Review Article

Internal mammary lymphadenopathy in breast cancer: a narrative review and update

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Background and Objective: While the axillary nodal basin is the most common lymphatic drainage pathway of the breast, the internal mammary (IM) lymph node chain plays a significant role in breast cancer staging and treatment. It has been identified as sentinel nodal drainage in approximately 13–37% of patients. Despite this, the data is still limited with regard to diagnosis and management when there is suspicion or confirmation of IM lymph node (IMLN) involvement by metastatic breast cancer. The objective of this publication is to provide a comprehensive assessment of the current body of literature surrounding the diagnosis, management and prognostic value of IMLNs in breast cancer treatment.

Methods: Review of the literature published regarding IMLN diagnosis, significance, and management was completed in PubMed. Additional focus was placed on reviewing articles published within the past 10 years as foundation for an update regarding the current practice and future directions in this space.

Key Content and Findings: Improved imaging techniques, with positron emission tomography-computed tomography and magnetic resonance imaging, have led to increase in the identification of IM lymphadenopathy, yielding surgical staging of the IM nodes nearly obsolete. While IM nodal metastases may play a role in overall survival (OS), it has not been demonstrated to be an independent risk factor for increased locoregional recurrence. IM nodal irradiation (IMNI) therapy has been a mainstay in the treatment of IM disease in the context of breast cancer. IMNI has demonstrated improvement in OS and risk of distant recurrence. Wide variations in radiation practices for patients with IM lymphadenopathy exist internationally, highlighting the lack of clear data driven consensus guidelines.

Conclusions: Herein, we provide an updated assessment of the current diagnosis, clinical significance, and management of IM lymphadenopathy for breast cancer patients.

Keywords: Internal mammary (IM); lymphadenopathy; breast cancer; nodal radiation

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Introduction

Background

Lymphatic drainage of the breast tissue is divided into three common nodal basins including the axilla, internal mammary (IM) and supraclavicular locations. Determination of lymphatic spread of breast cancer is important in assessing prognosis and determining treatment approaches. Evidence of IM lymphadenopathy is detected on imaging, though when detected is rarely biopsied (either percutaneously or surgically). As a result, IM lymphadenopathy on imaging suggests potential IM nodal involvement and herein we discuss management of IM lymphadenopathy as a surrogate for pathologic

Table 1 Search strategy summary

Items	Specification
Date of search	Nov 1, 2023
Database searched	PubMed
Search terms used	Internal mammary lymph nodes, breast cancer
Timeframe	Past 10 years
Exclusion criteria	Not in English, not relevant to breast cancer
Selection process	Multiple individuals reviewed and selected

involvement. IM nodal involvement has been shown to impact prognosis and is a component of the American Joint Committee on Cancer (AJCC) staging system. The presence of an involved IM lymph node (IMLN) when there is no evidence of axillary disease increases the clinical N category of a patient from N0 to N2b, and when there is presence of axillary and IM disease concomitantly from cN1 or cN2a to cN3b. Thus, IM nodal disease can impact overall clinical stage and correlate with patient outcomes (1).

The dominant drainage pathway of the breast is well documented and favors the ipsilateral axillary nodal basin in the absence of iatrogenic interventions that disrupt lymphatic drainage. Studies utilizing lymphoscintigraphy with imaging have shown the IMLN chain as the location of the sentinel lymph node(s) from the breast approximately 13–37% of the time (2-5). Additionally, the quadrant of the breast in which the tumor is located may impact the likelihood of IM sentinel node drainage of a breast cancer (4). Historically, surgical removal of the IMLNs was a common component of the surgical treatment of breast cancer. It has since been shown that when a multidisciplinary approach is taken, there is no improvement in oncologic outcomes or survival with surgical resection of the IMLNs, therefore this has fallen out of standard surgical practice (5,6). In current practice, if there is clinically suspicious or biopsy proven IMLN involvement, radiation therapy and systemic treatment options are the mainstay for management of that site of disease (1). Due to the limited utility of IMLN removal, compounded with the ongoing improvement in cross-sectional imaging, there has been a diminishing use of IMLN biopsies in the clinical workup of a breast cancer. Therefore, data on this patient population remains limited and studies reporting on IM lymphadenopathy include a heterogeneous population.

Objective

The goal of this publication is to provide a comprehensive assessment of the current body of literature surrounding the diagnosis, management, and prognostic value of IMLNs in breast cancer treatment. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-2/rc).

Methods

Review of the literature published regarding IMLN diagnosis, significance, and management was completed in PubMed. Additional focus was placed on reviewing articles published within the past 10 years as foundation for an update regarding the current practice and future directions in this field (*Table 1*).

