current study. The most common alteration of adjuvant therapy for the patients in the current study was delivery of IM LN chain radiation. Other investigators [3,4,6,33,34] have reported a change in adjuvant therapy as high as 45% among patients based on the identification of IM LN metastases. Although the benefit of regional nodal radiation for patients with biopsy-proven IM LN metastases remains an area of active research, recent studies have reported improved disease-free survival and distant metastasis-free survival among patients receiving regional radiation therapy after mastectomy.[35]

One limitation of the current study was the lack of comparisons between patients with IM LN metastasis and those with negative IM LN biopsies. Had we been able to make this comparison, independent risk factors for IM LN metastases might have been identified and used in a clinical pathway to determine the appropriateness of IM LN biopsy for high-risk patients. Additionally, given the low prevalence of IM LN metastasis for the entire population (with or without axillary LN metastasis), overall and disease-free survival rates likely are not affected by routine IM LN biopsies. However, 63% of the 28 patients upstaged in our study had a change in their adjuvant therapy that otherwise would not have taken place. Certainly, these IM + patients have more aggressive baseline disease requiring more comprehensive treatment. For these patients, without stage-appropriate adjuvant therapy, there is little debate that overall and disease-free survival is affected. Despite these weaknesses, the current study data suggest that IM LN biopsy is reasonable for all patients regardless of tumor size, tumor location, or preoperative imaging results if internal mammary vessels require exposure as part of free-flap breast reconstruction.

CONCLUSIONS

The clinical significance and benefit of IM LN biopsy remains an area of continued investigation in breast cancer treatment. Advances in microsurgical breast reconstruction have inadvertently facilitated a more comprehensive evaluation of lymphatic staging through routine access to the IM LN chain. The current study findings encourage pathologic evaluation of IM lymph nodes for all patients undergoing free-flap breast reconstruction. Further research is required for better identification of risk factors for IM lymphatic spread with or without axillary LN involvement.

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