

Intra-mammary Lymph Nodes, an Overlooked Prognostic Tool?

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Abstract

Background

Due to the high variability of incidence and prevalence of intra-mammary lymph nodes(IMLNs), they might be overlooked during clinical and radiological examinations. Properly characterizing pathological IMLNs and detecting the factors that might influence their prevalence in different stages of breast cancer, might aid in proper therapeutic decision making and could be of possible prognostic value.

Methods

Medical records were reviewed for all breast cancer patients treated at the National Cancer Institute of Cairo University between 2013-2019. Radiological, pathological and surgical data were studied.

Results

Intra-mammary lymph nodes were described in the final pathology reports of 100 patients. Five cases had benign breast lesion. Three cases had phylloides tumors and two cases had duct carcinoma in situ. All ten cases were excluded. The remaining 90 cases had all invasive breast cancer and were divided into two groups. One group for patients with malignant IMLNs (48) and another for patients with benign IMLNs (42). Pathological features of the malignant IMLN group included larger mean tumour size (4.7 cm) , larger mean size of the IMLN (1.4 cm), higher incidence of lymphovascular invasion(65.9%) and a higher rate of extracapsular extension in axillary lymph nodes (57.4%). All these criteria were statistically significant. In addition the pathological N stage was significantly higher in the malignant IMLNs group.

Conclusion

Intra-mammary lymph nodes are frequently overlooked by clinicians. More effort should be done to detect them during preoperative imaging, and during pathological processing of specimens. A suspicious IMLN should be biopsied by FNAC . Malignant IMLN are associated with advanced pathological features and should be removed during surgery.

Background

Intra-mammary Lymph Nodes(IMLNs) are lymph nodes surrounded completely by breast tissue, a feature that distinguishes them from low lying axillary lymph nodes(AxLNs).

IMLNs have received little attention compared to AxLNs as potential prognostic indicators in breast carcinoma. This ,probably ,is due to the relatively small number of reported cases and the rarity of studies that have focused on IMLNs.

Due to the high variability of the incidence and prevalence of IMLNs, they are sometimes overlooked during clinical and radiological examinations. Some authors believe that IMLNs have no clinical

significance unless they get infiltrated by breast cancer. Their clinical implications in this case remain controversial .

Reported pathological affections of IMLNs include malignant conditions as metastatic carcinoma of a clinically evident or occult breast carcinoma and non-Hodgkin's lymphoma.

Other inflammatory conditions such as tuberculosis have also been reported. [1]

Although IMLNs can be located in any part of the breast, they are most commonly found in the upper outer quadrant. The prevalence of IMLNs has been reported to range between 1% and 28% [2].

They are noted in approximately 5% of patients undergoing routine mammography [3].

At the National Cancer Institute of Cairo University, radiology department records show a description of IMLN in 418 out of 7100 diagnostic sono-mammography examinations performed in 2019, assuming a percentage of 5.9%.

According to the current 8th edition of the American Joint Committee on Cancer AJCC staging system, there is no distinction between axillary and IMLNs, and for the purpose of staging, they are considered axillary LNs. [4]

Patients with IMLN metastases are considered to be in stage II disease and are described as having positive regional metastasis even if axillary nodes are free. So, the presence of IMLNs metastasis can upstage the disease and change therapeutic decisions.

On the other hand, considerable attention has been paid to the significance of extra-axillary lymph node metastases during sentinel lymph node biopsy (SLNB). Several reports describe the identification of IMLNs as the sentinel node on lymphoscintigraphy in 0.7% and up to 14% of patients undergoing SLNB . [5]

According to MD Anderson Cancer Center experience, disease-free survival (DFS) and overall survival (OS) were significantly affected in breast cancer patients with IMLN metastases whether isolated or associated with axillary node involvement. [5] Other studies have also shown IMLNs metastasis to be associated with shorter DFS and OS. [6] On the other hand, some reports have found that IMLN positive/AXLN negative patients have better prognosis than IMLN negative /AXLN positive patients. [6]

On mammography, normal IMLNs can be seen as well circumscribed, homogenous, oval or round densities smaller than 1 cm. They typically have a central lucent hilum, which appears as a lower density at the centre than the periphery. This is called the hilar notch (Doughnut sign).

Suspicious mammographic features of IMLNs are a size larger than 1 cm, change in shape, spiculated margins, loss of the lucent centre or the hilar notch and increased density. IMLNs metastases can also be seen as microcalcifications.

By ultrasonography normal IMLNs appear as well circumscribed, oval or round, homogeneously hypoechoic structures with mild posterior acoustic enhancement and an echogenic line representing the hilum [7].

