Published in final edited form as:

Breast J. 2020 February ; 26(2): 197–205. doi:10.1111/tbj.13636.

The Clinical Significance of Metastatic Breast Carcinoma to Intra-Mammary Lymph Node

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Abstract

The incidence of involved intramammary lymph node (intra-MLN) with breast carcinoma (BC) is rare. Its clinical significance and impact on the clinical decision-making is unclear. A total of 113 BC cases with at least one positive intra-MLN were collected from 11 academic institutions. The inclusion criteria were: subsequent axillary lymph node dissection, and the availability of information on T-stage, size of node metastasis, extranodal extension status, biomarkers status, and clinical follow up. Stage 4 cases and/or neoadjuvant treated patients were excluded. AJCC TN-stage was calculated twice, with and without intra-MLN. Five-year overall survival (OS) and relapse (local and/or distant) free survival (RFS) were calculated and correlated with the clinicopathologic variables. Excluding intra-MLN, TN-stage correlated with OS ($p=0.016$) but not with RFS ($p=0.19$). However, when intra-MLN was included, TN-stage correlated with both OS ($p<0.001$) and RFS ($p=0.016$). In the multivariate analysis, when intra-MLN was excluded, only radiation therapy (RT) correlated with RFS (HR=0.19, 95% CI 0.054 to 0.66, $p=0.009$). However, when intra-MLN was included in the TN-stage both RT (HR=0.13, 95% CI 0.04 to 0.45, $p=0.001$)

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None of authors have any conflict of interest

and TN-stage 3 (HR=8.92, 95% CI 1.47 to 54, p=0.017) correlated with RFS. Tumor multifocality was the only variable correlated with OS when the intra-MLN involvement was excluded. When intra-MLN was included, multifocality became insignificant but TN-stage 3 correlated with OS (HR=8.59, 95% CI 1.06 to 69.71, p=0.044). Positive intra-MLN is an independent factor in predicting both RFS and OS.

Keywords

intramammary; sentinel; lymph node; prognosis

INTRODUCTION:

Breast cancer (BC) stage is one of the decisive variables that dictate tumor behavior and treatment. Regional lymph nodes status is one of the three variables, besides tumor size and distant metastasis status, integrated into the American Joint Committee on Cancer (AJCC) staging for BC. The AJCC defines regional lymph nodes as axillary, internal mammary, supraclavicular and intramammary (intra-MLN). The intra-MLN is included in the N-stage (1).

Intra-MLN is defined as a lymph node located within the breast parenchyma or the axillary tail and should be surrounded by mammary tissue (2–5). The majority of them are identified incidentally by imaging or by pathologic examination (4, 6, 7). Although the incidence has been reported to be up to 48% (8), other studies have shown this to occur only rarely (9, 10). In one meta-analysis that included 18 studies, the overall incidence was about 1% (11). The incidence of ipsilateral BC metastasis in an intra-MLN is also variable. In the same meta-analysis, it was reported to occur in 27% of the cases that had intra-MLN (11).

There have been multiple studies that have attempted to define the clinical significance of positive intra-MLN (4–8, 10, 12). However, all of these studies compared the clinical outcome of patients with positive intra-MLN vs. negative intra-MLN.

The standard of care for a patient with positive sentinel lymph node (SLN) had been to proceed with ALND. However, at least seven randomized controlled clinical trials including the ACOSOG-Z11 have evaluated the value of ALND. The patients were randomized into two arms, one treated with ALND and the other with whole breast irradiation (without ALND). There was no statistical significant difference in the clinical outcomes for these two arms (13).

Recent trials recommended omitting ALND for patients who have small (<0.2-mm) or occult metastasis in the SLNs, as ALND has no clinically significant survival benefits (14, 15). However, it is unclear if the clinical outcomes would be affected by positive intra-MLN. Moreover, it is a challenge for the clinical multidisciplinary team how to manage a patient with positive intra-MLN with or without positive SLN, particularly when the SLN metastasis is small.

