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Original Article

A Questionnaire Survey of Current Practice in the Management of Internal Mammary Lymph Nodes in Breast Cancer

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Abstract

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Background Radiotherapy (RT) is an important modality in the management of breast cancers (BC). Large randomized trials have suggested that prophylactic regional nodal irradiation inclusive of internal mammary lymph nodes (IMLN) reduces BC-related mortality. However, the adoption of IMLN-RT has been variable due to relative benefits and toxicity concerns.

Methods A survey was emailed to radiation oncologists (ROs) across the country wherein they were asked about their practice regarding IMLN-RT in BC.

Results We received 128 responses, which included radiation oncologists across both private institutions (PIs) and government institutions (GIs). Fifty-six (43.8%) routinely offer prophylactic(p) IMLN-RT and an additional 15 (11.71%) suggested they would have offered it in the absence of logistic constraints. Almost all, 121 (94.5%) radiate the IMLN in case of radiologically positive lymph nodes (LNs).

Fifty-six ROs (43.8%) offered prophylactic IMLN-RT in node-negative disease. Among those who did not offer IMLN-RT, most (84.72%) felt the clinical evidence was equivocal. Of the 56 who offered pIMLN-RT, 34/56 (60.71%) offered to locally advanced tumors, 20/56 (35.71%) offered to all inner and central tumors (ICQT), 29/56 (51.78%) to >4 axillary LN-positive and 9/56 (16.07%) to any axillary LN-positive. The majority, i.e., 36/56 (64.28%) radiated upper three intercostal spaces, 9 (16.07%) radiated upper five intercostal spaces, and 6 (10.9%) decided based on tumor location, while 5 (9%) irradiated one space below the involved space.

Keywords

- breast cancer
- radiotherapy
- internal mammary lymph nodes
- survey
- current practice

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Overall, simulation-based planning was undertaken in 99% of PIs as opposed to 89% of GIs ($p = 0.03$). The majority of ROs, i.e., 92 (72.4%) preferred IMRT to IMLN-RT.
In addition, the surgical approach to IMLN was practiced by surgeons at 18 (14%) centers, of which 13 (72.22%) operated the IMLN when radiologically evident. The IMLN dissection was preferentially performed for second and third intercostal spaces as suggested in 10 (55.55%) responses, while 8 (44.44%) performed thoracoscopic dissection of the IMLN chain. The distribution of prophylactic, definitive IMLN-RT, and IMLN dissection did not differ significantly between GI and PI ($p = $ NS).
Conclusions pIMLN-RT is still not the standard protocol in most centers citing equivocal evidence in the literature. Logistics, though different in GIs and PIs, did not impact the decision of pIMLN-RT. Further efforts would be required to standardize practice in IMLN across India.

Background

Breast cancer (BC) is the most common cancer diagnosed in women[1] and LN status continues to be an important prognostic factor. Overall, lymphatic drainage to the IMLN has been reported in various surgical and nuclear imaging studies to range from 4 to 16% of BC.[2] The incidence can be as high as 20 to 65% in inner quadrant tumors and 16 to 50% in axillary lymph node (ND)-positive disease. Treatment of IMLN has been an area of debate for decades.[3–5] Radiotherapy (RT), which is an important modality in the multidisciplinary management of BC,[6,7] has been evaluated for its role in IMLN management in large randomized trials such as the EORTC 22922, MA 20, and the Danish population-based study. These studies have suggested that prophylactic regional nodal irradiation inclusive of internal mammary lymph nodes (IMLN) reduces BC-related mortality with no effect on overall survival.[2–6] The updated EORTC 22922 results, with a 15-year follow-up, reiterated the lack of overall survival benefit.[3] Additionally, data from the Korean group also suggested that there was no survival benefit over 7 years with IMLN-RT.[8,9] With no evidence of overall survival benefit and toxicity concerns (pulmonary and cardiac fibrosis), the adoption of pIMLN-RT in routine clinical practice has been variable. Newer techniques of therapeutic RT with three-dimensional conformal radiotherapy (3DCRT), intensity-modulated RT (IMRT), volume modulated arc therapy (VMAT), and proton therapy compared to the conventional two-dimensional technique have partially abrogated the concerns of toxicity.[10,11] Also, the changing landscape of systemic therapy and advances in available options may have an impact on the patterns of recurrence, wherein the additional value of prophylactic IMLN-RT is not clear.

Thus, the evidence available is possibly not sufficient to be generalized to the real-world population in various geographic regions. This survey was thus conducted to identify the various practice patterns amongst radiation oncologists across the country, including the use of surgical options for treating IMLN. This would provide an opportunity for understanding the current practice of addressing the IMLN and the possible need for future studies.

