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Implication of Intramammary Lymph Node Metastasis in the Breast: A Review of the Literature

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ABSTRACT

Background: The impact of positive intramammary lymph node (IM LN) on the prognosis of patients with breast cancer has been debated for years; likewise, the standard management of patients with positive IM LN remains unclear, especially when it is identified by preoperative imaging or by sentinel lymph node biopsy. The present study aims at reviewing the level of concurrent involvement of IM LN and axillary nodes to clarify the management of patients with breast cancer with positive IM LN and clinically negative axilla or negative axillary sentinel lymph nodes.

Methods: We reviewed all published studies on IM LN metastasis in breast cancer from 1980 to 2016 in 4 major databases. Twenty-five studies containing data on pathologic examination of IM LN were included, in twenty-two of which, pathologic status of IM LN and axillary lymph nodes were exactly available.

Results: The incidence of positive IM LN is highly variable (0%-100%). Positive IM LNs were associated with positive axillary lymph nodes in more than half of patients, but isolated involvement of IM LN were documented in significant number of patients in various studies.

Conclusions: Although metastatic IM LN could often be associated with axillary nodal involvement, it could be the only site of breast cancer spread; hence, the concept stating that positive IM LN mandate further axillary dissection needs to be debated.

Introduction

Intramammary lymph node (IM LN) was first defined by Egan & Mc Sweeney in 1982 as a lymph node surrounded by breast parenchyma. They found an incidence of 28% by studying 158 total mastectomy specimens.¹ The prevalence of IMLNs has been reported in the range of 1% to 48.4%, according to the methodology of the study as well as

the specimen's characteristic which were examined.²

³ Rampaul *et al.* reported an incidence of 48.4% in a series of total mastectomy specimen's examination after breast conserving surgery, while Jadusingh reported only 5 IMLNs in 3 cases of 77 total mastectomy specimens.^{3,4}

IM LNs can be located anywhere within the breast, but most of them are recognized in the upper outer quadrant (38%-72%).⁵ Most of IM LNs are not clinically palpable and could be observed on mammography as a well-circumscribed, oval, or round density smaller than 1cm with a central lucent hilum. They were reported on 5% of normal mammograms in a review of 1500 mammography.⁶ On ultrasonography, they are well defined circumscribed hypo-echoic masses with an

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echogenic line representing the hilum. In a study conducted by Linfords *et al.* on 16000 mammographic examination, 4 metastasis to IM LN were found and all involved lymph nodes were larger than 1cm (range 1.2-2cm), since radiological differentiation was very difficult, they recommended the biopsy of every lesion larger than 1 cm unless associated with dermatitis or mastitis.⁷

IM LNs have no clinical importance until they are involved by breast cancer, but their clinical importance remains controversial. Patients with IM LN metastases were considered to be in stage II disease and had PN1 disease, yet in the lack of axillary node association. The presence of positive IM LN can upstage the disease and change the therapeutic decisions.

Considering the high incidence of axillary nodal involvement in patients with positive IM LN, an axillary lymph node dissection had been recommended, but now by increasing the

improvement in sentinel lymph node mapping technique, the position of axilla could be forecast by the position of axillary sentinel node rather than the status of IMLN.

The proper management of patients with positive IM LN and negative axillary lymph nodes is still under debate; the aim of this review is to provide a summary of the published data on IM LN metastasis in breast cancer to clarify the prognostic importance of this entity and to help in optimal management of this subset of patients with breast cancer.

Methods

A comprehensive review was conducted among the published articles from 1980 to 2016 using 4 electronic databases (ISI web of science, Scopus, Google scholar, PubMed). The keywords for this search were “intra-mammary lymph nodes”, “intramammary lymph nodes”, “extra-axillary lymph nodes”, and “sentinel lymph nodes”. These

Table 1. Studies With the Level of Positive IM LN and Positive Axilla + Positive IM LN

Author	No. of cases	No. of specimens with IMLN	No. of patients with positive IMLN	No. of positive Axilla & positive IMLN
Egan&McSweety 1983 ¹	173	45	15 (33%)	NA
Linfors 1986 ⁷	16000	4	4 (100%)	1 (25%)
Jadusingh 1992 ⁴	682	5	1 (20%)	NA
Spillane 1999 ⁶	3	3	2	1
Rull 1999 ⁷	1	1	1	
Cyrlak 1999 ⁸	1	1	1	1
Schmidt 2001 ²	4056	44	2 (4.5%)	NA
Upponi 2001 ¹⁹	3	3	2	0
Gajdos 2001 ²⁰	1	1	1	1
Gunhan-Bilgen 2001 ²¹	1655	16	16 (100%)	9 (56%)
Victorzon 2003 ²²		8	0	0
Tytler 2003 ²³	2	2	1	0
Shen 2004 ⁸	196	196	36 (28%)	29 (81%)
Kouskos 2004 ²⁴	2	2	2 (100%)	1 (50%)
Matheline 2005 ²⁵	1	1	1	0
Guth 2006 ²⁶	3601	64	20 (31%)	13 (72%)
Van Rijk 2006 ⁹	785	59	13 (22%)	1 (8%)
Rampaul 2008 ³	157	76	25 (29%)	15 (60%)
Cox 2008 ¹⁰	15000	91	29 (32%)	18 (62%)
Nasser 2008 ¹¹	116	116	15 (26%)	12 (80%)
Intra 2008 ¹²	9632	22	6/15 (40%)	0
Kijima 2008 ²⁷	4	4	2 (50%)	0
Vijan 2009 ¹³	9800	93	32 (34%)	22 (69%)
Pugliese 2009 ¹⁴	7140	151	36 (24%)	22 (67%)
Hogan 2010 ¹⁵	100	113	21 (21%)	14 (67%)