The purposes of this study were to better define the role of positive intra-MLN in BC prognosis and to investigate its role in the clinical decision making. Toward those goals, we collaborated among 11 academic institutions in order to collect adequate number of cases with positive intra-MLN.

METHODS:

Cases:

Each institution performed a system search for intra-MLN using specific keywords including “breast”, “cancer”, “carcinoma”, “lymph node”, “intramammary” and “intra-mammary” at various time frames. The Text Information Extraction System (TIES), which is natural language processing system, was used to retrieve cases from four institutions that are members of the TIES Cancer Research Network (TCRN) including Roswell Park Comprehensive Cancer Center, Buffalo, NY; Magee Women’s Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA; University of Pennsylvania, Philadelphia, PA; and Augusta University, Augusta, GA (16). Portable Document Format files of pathology reports from the Women Circle of Health Study were manually reviewed to retrieve candidate cases using key words (intramammary and intra-mammary). The contributing breast pathologists at their respective institutions performed similar retrieving methods using similar key words. These included Emory University, Atlanta, GA; University of California San Diego, San Diego, CA; Vanderbilt University Medical Center, Nashville, TN; Montefiore Medical Center, Bronx, NY; University of Texas Southwest, Dallas, TX; and Washington University, Saint Louis, MO.

The following clinical and pathologic information were abstracted, patient’s age, primary tumor histologic type (invasive carcinoma no special type, invasive lobular carcinoma, or other), tumor size, Nottingham grade, focality (uni- vs. multi-), lymphovascular invasion (LVI) (present vs. absent), biomarkers status [Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2], and variables related to intra-MLN and SLN, including the total number of excised lymph nodes, number of positive nodes, size of metastasis (mm), and extranodal extension (ENE) status (present vs. absent). The sequence of ALND procedure in relation to the primary surgical excision (concurrent vs. subsequent) was recorded. ALN positive was defined as at least one of the lymph nodes in the ALND was positive. When any of the variables were missing from the pathology report then the slides (when available) were reviewed by the breast pathologist at the respective institution. The node (intra-MLN, SLN, or ALN) was considered positive when the tumor metastases measured >0.2-mm. Extranodal extension was defined as tumor breaching the lymph node capsule extending to the surrounding soft tissue (1).

In the following four analyses, we included all the cases that had known status of axillary lymph node dissection (ALND) [with ALND (n=177), and without ALND (n=64)]. We evaluated the rate of patients who underwent ALND without SLN biopsy and correlated it with the status of ALN (positive vs. negative). In order to study the role of positive intra-MLN in the decision making to proceed with ALND, we correlated the status of SLN (positive vs. negative) with ALND (performed vs. not performed). In order to evaluate the risk of having positive ALN when positive intra-MLN was detected, we correlated the status

of SLN (positive vs. negative) and the status of ALN (positive vs. negative). Finally, we focused on cases that had negative SLN and correlated it with the status of ALN (positive vs. negative).

To investigate if ALND procedure is useful for patients with negative SLN and positive intra-MLN, we combined all cases that had negative SLN biopsy. Then, we divided them into two groups based on ALND (performed vs. not performed). We compared the clinical outcomes between these two groups.

To investigate the role of intra-MLN in disease staging, the following exclusion criteria were applied (in the following order): 1) No ALND or unknown ALND status; 2) neoadjuvant therapy; 3) stage 4 disease; 4) unknown tumor size/T-stage; 5) unknown node metastasis size unless one of the positive nodes (intra-MLN, SLN) was >2-mm (macrometastasis); 6) unknown tumor focality status; 7) unknown LVI status; or 8) unknown biomarkers status.

Staging with and without intra-MLN:

We followed the AJCC staging system to stage 113 BC patients, once when the intra-MLN was included in the total LN count and once when it was not (1). Two survival analyses were performed, 5-year overall survival (OS) and 5-year relapse (local and/or distant) free survival (RFS).