Suspicious sonographic criteria are: marked hypoechogeneity, thickening of the cortex and alterations in the central echogenic hilum (reduced size, eccentric displacement or absence). Changes in shape can also be present. On the other hand, enlargement to a size more than 1 cm is not considered an absolute diagnostic criteria of metastasis. Peripheral instead of hilar vascularity can also be noted in pathological IMLNs.[8]

A controversy exists regarding optimal management in case of a sentinel IMLN harboring metastasis without identification of sentinel axillary nodes. Some authors believe that a positive sentinel IMLNs does not necessarily predict AxLN metastasis and that the chances of finding further axillary lymph node metastasis is low. Thus, axillary lymph node dissection (ALND) could be spared. The concept behind this opinion is, that axillary staging is dependant on axillary lymph node status and not extra –axillary lymph nodes. [9]

On the other hand, other authors suggested performing level I ALND for the management of the axilla when only a sentinel IMLN is positive without detection of axillary SLNs. [10]

Other studies concurred that a sentinel IMLN could act as a real SLN in those cases based on high correlation of metastases between IMLN and AxLNs according to their results. [11]

Properly characterizing pathological IMLNs and detecting the factors that may influence their prevalence and occurrence in different stages of breast cancer may aid in proper therapeutic decision making and could possibly be of prognostic value.

Patients And Methods

This is a retrospective study focusing on the pathological, radiological and clinical features of IMLNs.

The records were reviewed for all breast cancer patients treated at the National Cancer Institute of Cairo University between 2013 and 2019.

Inclusion criteria were patients with full records, who have shown the presence of IMLNs on their pathology report. The clinical, radiological and surgical data have been studied. A comparison was done between patients with pathologically positive IMLNs for breast cancer metastases and those with negative IMLNs to determine possible effects of patient and tumor factors on the probability of IMLNs metastases. A correlation between the status of IMLNs and axillary lymph nodes was also sought.

Data were statistically described in terms of mean \pm standard deviation (\pm SD), and, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student t test for independent samples in normally distributed data and

Mann-Whitney U test for independent samples in not normal data. For comparing categorical data, chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

IMLNs were described in the postoperative pathological specimens of 100 patients. Five cases did not suffer from breast cancer. They underwent wide excision of suspicious masses which revealed to be benign. Three other cases had malignant phylloides for which they had a mastectomy. Another two cases had ductal carcinoma insitu. All ten cases were excluded. The remaining 90 patients had all a final pathological diagnosis of invasive breast carcinoma and included IMLNs in their specimens. The mean age of the study group was 48.2 ± 10.2 years.

Seventy- three of the cases (81.1%) had Invasive Duct Carcinoma Not Otherwise Specified (IDC NOS), three cases (3.3%) had IDC with medullary features, four cases (4.4%) had IDC with neuroendocrine features, two cases (2.2%) had IDC with tubular and cribriform differentiation, seven cases (7.8%) had invasive lobular carcinoma, and one case (1.1%) had mucinous carcinoma.

All cases underwent preoperative conventional sonomammography evaluation of both breasts and axillae. The preoperative imaging was able to detect IMLN definitely in 47 cases (52.2%) and commented on them as likely IMLN in 17 cases (18.8%). In 12 (13.3%) cases the IMLN was seen as a mass of ill-defined nature. Conventional sono-mammography failed to identify IMLN in 14 cases (15.5%). The age and radiological features of study group are illustrated in Table 1.

Table 1
Age and radiological features of study group

Variables	Benign IMLNs (N = 42)	Malignant IMLNs (N = 48)	P-value
Age in years Mean ± SD	46.7 ± 10.2	49.54 ± 10.1	0.19
Tumor Size Mean ± SD	4.4 ± 1.3	5.1 ± 2.5	0.152
Laterality, No. (%)	24 (57.1%)	21 (43.8%)	0.42
- Left	17 (40.5%)	26 (54.2%)	
- Right	1 (2.4%)	1 (2.1%)	
- Bilateral			
Tumor Site, No. (%)	6 (14.3%)	7 (14.6%)	0.32
- Central	7 (16.7%)	2 (4.2%)	
- LIQ	3 (7.1%)	1 (2.1%)	
- LOQ	13 (31%)	23 (48.9%)	
- Multicentric	4 (9.5%)	4 (8.3%)	
- UIQ	9 (21.4%)	11 (22.9%)	
- UOQ			
No. of IMLNs in Radiology, No. (%)	9 (21.4%)	17 (35.4%)	0.14
- 0	29 (69%)	24 (50%)	
- 1	1 (2.4%)	5 (10.4%)	
- 2	3 (7.1%)	2 (4.2%)	
- 3			
IMLNs Radiological Diagnosis	24 (57.1%)	23 (47.9%)	0.46
- Definitive	9 (21.4%)	8 (16.7%)	
- Likely	5 (11.9%)	7 (14.6%)	
- Not Identified as IMLN	4 (9.5%)	10 (20.9%)	
- Not Identified at all			
IMLNs Radiological Criteria	7 (16.7%)	3 (6.3%)	0.13
- Benign	4 (9.5%)	10 (20.8%)	
- Not Identified	31 (73.8%)	35 (72.9%)	
- Suspicious			