Review of current literature regarding IMLNs in breast cancer

Prevalence & risk factors influencing IM nodal metastasis

When IMLNs are involved by metastatic malignancy, the presence of isolated IM nodal positivity is far less common (4–17%) than concomitant axillary and IM nodal positivity (28–52%) (5,7,8). A cohort of 72 patients with clinically negative axillae but sentinel node drainage to the IM chain on lymphoscintigraphy underwent IMLN sentinel lymph biopsy along with axillary sentinel lymph node biopsy at the time of their mastectomy or lumpectomy. Of these, 10 (14%) had IMLN metastasis and all but one of these patients had concurrent axillary nodal metastasis. Information from IMLN sentinel lymph biopsy regarding IM nodal positivity changed the patient's pathologic stage in 8 patients (11%) (9). However, in this study the 6th edition AJCC

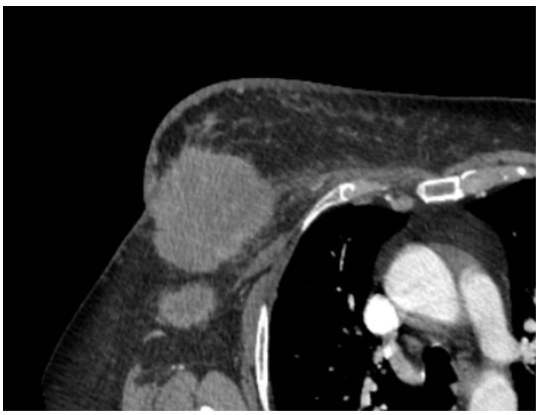

Figure 1 Focused image of magnetic resonance imaging with the presence of an abnormally enlarged internal mammary lymph node with loss of fatty hilum.

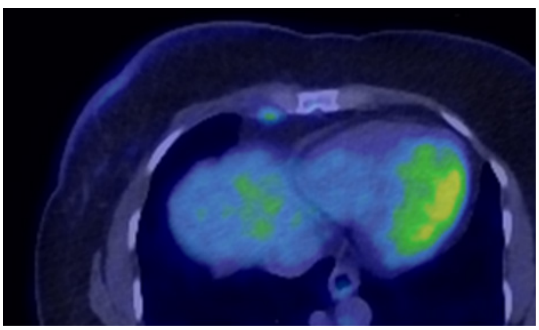

Figure 2 Focused image of positron emission tomography-computed tomography with the presence of an abnormally enhancing internal mammary lymph node.

staging system was utilized and routine IM sentinel node surgery was performed at the institution. Details regarding the pre-operative imaging were not reported, making it difficult to apply to current clinical practice standards. Another cohort of 506 patients with cT1–T2, cN0 breast cancer underwent pre-operative lymphoscintigraphy combined with pre-operative gamma probe analysis for evaluation of sentinel lymph node drainage patterns. Ipsilateral IMLNs were sentinel nodes in 22% of patients and were able to be safely removed in 78% of those patients (2). A subsequent retrospective evaluation of three randomized control trials visualized IMLNs as sentinel lymph nodes in 13–37% of cases with pre-operative lymphoscintigraphy (5).

A trial including 3,685 patients with breast cancer injected radioactive tracer at either peritumoral or intratumoral locations, and 20.5% of patients had ipsilateral IMLN identified on pre-op lymphoscintigraphy. Operative retrieval of IMLNs was completed in 81% of patients with sentinel IMLNs, with 130 (21.3%) of these patients (3.5% of all patients) noted to have IM nodal metastasis. In 43 of these cases, IM nodal metastasis was observed in isolation and not in association with axillary nodal metastasis (10).

A recent narrative review which examined nodal basins with a variety of methods including sentinel lymph node biopsy, ultrasound, magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT), and opportunistic biopsy during surgery for free flap breast reconstruction included 22 retrospective studies and reported a wider range in the prevalence of isolated metastasis to IMLNs (without the presence axillary nodal metastasis) between 1.2–17.9% (11). In summary, IM nodal metastasis is seen much more often in the setting of axillary lymph nodes that are pathologically positive for metastatic carcinoma. Isolated IM nodal metastasis is rare.