Statistical Analysis:

Univariate survival analysis was performed to investigate the association between survival and clinicopathologic variables by performing logrank tests. The significant variables in the univariate analysis were then included in the multivariate Cox regression model. Fisher exact test was used to compare categorical variables. All reported tests were conducted at a nominal significance level of 0.05. Statistical analysis was performed using R version 3.4.1 (<http://www.r-project.org>).

RESULTS:

The median and range of the rate of positive intra-MLN were 20.8% (3.7% to 32.5%) (Table 1). Among the cases with positive intra-MLN (n=267), 2 (0.7%) were mapped as SLN, 21 (7.9%) detected clinically and labeled by the surgeon as intra-MLN and 244 (91.4%) were identified by the pathologist during the gross examination or incidentally during the microscopic examination.

Overview of the relationship between intra-MLN, SLN and ALN:

We first included all the cases (n=267) in the analysis (Figure 1). There were 177 patients who received ALND, 150 (84.7%) concurrent to the removal of the tumor and 27 (15.3%) subsequently. Eleven of 27 (40.7%) patients who had subsequent ALND had no SLN biopsy. SLN biopsy was not performed in 101 (57.1%) patients, 79 (78.2%) of whom had positive ALN. There were 75 (42.4%) patients who had SLN biopsy, 31 (41.3%) of whom had positive ALN (p<0.0001). Eleven patients had neither SLN nor ALND.

There were a total of 129 patients who underwent SLN biopsy. ALND was performed on 76 (58.9%) patients, 14 (18.4%) of whom had negative SLN. ALND was not performed on 53 (41.1%) patients, 44 (83%) of whom had negative SLN. The difference between these groups was statistically significant ($p<0.0001$).

Among the patients who underwent ALND, there were a total of 75 patients who had SLN biopsy. There were 61 (81.3%) patients with positive SLN, 26 (42.6%) of whom had positive ALN. There were 14 (18.7%) patients with negative SLN, 5 (35.7%) of whom had positive ALN. There was no statistical significant difference among these groups. Among the 14 patients who had negative SLN, 5 (35.7%) had positive ALN.

The Role of Intra-MLN in Patients' Survival:

1. The role of ALND in patients with positive intra-MLN and negative

SLN: There were 12 of 46 (26.1%) patients with ALND and 34 (73.9%) without ALND. While 5 patients had local /distant relapse, 2 died from disease. Four of 5 patients who had local/distant relapse did not undergo ALND. However, the number of events was very small to calculate its statistical significance.

2. The Role of Intra-MLN in Disease Staging: A total of 113 cases met the above criteria and had all the required clinicopathologic variables. While 11 (9.7%) cases with positive intra-MLN were detected clinically (surgically removed and labeled as intra-MLN), 102 (90.3%) cases were identified during pathologic gross examination, or incidentally during the microscopic examination (Figure 2).

Excluding intra-MLN, there were 12 (10.6%) cases TN-stage 1, 56 (49.6%) TN-stage 2, and 45 (39.8%) TN-stage 3. Including intra-MLN, there were 3 (2.7%) cases TN-stage 1, 51 (45.1%) TN-stage 2, and 59 (52.2%) TN-stage 3. There were 8 (66.7%) TN-stage 1 cases upstaged to TN-stage 2, and 1 (8.3%) to TN-stage 3. There were 13 (23.2%) cases with TN-stage 2 upstaged to TN-stage 3.

Relapse Free Survival: There were 20 (17.7%) patients who developed disease relapse within 5-years. TN-stage did not correlate with RFS when intra-MLN was excluded from the TN-stage ($p=0.19$). However, when intra-MLN was included, TN-stage correlated with RFS with statistical significance ($p=0.016$) (Table 2) (Figures 3A and 3B). The following variables correlated with RFS with statistical significance, RT, TN-stage and ENE (Table 2) (Figures 3C and 3D).

When these significant variables (excluding intra-MLN) were included in the multivariate analysis, only RT correlated with RFS. However, when intra-MLN was included in the TN-stage, in addition to RT, TN-stage 3 became statistically significant (Table 3).