Variables	Benign IMLNs (N = 42)	Malignant IMLNs (N = 48)	P-value
IMLNs Site Radiologically, No. (%)	27 (64.3%)	27 (56.3%)	0.319
- UOQ	1 (2.4%)	1 (2.1%)	
- LIQ	7 (2.4%)	5 (10.4%)	
- LOQ	6 (14.3%)	4 (8.3%)	
- UIQ	1 (2.4%)	0	
- UIQ LOQ	0	1 (2.1%)	
- UOQ UIQ	1 (2.4%)	0	
- UOQ LOQ	1 (2.4%)	0	
- UOQ UIQ			
IMLN in other breast,	4 (9.5%)	2 (4.2%)	0.277
Preoperative FNAB of IMLN	9 (20.4%)	10 (20.8%)	0.51
FNAB of IMLN Findings	2 (4.8%)	0	0.066
- Benign	2 (4.8%)	1 (2.1%)	
- Inconclusive	5 (11.9%)	6 (12.5%)	
- Suspicious	0	3 (6.3%)	
- Metastatic			
Axillary LN by Ultrasound	6 (14.3%)	2 (4.2%)	0.095
- Non-specific	36 (85.7%)	46 (95.8%)	
- Pathological			

The sonographic features of detected IMLNs were seen as benign in 10 (11.1%) cases and as suspicious IMLN or mass in 66 cases (73.3%). Pathology reports revealed that 31 of the suspicious IMLN were benign, while 35 turned to be malignant. Thus, sonography in this study had 53% sensitivity of detecting malignant IMLN and a specificity of 73%, with a positive predictive value of 92%. The diagnostic accuracy of ultrasound is illustrated in Table 2.

Table 2
Diagnostic accuracy of ultrasound

Variables	US Findings			
	Benign		Suspicious	
	No	%	No.	%
Pathological Findings				
- Benign	7	16.7	3	6.3
- Malignant	31	73.8	35	72.9
- Total	38		38	
- Sensitivity of US	53%			
- Specificity	70%			
- PPV	92%			
- NPV	82%			

Overall, pathology reports showed that 42 (46.7%) cases had benign IMLNs, while 48 cases (53.3%) had malignant deposits in IMLNs. Accordingly, patients were categorized into two groups. One group for patients with malignant IMLNs and another for patients with benign IMLNs.

Thirteen cases in each group received neoadjuvant chemotherapy. The response to chemotherapy in axillary and IMLNs was described using Sataloff's classification. The response of the primary tumor was determined by Miller Grade.

Pathological features of the malignant IMLN group included larger mean tumour size (4.7 cm), larger mean size of the IMLN (1.4 cm), higher incidence of lymphovascular invasion (65.9%) and a higher rate of extracapsular extension in axillary lymph nodes (57.4%).

All these criteria were statistically significant. In addition the pathological (N)-stage was significantly higher in the malignant IMLNs group.

In thirteen cases out of 48 (27.6%), positive IMLNs were associated with negative axillary lymph nodes. On the other hand, 20 cases out of 42 (47.6%) had a benign IMLN with positive axillary lymph node metastasis. The pathological features of both study groups are highlighted in Table 3.

Table 3
Pathological features of both groups

Variables	Benign IMLNs (N = 42)	Malignant IMLNs (N = 48)	P-value
Tumor Pathology, No (%)	34 (80.9%)	39 (81.3%)	0.58
- Invasive duct carcinoma,	0	3 (6.3%)	
- IDC with medullary features	1 (2.4%)	3 (6.3%)	
- IDC with neuroendocrine features	2 (4.8%)	0	
- IDC with tubular cribriform differentiation	4 (9.5%)	3 (6.3%)	
- Invasive lobular carcinoma	1 (2.4%)	0	
- Mucinous carcinoma			
Associated DCIS, No. (%)	14 (33.3%)	20 (41.7%)	0.43
Pathological Tumor Size	3.3 ± 1.2	4.7 ± 2.6	0.001
- Mean ± SD			
No. of IMLNs	1.2 ± 0.61	1.4 ± 0.84	0.377
Mean ± SD			
Pathological IMLNs Size	1.1 ± 0.2	1.7 ± 0.6	0.001
- Mean ± SD			
Lymphovascular Invasion, No. (%)	6 (14.3%)	31 (65.9%)	0.001
- Yes	36(85.7%)	16 (34%)	
- No			
IMLNs Site Pathologically, No. (%)	0	2 (4.2%)	0.48
- Central	1 (2.4%)	1 (2.1%)	
- LIQ	1 (2.4%)	4 (8.3%)	
- LOQ	6 (14.3%)	7 (14.6%)	
- UIQ	32 (76.2%)	33 (68.8%)	
- UOQ	1 (2.4%)	0	
- UOQ UIQ LOQ	1 (2.4%)	0	
- UOQ LOQ	0	1 (2.1%)	
- UOQ UIQ			