Although IM nodal metastasis is strongly associated with axillary nodal positivity, there are several additional patient and tumor characteristics that put a patient at elevated risk of developing IM nodal metastasis. A review of 1,697 patients who underwent extended radical mastectomy without pre-operative treatment from 1956–2003 identified factors associated with a >20% risk of having IM nodal involvement including any breast tumor with >4 positive axillary nodes, a medially located T2 tumor or medial tumor with axillary node involvement, age <35 with a T3 tumor, and T2 tumor with associated positive axillary lymph nodes (12). A nomogram was developed and validated in 2023 to facilitate clinical estimation of the presence of IM nodal metastasis (13). Predictive modeling directed inclusion of tumor size, tumor location, lymphovascular invasion, number of positive axillary nodes, and histologic grade into the nomogram calculation. All factors except histologic grade had a significant relationship with IM nodal metastasis on multivariate analysis, consistent with the findings published by Huang *et al.* in 2008 (12,13).

IM nodal detection by imaging

Improved imaging techniques have helped improve identification of IM lymphadenopathy. IMLN detected at the time of staging with cross sectional imaging (MRI, PET-CT) guides locoregional and systemic treatments, which are often escalated in the presence of IM disease (*Figures 1,2*). Few studies have evaluated the use of MRI or PET-CT

specifically for the detection of IM lymphadenopathy. In a head-to-head evaluation of MRI and PET-CT, 13 patients in a cohort of 90 had IM disease detected by both MRI and PET-CT with a single additional patient with IM disease detected by MRI only (14). Investigators of this study concluded that there was no difference in performance between the two imaging modalities, but were limited by small cohort size. In a large retrospective review of 13,996 breast MRIs, 473 MRI reports mentioned an enlarged IMLN. MRI results were cross referenced with the results of percutaneous sampling of these nodes and PET-CT findings. One hundred and sixty-eight patients were noted to have confirmed metastatic IMLN on biopsy and were compared to 81 patients with negative biopsies and/or no associated uptake on PET-CT categorized as benign IMLN. Metastasis was more common with the following MRI features; longer lymph node axes, absence of fatty hilum, internal necrosis, indistinct margin appearance, restricted diffusion (all P<0.001) and multi-level interspace involvement (P=0.006) (15).

In a 2013 publication by Wang *et al.* looking specifically at PET-CT, 1,259 patients underwent PET-CT for breast cancer and 110 (9%) had IM nodes deemed positive by imaging with PET-CT. Of the 102 patients with complete data, 25 patients underwent percutaneous biopsy and 20/25 (80%) had positive histopathologic findings confirming metastatic involvement (16). Because IMLN involvement is relatively rare, it is difficult to obtain large cohorts of patients to more clearly define the sensitivity and specificity of each imaging modality. However, IMLN detection has largely shifted from surgical resection to pre-treatment imaging for staging in the modern era (17,18).

Prognostic value of positive IM nodes

IM nodal status has historically been strongly valued in determining a patient's prognosis, though removal of IMLNs has not demonstrated improvement in overall survival (OS). A 30-year retrospective review of a 737-patient cohort who underwent either Halsted mastectomy or extended mastectomy plus IMLN dissection did not demonstrate significant difference in OS and disease specific survival between groups at 30 years of follow-up (19). This principle was again demonstrated in three randomized controlled trials, all of which have not demonstrated survival benefit from extended mastectomy inclusive of IM nodal dissection with comparison to radical or modified radical mastectomy alone (19-21). Analysis of the Madsen *et al.* cohort including 3,685 patients did not demonstrate a significant relationship between IM nodal metastasis and OS, except in the absence of axillary metastasis [hazard ratio (HR) =2.68, 95% confidence interval (CI): 1.30–5.54] (10).

While IM nodal positivity may play a role in OS when present in isolation, an independent contribution to locoregional recurrence has not been identified. IM nodal recurrence rates without distant disease were observed in <1% of patients (n=6) in a cohort of 6,000 patients observed for locoregional recurrences, confirmed by cytology and/or CT scan. Five of the 6 patients with IM recurrence ultimately progressed to distant disease and death (22).

Surgical management of IM nodes

Biopsy and dissection of the IM nodal chain poses a significant surgical challenge. Due to the location of the IM nodes (lateral to the sternum in the intercostal space, just anterior to the pleural space) the surgical approach to retrieving these nodes can be tedious, unyielding, precarious and possibly require additional incision(s) in cases of breast conservation or mastectomy with reconstruction. In one study evaluating patterns of sentinel lymph node drainage in 581 patients, 95 demonstrated drainage to the IMLNs on pre-operative lymphoscintigraphy. Of these patients, 51 had IM chain exploration with nodes found in only 35 patients. This represents a 69% success rate of retrieval. Of these patients, 7.8% (n=4) experienced pneumothoraces as a complication of surgical exploration (3).