Overall Survival: Fifteen (13.3%) patients died within 5 years due to disease. Tumor multifocality correlated with OS with statistical significance ($p=0.008$). N-stage correlated with OS with statistical significance regardless whether the intra-MLN was included in the N-stage or not ($p<0.001$, each). However, including the intra-MLN in the TN-stage or ENE showed better separation between the categories (Table 2) (Figures 3E to 4H).

When the significant variables were included in the multivariate analysis, only multifocality correlated with OS with statistical significance. However, when intra-MLN was included in the TN-stage, multifocality became statistically insignificant but TN-stage 3 became statistically significant (Table 3).

DISCUSSION:

The AJCC staging system indicates that a positive intra-MLN should be counted in the N-stage (1). That is based on prior clinical studies where the clinical significance of cases with positive intra-MLN was compared with cases with negative intra-MLN (5, 6, 12). However, these studies did not investigate if the number of positive intra-MLN would have similar role in the staging like any positive lymph node detected in the axillary region.

In this study we were able to collect the largest group of cases with positive intra-MLN published to-date. About three quarters of TN-stage 1 disease and one quarter of TN-stage 2 disease were upstaged. We found that including intra-MLN in the staging system correlated with both OS and RFS, while excluding it showed no correlation. When we performed multivariate analyses, we found that a patient with TN-stage 3 disease (counting intra-MLN) had 8.92 times risk of developing local or distant recurrence and 8.59 times risk of dying due to disease than a patient with TN-stage 2.

Surgeons proceeded with ALND without doing SLN biopsy in 101 patients. There are two possibilities for not performing SLN biopsy, first, the patients clinically presented with locally advanced disease and ALND was planned beforehand. We found that 31 (30.7%) patients received neoadjuvant therapy and additional 36 (35.6%) were stage 3 or 4 without including intra-MLN in the staging. The second possibility is that SLN biopsy was not the standard of care at the time of surgery (17–19). However, we think that positive intra-MLN was at least in part driving the surgeon decision to go forward with the ALND. There were 32 (31.7%) patients treated with adjuvant therapy or received no therapy at all had TN-stage 1 or 2. Moreover, when we evaluated the timing of the ALND compared to the surgical excision of the tumor (concurrent vs. subsequent), we found that 11 of 101 (10.9%) patients with no SLN biopsy, and 3 of 14 (21.4%) patients with negative SLN subsequently underwent ALND. We conclude that there is non-uniform approach to how to manage a patient with positive intra-MLN in terms of proceeding with ALND.

There were 5 of 14 (35.7%) patients with negative SLN who underwent ALND and were found to have positive ALN. There were 44 patients who had negative SLN but did not undergo ALND. In the meta-analysis, the authors found that positive intra-MLN and intra-mammary SLN metastasis significantly predicted axillary LN involvement. That was based on the analysis of four possibilities (positive intra-MLN/positive ALN, positive intra-MLN/negative ALN, negative intra-MLN/positive ALN, and negative intra-MLN/negative ALN). The rates were 59.1%, 36.1%, 14.4%, and 18.5%, respectively. However, the status of the SLNs (performed or not performed, positive or negative) in these studies was unknown. Moreover, the higher rate of positive intra-MLN/positive ALN might be related to the fact that a good proportion of these patients might have already presented with locally advanced disease, as we outlined above in our group of patients. Nonetheless, they concluded that a

patient with positive intra-MLN should have ALND (11). We have shown that positive intra-MLN predicted positive ALN when SLN was negative in about one third of the patients. It is worth noting, however, that these studies have not taken into consideration the ACOSOG-Z11 clinical trial results (13). It is unclear if performing ALND on patients with negative SLN and positive intra-MLN would be beneficial. Although 4 of the 5 patients who had local/distant relapse did not undergo ALND, we could not perform statistical analysis due to the small number of cases. Therefore, it is not entirely clear if a patient with negative SLN and positive intra-MLN would require or benefit from ALND. However, our results may aid the surgeons in the decision making on a case by case basis.