Methods

A survey was emailed to radiation oncologists (ROs) across the country wherein they were asked about their practice regarding IMLN-RT in BC. The questionnaire was designed by the surgeons and the ROs at our center (a tertiary cancer center). The study was conducted and analyzed in 2020. The survey was opened in July 2020 and closed at the end of October 2020, i.e., a span of 4 months. A reminder was sent to all clinicians in the form of emails and messages. The questionnaire included demographic details including the type of institution, the facility available for RT planning, and the type of RT given. They were also asked about their practice of IMLN RT, whether prophylactically or not, and their indications for IMLN RT. They were also enquired about the surgical practice in their institution, the indications for IMLN dissection, and the modality used. The responses (128) were tabulated and analyzed with Statistical Package for the Social Sciences version 23. Out of the 300 emails sent, the response rate among RO was 42.6%. Descriptive analysis was done and a p-value of less than 0.05 was considered significant. Cross-tabulation and chi-square analysis were done to quantitatively analyze the categorical data and assess the significance.

Results

We received 128 responses that included ROs across both private institutions (100-PIs), government institutions (25-GIs), and trust institutions (3 TIs). Overall, 56 participants (43.8%) routinely offer prophylactic IMLN-RT and an additional 15 (11.71%) suggested they would have offered pIMLN-RT in the absence of logistic constraints. Among the 72 who did not offer pIMLN-RT, 61/72 (84.72%) felt the clinical evidence was equivocal. Almost all, 121/128 (94.5%) radiate the IMLN when it is radiologically evident at the baseline staging investigations (RT was given after receipt of appropriate systemic therapy). The institutions were equipped with various modalities of delivering RT as mentioned in ►Table 1. The technique most commonly used to irradiate the IMLN was IMRT 92 (72.4%) and 4% did not have

Table 1 Radiotherapy treatment modalities available at institutions

Radiation facilities	Number (%)
External beam	198
• IMRT/IGRT	84 (65.6)
• 4DRT	57 (44.9)
• 3DCRT	22 (17.18)
• Both	9 (7.03)
• Telecobalt	26 (20.31)
Brachytherapy	48 (37.5)

the required facilities or logistic support for the delivery of advanced RT procedures.

Of the 56 who offered pIMLN-RT, 34/56 (60.71%) offered to locally advanced tumors, 20/56 (35.71%) offered to all inner and central tumors (ICQT), 29/56 (51.78%) to > 4 axillary LN positive and 9/56 (16.07%) to any axillary LN positive. The majority, 36/56 (64.28%) radiate upper three intercostal spaces, 9 (16.07%) radiate upper five intercostal spaces, and 6 (10.71.9%) decide based on tumor location, while 5 (9%) irradiated one space below the involved space.

Overall, simulation-based planning was undertaken in 99% of PI as opposed to 89% of GI ($p = 0.03$) (►**Table 2**). The distribution of prophylactic, definitive IMLN-RT and IMLN dissection did not differ significantly between GI and PI ($p = $ NS).

The survey also addressed the surgical approach to IMLN and only 18/128 (14%) suggested their surgeons did dissect the IMLN, of which 13/18 (72.22%) did so in patients with radiologically evident IMLN (►**Fig. 1**). IMLN dissection was preferentially performed for second and third intercostal spaces as suggested by 10/18 (55.55%) responders, while 8/18 (44.44%) performed thoracoscopic dissection of the IMLN chain.

Table 2 Simulation-based RT planning in GIs and PIs

Simulation	Govt/Trust	Private
Yes	25 (89%)	99 (99%)
No	3 (10.7%)	1 (1%)

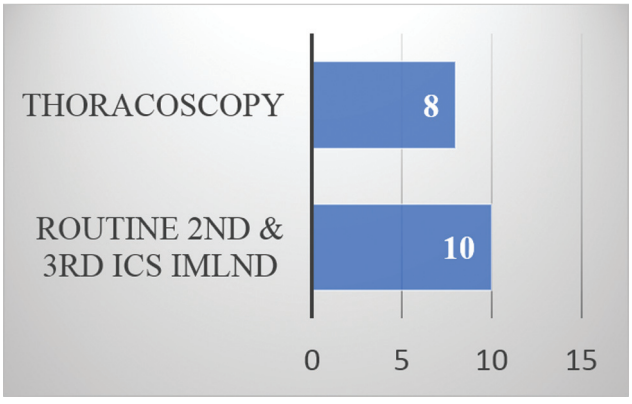

Fig. 1 Type of surgery for IMLN.