Abbreviations: IMLN: Intramammary lymph nodes; NA: Not Available



keywords and some other like “breast cancer” and “metastasis” were combined to execute the search. The full texts of all relevant studies were retrieved and all references were searched. Among 36 studies, 25 had mentioned the level of IM LN involvement and 22 studies had provided sufficient data on pathologic status of IM LN and axillary lymph nodes in the same patients.

Results

The results of the present research were highly variable; the level of IM LN metastasis was in a range of 0% to 100% in specimens with IM LNs (Table 1). Excluding the case report studies, the concurrent involvement of IM LN and axillary lymph nodes was between 0% to 84%.

In studies reporting more than 100 patients, more than half of the patients had concurrent IM LN and axillary lymph node involvement, meaning that approximately less than half of the patients with IM LN metastasis had no need further axillary dissections and the status of the axilla could be identified by sentinel node biopsy.^{3,7-15}

Discussion

The biopsy of intramammary sentinel lymph node was first described by Rull in 1999.¹⁷ Uren *et al.* found them as sentinel lymph nodes in about 12% of their patients.²⁸

The reported incidence of intramammary sentinel lymph nodes ranged between 0.2% and 14%, but there were a few reported cases of positive intramammary sentinel lymph nodes in the literature.^{12,15,25,28}

Generally, 50% of the metastatic IM LNs was in the same quadrant as the tumor in the Egan’s studies.^{1,29} The sensitivity of breast imaging study for the detection of IM LN before surgery was low. It was only 18.5% in a study by Shen on 196 specimens, which had IM LN in pathologic examination.¹⁵ A histological study by Schmidt on cadaver breasts detected IM LNs in 7.5%, half of which was not known radiologically.²

In a research conducted by Vijan *et al.*, IM LN were identified in 93 breast specimens: in 23 patients, they were found on preoperative imaging studies (15 on mammography, 4 on MRI, and 4 on lymphoscintigraphy), and 70 IM LN were known incidentally (48 by surgeon intraoperative and 22 by pathologist).¹³

The patients and tumor characteristics correlated with IM LN metastasis were age, grade, tumor multifocality, the presence of lympho-vascular invasion, and axillary nodal involvement. The age of patients and tumor grade were not correlated with IM LN metastasis in other studies.^{9,12,14,25,28}

Patients with IM LN metastases are considered to be in stage II disease and have PN1 disease, yet in the lack of axillary node association. This practice is

based on Egan & Mc Sweeney’s study in 1983, which reported outcomes of 15 positive IM LN patients with 13 to 17 years follow-up.²⁹ Among 6 patients, who had isolated IMLN metastasis without axillary nodes involvement, only 2 patients survived for 10 years. The presence of IM LN metastasis was correlated with poor prognosis in patients with stage I, but in patients involved in stage II illness, the existence of IM LN metastasis was not correlated with a lesser prognosis in comparison with patients without IM LN metastasis. It was obviously was the first study that addressed the prognostic significance of IM LN metastasis in breast cancer.

Later studies have had small number of populations, but Shen *et al.* from MD Anderson Cancer Center, in 2004, reported the clinical and pathologic data of 186 patients who had IM LNs in their mastectomy specimens.¹⁵ IM LN metastasis was found in 36 patients (28%). Most patients, who had IM LN metastasis (81%), had axillary metastasis as well. The presence of IM LN metastasis was associated with reduced disease free survival (DFS) and overall survival (OS) in patients with axillary metastasis as well as in those without axillary metastasis. In the multivariate analysis, IM LN metastasis was an independent predictor of poor outcome; hence, they recommended further axillary lymph node evaluation as well as an adjuvant systemic therapy for patients with positive IMLNs.

In a review of all kinds of breast cancer with IM LNs from 1991 to 2005 in their center, Guth *et al.* reported the same results.²⁶ Also, 75% of patients with IM LN metastases had axillary nodal metastasis; thus, they agreed with Shen *et al.* about further axillary dissection in the setting of positive IMLN.