We believe that intra-MLNs are integral part of the lymphatic network that drains breast carcinoma cells to the axillary lymph nodes. It has been suggested that the axilla receives most of the lymphatic flow from the breast, ranging from 75%, shown by autoradiographs of surgical specimens to 97%, demonstrated by post-radical mastectomy with radioactive colloidal gold uptake studies. The rest of the breast lymphatic flow (3% to 25%) is drained via the internal thoracic lymphatic route (20, 21). Since the majority of the intra-MLNs are located in the upper outer quadrant (22), they are most likely in the path of the lymphatic drainage to the axilla. Moreover, it has been reported that a fraction of the intra-MLNs could be marked as SLN (8, 10, 23, 24).

Therefore, while we were able to show that intra-MLN correlated with the clinical outcomes, we were not entirely certain that ALND is required for patients with negative SLN and positive intra-MLN. However, our results may assist the clinical team on the decision making.

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Figure 1:
Schematic figure showing the distribution of cases in relation to the status of ALND, ALN, and SLN. * A single intra-MLN was designated as SLN.

Figure 2:
Schematic figure showing the distribution of cases in relation to the status of ALND, ALN, and SLN, excluding cases that did not meet the inclusion criteria for the clinical outcome studies.

Figure 3:

Relapse free survival and overall survival; Relapse free survival, A, TN-stage 2 vs. TN-stage 3 excluding intra-MLN; B, : B, TN-stage 2 vs. TN-stage 3 including intra-MLN; C, ENE present vs. absent excluding intra-MLN; D, ENE present vs. absent including intra-MLN. Overall survival; E, TN-stage 2 vs. TN-stage 3 excluding intra-MLN; F, TN-stage 2 vs. TN-stage 3 including intra-MLN; G, ENE present vs. absent excluding intra-MLN; H, ENE present vs. absent including intra-MLN.

Table 1:

Cases distribution among contributing institutions

	Institution	Overall cases (n=267)	Cases met clinical inclusion criteria (n=113)	Time frame
1	Roswell Park Cancer Institute *	37/190 (19.5%) ^	20 (17.7%) ^^	1996–2016
2	Emory University	11/300 (3.7%)	2 (1.8%)	2000–2016
3	University of California San Diego	11/116 (9.5%)	6 (5.3%)	1991–2016
4	Vanderbilt University Medical Center	33/105 (31.4%)	16 (14.2%)	1999–2016
5	Montefiore Medical Center	15/57 (26.3%)	4 (3.5%)	2000–2014
6	University of Texas Southwest at Dallas	16/77 (20.8%)	2 (1.8%)	2000–2016
7	University of Pennsylvania *	43/164 (26.2%)	23 (20.4%)	1994–2016
8	University of Pittsburgh Medical Center *	62/191 (32.5%)	30 (26.5%)	2000–2016
9	Augusta University *	2/27 (7.4%)	0 (0%)	2000–2016
10	Women Circle of Health Study	7/31 (22.6%)	0 (0%)	2000–2016
11	Washington University	30/166 (18.1%)	10 (8.8%)	1999–2013
	Total	267/1424 (18.8%)	113 (100%)	

* Data abstracted using Text Information Extract System (TIES);

^ number of cases with positive intra-MLN/total number of cases with detected intra-MLN (%);

^^ number of cases that met the inclusion criteria to correlate with the clinical outcomes (%)

Table 2:

5-year local/distant RFS, and 5 year OS with clinicopathologic characteristics.