Traditionally, surgical retrieval of the IM nodal chain has been completed through an open approach. In patients with pre-operative lymphoscintigraphy demonstrating drainage to the IM nodal basin, a gamma probe can be used intraoperatively to localize the sentinel IMLN. A pilot study of video-assisted thoracoscopic (VAT) IM nodal biopsy was performed recently in patients with breast cancer and PET avidity in the IM nodal chain. Of 34 patients identified with PET avidity in IMLNs, 11 patients underwent VATs resection of IMLNs without any complications noted. However, patients required an average 2–3-day hospital stay following this procedure (23). Importantly, without strong evidence that retrieval of involved IMLNs impacts oncologic outcomes, there would not be a benefit to removal that would outweigh the associated surgical risk. If knowledge of the pathologic status of an IMLN will impact treatment regimens, percutaneous biopsy should be considered first.

IM nodal radiation

Considering the complexities and risk of obtaining pathologic confirmation of IM nodal status, radiation therapy is commonly utilized to treat suspicious IM nodal disease. Additionally, IM nodal irradiation (IMNI) has been a common component of postmastectomy radiation therapy (PMRT), with or without evidence of IM disease on pre-treatment imaging. Several studies examining the role of post mastectomy radiation with the inclusion of IMNI either alone or as part of regional nodal irradiation (RNI) have demonstrated a reduced risk of recurrence and breast cancer mortality (24,25). A non-randomized Danish cohort of 3,089 patients with early-stage, node positive breast cancer who underwent breast surgery with axillary clearance were followed for 8 years after treatment, either with or without IMNI. A significant improvement in OS was seen in patients who received IMNI (75.9% *vs.* 72.2%) after 8 years of follow-up (26). These findings influenced the most recent update of the American Society of Clinical Oncology (ASCO) guidelines regarding PMRT to include recommendation for inclusion of IMLN irradiation in patients with T1–2 tumors with one to three positive axillary sentinel lymph nodes (27). Fifteen-year follow-up of this patient cohort evaluated by Thorsen *et al.* demonstrated sustained improvement in OS in patients receiving IMNI (60.1% *vs.* 55.4%, HR =0.86). The distant recurrence risk at 15-year follow-up was also significantly decreased in patients receiving IMNI, as was the breast cancer mortality rate (35.6% *vs.* 38.6% and 31.7% *vs.* 33.9% respectively, P≤0.05) (6). An additional 12-year retrospective review examining the long-term survival of patients after IMNI demonstrated a 10-year disease-free survival of 65% *vs.* 57% (P=0.05) in patients who did not receive IMNI. This study also summarized that patients with N2 disease derived the greatest benefit from IMNI (HR =0.44) (28). In a recently published meta-analysis evaluating RNI practices in early breast cancer, a significant reduction in disease recurrence, breast cancer mortality and all-cause mortality was shown with the addition of RNI with no effect on non-breast cancer mortality. Studies completed prior to the 1990's showed little effect on breast cancer mortality but a significant increase in non-breast cancer mortality, highlighting improvement in technique over the past 20 years (29).

Attempt has been made to better clarify the role of IMNI and provide more specificity to which patients derive the greatest benefit from the addition of this therapy, to outweigh the risk of radiation associated cardiopulmonary toxicity. A phase three randomized controlled trial enrolled 735 patients with node positive breast cancer undergoing either breast conserving therapy or mastectomy and randomized patients to receive RNI with or without IMNI. No statistical differences were observed in OS, breast cancer mortality, disease-free survival, or distant metastasis-free survival at 7 years, though all trended toward improvement with the addition of IMNI. Interestingly, subgroup analysis showed an improvement in 7-year disease-free survival by 10% in patients with central/medially located tumors who underwent IMNI (30). Of note, the results of this study and its evaluation of survival endpoints have been critiqued as the study design was not powered as a noninferiority study to compare RNI with and without IMNI (31). In contrast, EORTC 22922/10925, a phase three randomized control trial, assigned patients to either IM and medial supraclavicular (IM-MS) irradiation or no irradiation. Patients with stage I–III breast cancer with involved axillary nodes or a central or medially located primary tumor were enrolled (n=4,004), though IM lymphadenopathy was not a component of the enrollment criteria (32). At median follow-up of 15.7 years, OS was 73.1% in the IM-MS irradiation group and 70.9% in the control group [HR =0.95 (95% CI: 0.84–1.06), P=0.36]. In the IM-MS irradiation and the control patients, 24.5% *vs.* 27.1% experienced any breast cancer recurrence (P=0.024) and breast cancer related mortality was 16.0% *vs.* 19.8% (P=0.0055). No differences in disease-free survival [HR =0.93 (95% CI: 0.84–1.03), P=0.18] or distant metastasis-free survival [HR =0.93 (95% CI: 0.83–1.04), P=0.18] were noted between groups. Overall, significant reduction in breast cancer related mortality and breast cancer recurrence was noted in patients who received IM-MS irradiation in stage I–III breast cancer, though no improvement in OS was seen (32). It is also worth noting that the studies discussed here do not stratify patients by biologic subtype of breast cancer which may play a role in prognosis and oncologic outcomes in the parallel of improved systemic therapies.