Discussion

NCCN states that IMLN RT is to be 'strongly considered' in pN1 disease, irrespective of the number of nodes based on the results of the large randomized trials.[12]

Regional nodal irradiation has been a constant topic of debate. The landmark trials, EORTC 22922,[3] MA 20,[13] and the Danish group[4] evaluated the role of comprehensive regional nodal irradiation, and the French group[6] studied the incremental benefit from IMLN radiation in particular and suggested that prophylactic regional nodal irradiation inclusive of internal mammary lymph nodes reduces breast cancer-related mortality with no effect on overall survival.[2–4] However, subgroup analysis has suggested the benefit of prophylactic IMLN radiotherapy for central or inner quadrant tumors.[8] We report that 43.8% of the respondents to our survey practice prophylactic RT to IMLN compared to 17% as reported by the EORTC group.[3] This survey gives an overview of the real-world management of IMLN in breast cancer across the country. It highlights the differences in practice, differential interpretation of published literature, and clinical practice. It also captures the general attitude toward treatment and techniques used in clinical practice. There have been other similar other surveys reported in the literature (►**Table 3**) from across the globe. Taghian et al,[14] in their survey across North America and Europe, conducted in 2001, reported that 64% of radiation oncologists from Europe and 49% from North America practiced prophylactic IMLN-RT and those who practiced IMLN RT were in academic practice.

The EBCTCG meta-analysis included 14 trials with regional nodal irradiation and showed an increase in non-breast cancer-related mortality for older trials.[5] Newer techniques of radiation are associated with less toxicity.[10] The survey by Roumeliotis et al[10] focused on the various techniques used for radiation of the intermammary lymph nodes. They reported lesser toxicity with VMAT techniques and 3DCRT. This highlighted the importance of techniques used despite increased exposure of normal tissues to radiation. In our survey, we found that 96.9% of oncologists used simulation-based planning and 72.4% preferred the use of IMRT.

The case selection for prophylactic radiotherapy to the IMLN is difficult in modern times when the patient receives effective systemic therapy, which is likely to impact the recurrence patterns. Nonetheless, several high-risk cases can be considered for IMLN-RT, where the risk–benefit ratio may be in favor of the inclusion of IMN in the radiation target. Though the toxicity from modern radiotherapy techniques is remarkably less, the equipoise will remain, a robust clinical benefit in the form of overall survival improvement is yet to be shown.[15–17]

Surgery for IMLN was described with extended radical mastectomies. In this era of conservativism, there is much debate on the surgery for non-axillary regional LNs. In radiologically evident IMLN, the patterns of recurrence

Table 3 Comparison between our study and other surveys in the literature

Characteristics	Our study	Roumeliotis et al[10]	NORA survey-Belkacemi et al[30]
Region	India	Canada	EORTC
Year	2020	2018	2014
Sample size	128	135	84
RT planning (simulation-based)	96.9%	Conventional planning-100%	96%
IMLN RT	43.8%	61%	17%
Type of RT	4D,3DCRT, IMRT, photon	Static photons, electrons, VMAT, IMRT protons	Part of PMRT
N 0, inner central tumors	79.29%	–	27%

have often included ipsilateral pleural disease.[18] Hence, the constant need to modify our management and improve disease-free survival. Handley was a pioneer in describing the technique of intercostal space dissection. Handley reported a 33% IMLN positivity in biopsies. Urban et al and a Japanese trial went on to prove no survival benefit with extended radical mastectomy including IMLN dissection.[19–24] French and Italian trials also reaffirmed the absence of survival benefits though they were underpowered and had lesser use of chemotherapy.[6,25–29] Our survey showed that 14% of surgeons dissected the IMLN, of which 13/18 (72.22%) did so in patients with radiologically evident IMLN.

Our survey highlights the differential interpretation of data on the management of IMLN by radiation oncologists in India and adoption in clinical practice. The limitations of this study are that the survey could not capture the difference in practice based on laterality of presentation, doses utilized, and toxicity with prophylactic RT. Another notable concern is the lower response rate in our survey among the radiation oncologists, which cannot be used to generalize the practice across the country. Also, there could have been a bias toward a particular modality of treatment in GIs and PIs due to logistic differences.

Conclusions

Our survey is the first from India to highlight clinical practice in the management of IMLN in breast cancer. Prophylactic IMLN radiotherapy is still not the standard protocol in most centers citing equivocal evidence in the literature, irrespective of available logistics. In an attempt to extrapolate international guidelines, we need to amend methodologies with a risk–benefit approach. Further studies would be required to standardize practice in IMLN across India.

Disclaimer

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.

Conflict of Interest

None declared.

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