	Category (n)	5y local/distant RFS N (%)	P value	5y OS N (%)	P value
Age	50 (36)	32(88.9)	0.15	31(86.1)	0.83
	>50 (77)	61(79.2)		67(87)	
Histology Type	ILC (12)	10(83.3)	0.3	11(91.7)	0.11
	NST (97)	81(83.5)		85(87.6)	
	Special type (4)	2(50)		2(50)	
Nottingham Grade	1 (5)	3(60)	0.45	5(100)	0.41
	2 (53)	44(83)		47(88.7)	
	3 (48)	46(83.6)		46(83.6)	
LVI	Yes (65)	40(83.3)	0.58	43(89.6)	0.34
	No (73)	53(81.5)		55(84.6)	
Multifocality	Yes (73)	63(86.3)	0.07	68(93.2)	0.008
	No (39)	29(74.4)		30(76.9)	
HR	Negative (37)	31(83.8)	0.74	31(83.8)	0.52
	Positive (76)	62(81.6)		67(88.2)	
HER2	Negative (86)	70(81.4)	0.96	75(87.2)	0.95
	Positive (25)	21(84)		22(88)	
Molecular Subtype	HER2+ (25)	21(84)	0.93	22(88)	0.76
	HR+/HER2- (60)	49(81.7)		53(88.3)	
	TNBC (24)	19(79.2)		20(83.3)	
Hormonal Therapy	No (38)	30(78.9)	0.52	31(81.6)	0.25
	Yes (75)	63(84)		67(89.3)	
Radiation Therapy	No (27)	17(63)	0.001	22(81.5)	0.29
	Yes (86)	76(88.4)		76(88.4)	
Chemo Therapy	No (17)	12(70.6)	0.14	13(76.5)	0.11
	Yes (96)	81(84.4)		85(88.5)	
T-stage	1 (39)	33(84.6)	0.73	35(89.7)	0.29
	2 (55)	45(81.8)		48(87.3)	
	3 (19)	15(78.9)		15(78.9)	
N-stage (excluding intra-MLN)	0 (23)	19(82.6)	0.02	20(87)	<0.001
	1 (50)	44(88)		48(96)	
	2 (27)	22(81.5)		22(81.5)	
	3 (13)	8(61.5)		8(61.5)	
N-stage (including intra-MLN)	1 (62)	55(88.7)	0.009	59(95.2)	<0.001
	2 (34)	27(79.4)		28(82.4)	
	3 (17)	11(64.7)		11(64.7)	
ENE (excluding intra-MLN)	No (37)	34(91.9)	0.03	35(94.6)	0.039
	Yes (42)	31(73.8)		34(81)	

	Category (n)	5y local/distant RFS N (%)	P value	5y OS N (%)	P value
ENE (including intra-MLN)	No (45)	41(91.1)	0.012	43(95.6)	0.01
	Yes (61)	46(75.4)		50(82)	
TN stage (intra-MLN excluded) *	2 (57)	47(82.5)	0.23	52(91.2)	0.014
	3 (45)	35(77.8)		35(77.8)	
TN stage (intra-MLN included) *	2 (51)	46(90.2)	0.016	50(98)	<0.001
	3 (59)	45(76.3)		45(76.3)	

* Stage 1 was excluded

Table 3:

Multivariate analysis correlation with RFS and OS

Recurrence Free Survival			
	HR	95% CI	P-value
Intra-MLN excluded			
RT-Yes	0.19	0.055 to 0.66	0.009
TN-stage-3	2.56	0.65 to 10.1	0.18
ENE-Yes	2.94	0.74 to 11.67	0.12
Intra-MLN included			
RT-Yes	0.13	0.04 to 0.45	0.001
TN-stage-3	8.92	1.47 to 54	0.017
ENE-Yes	1.76	0.42 to 7.36	0.44
Overall Survival			
	HR	95% CI	P-value
Intra-MLN excluded			
Multifocality-Yes	5.35	1.07 to 26.89	0.042
TN-stage-3	1.92	0.37 to 10.06	0.44
ENE-Yes	3.1	0.62 to 15.77	0.167
Intra-MLN included			
Multifocality-Yes	3.08	0.91 to 10.40	0.069
TN-stage-3	8.59	1.06 to 69.71	0.044
ENE-Yes	2.68	0.57 to 12.66	0.21