While IMNI seems to confer a benefit to patients with significant axillary disease burden, it is not completed without consequence. Left sided IMNI in particular is associated with increased cardiac and pulmonary toxicity. Several studies, including the Thorsen *et al.* cohort have excluded patients with left sided cancer because of concerns regarding this potential toxicity (6,26,30).

Another concern is the variation in implementation of this practice, as shown by differing national guidelines.

Table 2 North American society guidelines for management of IMLNs in the treatment of stage I–III breast cancer, 2016–2024

Society	Indications for postoperative RNI	Recommendations
NCCN	T1–3, cN0 or cN+ undergoing BCT—strength of recommendation for RNI depending upon number of involved nodes, tumor location and associated high risk features	When considering RNI, anatomic variations across patients result in significant differences in prescription depth and field design. Recommend contouring the individual nodal basins that are at-risk using one of the various breast atlases
	T1–3, cN0 or cN+ undergoing mastectomy—strength of recommendation for RNI depending upon margin width, number of involved nodes and associated high risk features	A supplemental RT boost can be delivered to grossly involved or enlarged lymph nodes (i.e., internal mammary or clavicular) that have not been surgically addressed (25,32)
	Strongly consider for any cN+, ypN0 post neoadjuvant therapy	
	Any ypN+	
	Any T4d patients	
ASCO	Recommendations only exist for postmastectomy circumstances	PMRT or breast radiation plus RNI reduces the risks of LRF, any recurrence, and breast cancer mortality for patients with T1–2 breast cancer with 1–3 positive axillary nodes. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit is outweighed by its potential toxicities
		Axillary nodal involvement after neoadjuvant systemic therapy should receive PMRT or breast radiation plus RNI. Treatment should generally be administered to both the IM nodes and the supraclavicular-axillary apical nodes in addition to the chest wall or reconstructed breast (24,32,34)

IMLN, IM lymph node; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; RNI, regional nodal irradiation; BCT, breast conserving therapy; RT, radiotherapy; PMRT, postmastectomy radiation therapy; LRF, locoregional failure; IM, internal mammary.

In 2019, Duane *et al.* completed a systematic review of international guidelines regarding IMNI. They evaluated a cohort of patients treated with adjuvant radiation in England from 2012 to 2016 and found that 13% would have been recommended IMNI in the UK, whereas 59% in the US, 32% in Germany, and 56% in Ireland would have been recommended IMNI (33). Even within the US & Canada, several organizations have released guidelines that also vary in IMNI recommendations, most commonly based on tumor biology, staging, and type of surgery completed (*Table 2*) (34). This historical lack of consensus further highlights the deficit in high quality data to support best practice strategies.

Conclusions

The IM nodal chain remains an area of breast cancer diagnosis and treatment with gaps in the literature. As a result, there is large international variation in consensus recommendations for disease management. With several studies demonstrating that >20% of patients experience lymphatic drainage to the IM nodal basin, it is imperative we endeavor to better understand how to best manage this nodal basin in breast cancer treatment. As the behavior of different tumor histologic subtypes is better understood, the opportunity for increased granularity in study design may reveal a patient population that benefits more or less from treatment of the IMLN. The data currently supports omitting the pursuit of surgical excision of IMLNs in most breast cancer patients, and suggests that patients with large, central or medially located tumors, and known axillary disease (particularly patients with N2 disease) should be given strong consideration for IMNI. Until more data becomes available, consensus guidelines and multidisciplinary disease management should be utilized to guide treatment recommendations.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-2/rc

Peer Review File: Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-2/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-2/coif). M.A.P. received travel and research funding from Intuitive Surgical as well as honoraria from Kubtec Medical Imaging and OncLive; she is an Internal Department of Surgery Data and Safety Monitoring Board (DSMB) participant. J.C.B. receives grant funding paid to her institution from Eli Lilly and SimBioSys and is on data safety monitoring committee for CairnsSurgical. She has received honoraria for speaking from OncLive, PER and PeerView; and royalties from writing for UpToDate. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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