Variables	Benign IMLNs (N = 42)	Malignant IMLNs (N = 48)	P-value
Extracapsular Extension Ax LNs, No. (%)	7 (16.7%)	27 (57.4%)	0.001
Yes	35 (83.3%)	21(44.6%)	
No			
Pathological T Stage	2 (4.8%)	3 (6.3%)	0.006
- I	34 (81%)	22 (45.8%)	
- II	4 (9.5%)	13 (27.1%)	
- III	2 (4.8%)	10 (20.8%)	
- IV			
Variables	Benign IMLNs (N = 42)	Malignant IMLNs (N = 48)	P-value
Pathological N Stage for axilla only	0	1	0.002
- Nx	22 (52.4%)	13 (27.6%)	
- N0	13 (31%)	9(19.1%)	
- N1 1–3	7 (16.7%)	14(29.7%)	
- N2 4–9	0	11 (23.4%)	
- N3 ≥ 10			
Pathological N stage Including IMLN	0	1	0.002
- Nx	22 (52.4%)	0	
- N0	13 (31%)	22 (46.8%) 14(29.7%)	
- N1 1–3	7 (16.7%)	11 (23.4%)	
- N2 4–9	0		
N3 ≥ 10			
Hormone Receptor Status	18(42.8%)	24(50%)	0.45
Luminal A	5(11.9%)	7(14.5%)	
Luminal B	5(11.9%)	9(18.7%)	
Luminal Her2	8(19%)	5(10.4%)	
Her 2 Enriched	6(14.2%)	3(6.2%)	
Triple Negative Breast Cancer			

Discussion

IMLNs may be overlooked during breast imaging and during specimen processing in cases of breast cancer. They might not be excised in cases of breast conserving surgery. Thus, it is important to define the significance and the incidence of metastasis in these nodes.

In cases of early-stage breast cancer, the identification of IMLN metastases in a patient with otherwise negative AxLNs will not only result in upstaging but also may alter adjuvant therapy planning.

This study indicates that malignant IMLN seem to be associated with aggressive and advanced disease. On the other hand, a malignant IMLN does not indicate aggressive disease per se.

The IMLN are not accurate indicators of axillary lymph node status. In this study, almost thirty percent (27.6%) of patients with malignant IMLN had negative axillary lymph nodes. This comes in concordance with previous reports observing that one third of patients with positive IMLN have free axillary nodes.[12]

On the other hand, this study shows a considerable percentage of patients with axillary lymph node metastasis to have benign IMLN(47.6%). This is slightly higher than previous reports of only 15%.[12]

IMLNs have proved to be a separate possible site of metastases in breast cancer .Preoperative lymphoscintigraphy may help identify these extra-axillary metastases and help control them during management.

Further radiological, pathological and clinical attention should be given to IMLN detection for its possible direct effect on therapeutic planning.

Increased care should be taken, and the scope of suspicion should be widened during preoperative radiological evaluation.

If a suspicious IMLN is found, FNAC should be performed in order to verify it's status. Data suggest that it should not be regarded as an indicator for axillary lymph node status. And a thorough clinical evaluation of axilla is warranted in every patient.

This study has several limitations. First ,the retrospective study design mandates careful evaluation of the results. In addition, the small study population is also a weak point. There is a degree of bias regarding the true incidence of IMNLs due to two factors. First ,the IMLN may not be excised during breast conserving surgery. Second, the routine pathological processing of specimens might overlook an excised IMLN.

Despite these limitations, this study is one of the largest to evaluate IMLNs and its relation to patient and tumor factors. To overcome the study's shortcomings, a multi-center prospective study involving a larger cohort with long-term follow-up is necessary to define the true significance and prognosis of IMLN.

Conclusion

Intra-mammary lymph nodes are frequently overlooked by clinicians. More effort should be done to detect them during preoperative imaging, and during pathological processing of specimens. A suspicious IMLN should be biopsied by FNAC. Malignant IMLN are associated with advanced pathological features and should be removed during surgery.

Declarations

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Availability of data and materials

Please contact the author for data request.

Authors' contributions

All authors contributed evenly in the accomplishment of this study. They have all read and approved this final manuscript.

Ethics approval and consent to participate

The study was done after approval of the ethical committee of the National Cancer Institute of Cairo University.

Consent for publication

Consent for publication was obtained from patients.

Competing interests

The authors declare that they have no competing interests.

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