Rampaul *et al.* claimed that 48% of patients, undergoing complete mastectomy after breast conserving surgery, had IM LNs.³ They found 15 patients with positive IMLN in the presence of negative axillary sampling. In this study, 60% (15 from 25) of patients with IM LN metastasis had axillary nodal metastasis.

Nasser *et al.* examined 116 specimens contain IM LNs.¹¹ In these series, 57 specimens had primary breast cancer. Most patients (80%), who had IM LN metastasis, had axillary node metastasis, too. The patients with IMLN metastasis had a minor 4- year’s overall and disease free survival compared with the patients with a negative IM LN, but in contrary with the Shen *et al.*, they did not find it as an independent predictor of poor outcome on their multivariate analysis.

Another study, which is in favor of axillary dissection in the presence of IM LN metastasis, belongs to Hogan *et al.* from the UK.¹⁵ They found that 67% of patients with IM LN metastasis owned more axillary metastasis; likewise, 1 patient, who had an involved IM LN with a negative axillary



sentinel node, found axillary nodal recurrence 19 months later; consequently, they concluded that IM LN metastasis is associated with poorer overall survival and predicts strongly for axillary metastasis and they recommended axillary node clearance in the setting of positive IM LN. In this study, IM LN metastasis was an independent predictor of poor outcome on multivariate analysis.

In a study conducted by Vijan *et al.* in 2009, the rate of axillary metastasis in the presence of positive IM LN was 69%, and they proposed axillary dissection in the setting of positive IMLN so that more investigations verified the validity of SLN decision making in such condition.¹³ A systematic review and meta-analysis on 18 studies by Abdullgaffar *et al.* found positive IM LN reliable predictors of axillary nodal involvement and, consequently, a director for additional surgical administration of the axilla.³⁰

Some studies do not agree to the necessity of axillary clearance in the presence of positive IM LN.^{10, 12, 14} Cox *et al.* found that positive IM LN and negative axilla patients have better prognosis than negative IMLN and positive axilla patients.¹⁰

Intra *et al.* reported 15 patients with sentinel lymph nodes both in axilla and in breast parenchyma.¹² In this study, all 15 axillary SLN were reactive and 6 of intramammary sentinel nodes were involved. Three of these 15 patients (2 of whom had positive IM LN) had an axillary node clearance and all nodes were reactive. With an average follow up of twenty-four months, no regional or local or systemic failures had happened. In a study conducted by Pugliese *et al.*, the status of IM LNs were compared with the status of axilla.¹⁴ In general, 61% of IM LN patients had axillary node metastasis. No further axillary involvement was recognized when axillary separation was accomplished in 7 patients with positive IM LN and negative axillary sentinel node. No axillary recurrence had occurred in other 7 patients with IM LN metastases and negative axillary sentinel node, with a median follow up of seventy-five months. According to Intra and Pugliese's study, axillary sentinel node biopsy can be used to guide axillary decision making in the presence of IM LN metastasis. Tytler *et al.* introduced 2 cases of intramammary sentinel node, one of whom was metastatic and further axillary dissection in this patient identified 13 reactive lymph nodes.²³ Bat *et al.* introduced 2 cases of metastatic IMLN in patients with breast cancer with a negative axillary sentinel lymph node.³¹ The results of complete axillary lymph node dissection in these 2 patients were negative.

Fujii *et al.* reported a 70-year-old woman with metastatic IM sentinel node and reactive axillary sentinel nodes, who had been alive 11 months after surgery without any loco regional or systemic recurrence.³² Similarly, Rivera *et al.* reported a

similar 78-year-old woman with positive IM sentinel node and negative axillary sentinel node who had not undergone axillary dissection.³³

Lee *et al.* in a study performed on twenty-two patients with IM LN metastases, concluded that these patients had more aggressive tumors with more lymphovascular invasion and increased the rate of axillary node involvement, proposing axillary dissection by the status of IM LN itself.³⁴

According to a review research by Troupis *et al.*, there is no consensus in the case that intramammary sentinel node is positive, but axillary sentinel node is not involved.³⁵

In a literature review of 386 publications, published by Diaz *et al.* in 2012, twenty-three patients with positive IM LN and negative axillary SLN, who underwent a complete axillary lymph node dissection, were identified. In all twenty-three patients, the result of axillary dissection was negative.³⁶ They concluded that axillary lymph node separation may be eluded in the setting of a positive IMLN and a negative axillary sentinel lymph node.

In conclusion, it seems that further studies are needed to define the clinical and prognostic impact of IM LN involvement on disease outcome. Although metastatic IM LN can often be associated with axillary nodal involvement, it can be the only site of breast cancer metastasis and can be increasingly identified by sentinel node biopsy technique. Today, SLN biopsy has become the standard care in the evaluation of axillary status in patients with breast cancer. It seems that by increasing the experience in technique of sentinel node biopsy, decision about axillary node dissection in IM LN positive patients could be founded merely on the histopathologic status of axillary sentinel lymph node.

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