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Original Article

Incidental Radiation Exposure to the Internal Mammary Lymph Nodes in Breast Cancer Patients Undergoing Intensity–Modulated Radiation Therapy: A Retrospective Analysis

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Abstract:

Background: Breast cancer (BC) remains the most common malignancy among Indian women, with Stage III being the most frequent at diagnosis. While radiation therapy (RT) plays a pivotal role in the adjuvant treatment of breast cancer, the inclusion of internal mammary lymph nodes (IMLNs) in the radiation field remains controversial due to potential cardiopulmonary toxicity. However, the extent of incidental radiation to the IMLNs, especially with forward planning intensity–modulated radiation therapy (IMRT), remains under–explored.

Objective: This study aimed to evaluate the incidental radiation dose received by the IMLNs in patients with left–sided breast cancer treated with forward planning IMRT.

Materials and Methods: A total of 36 left–sided breast cancer patients, aged 35–60 years, who underwent modified radical mastectomy followed by adjuvant RT using IMRT, were retrospectively analyzed. CT–based planning and contouring were performed according to RTOG guidelines, with IMLNs contoured retrospectively using Jetwa et al.'s method. Dosimetric parameters for the planning target volume (PTV) and IMLNs were extracted and analyzed using dose–volume histograms. Statistical comparisons were made using the dependent Student's t–test.

Results: The PTV received effective radiation coverage with a mean D95 of 38.47 Gy and a mean Dmean of 40.10 Gy. The IMLNs, although not directly targeted, received significant incidental radiation, with a mean D95 of 8.49 Gy, D50 of 21.59 Gy, and Dmean of 21.40 Gy. The maximum dose to the IMLNs (Dmax) reached 38.14 Gy. Comparative analysis revealed statistically significant differences in both Dmax and Dmean between PTV and IMLNs ($p = 0.004$ and $p < 0.001$, respectively).

Conclusion: Forward planning IMRT provides substantial incidental radiation exposure to the IMLNs, which may have therapeutic implications in reducing recurrence risk. However, this exposure also necessitates careful consideration of potential long–term toxicities to adjacent organs. Further prospective studies are warranted to evaluate the clinical outcomes associated with incidental IMLN irradiation.

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Introduction

Breast cancer (BC) remains the most prevalent malignancy among Indian women, with Stage III being the most frequently diagnosed stage at presentation [1]. The management of BC often involves a multimodal approach, including surgery, chemotherapy, and radiation therapy (RT). Adjuvant RT is a critical component for nearly all patients with early–stage and locally advanced breast cancer, aiming to reduce the risk of local recurrence and improve overall survival [2]. A significant area of ongoing debate in the treatment of BC is the optimal approach to lymph nodal irradiation. The latest guidelines from the National Comprehensive Cancer Network (NCCN) recommend the inclusion of the internal mammary lymph node (IMLN) area in the radiation field for patients with N1 nodal disease [3]. This recommendation is supported by landmark studies such as the MA.20 trial and the European Organization for Research and Treatment of Cancer (EORTC) 22922/10925 trial, which demonstrated a survival benefit with comprehensive nodal irradiation, including the IMLNs, even in patients with limited nodal involvement [4][5]. Despite these recommendations, many institutions are hesitant to routinely irradiate the IMLN area due to concerns about the potential for increased late toxicities to the heart and lungs. Interestingly, in patients who have undergone treatment for breast cancer, the rate of isolated IMLN recurrence is reported to be less than 1% [6]. This low recurrence rate raises questions about the necessity and benefit of routine IMLN irradiation, particularly considering the incidental radiation dose that these nodes may receive during treatment targeting other regional lymph node areas, such as the axillary lymph nodes (ALNs) [7]. The potential toxicity associated with IMLN irradiation includes significant concerns regarding cardiopulmonary health. Studies have shown that RT can lead to increased risks of heart disease and lung complications, particularly when the internal mammary chain is included in the treatment field [8]. Techniques such as deep inspiration breath hold (DIBH) have been developed to mitigate these risks by reducing the radiation dose to the heart and lungs, but their implementation is not yet universal [9]. Forward planning intensity–modulated radiation therapy (IMRT) is a sophisticated radiation technique that allows for precise targeting of the tumor while minimizing dose to surrounding healthy tissues. Given the ability of IMRT to conform doses to complex target volumes, it is crucial to understand the incidental doses delivered to non–targeted lymph node areas, including the IMLNs, and their potential clinical implications [10]. Furthermore, the delineation of target volumes in radiation therapy is a critical factor in achieving optimal therapeutic outcomes while minimizing side effects. Accurate contouring of lymph node regions, including the IMLNs, is essential for ensuring that these areas receive adequate incidental radiation doses without exceeding tolerance levels for surrounding organs at risk (OARs). Advanced imaging techniques and treatment planning systems continue to evolve, providing better tools for radiation oncologists to balance efficacy and safety [11]. This study aims to investigate the incidental radiation dose to the internal mammary lymph nodes in breast cancer patients treated with forward planning IMRT. By evaluating the dosimetric data, this research seeks to provide insights into the extent of incidental IMLN irradiation and its potential impact on clinical outcomes, contributing to the ongoing discussion regarding optimal nodal irradiation strategies in breast cancer treatment.

Material and Method

Thirty Six patients with left–sided breast cancer, aged between 35 and 60 years (mean age: 56.5 years), who had undergone a modified radical mastectomy and received radiotherapy using the IMRT technique in our department, were included in this study. All patients were treated between January and July 2023, and the majority presented with a palpable lump in the left breast and axillary swelling. Histological analysis confirmed infiltrating ductal carcinoma in most cases. Exclusion criteria for the study included patients who had undergone prior breast surgery or radiotherapy, those with metastatic disease, or patients who had received breast–conserving surgery.

Radiotherapy planning involved contrast–enhanced CT simulation with a 3 mm slice thickness, performed with patients in a supine position and arms raised. Target volumes were delineated according to the Radiation Therapy Oncology Group (RTOG) Breast Cancer Atlas, while the internal mammary lymph nodes were retrospectively contoured based on the methodology outlined by Jetwa et al. Inverse planning for IMRT was performed using five to seven semi–opposing tangential beams, ensuring dose coverage of the planning target volume (PTV) from 95% to 107% of the prescribed dose, which was 40 Gy delivered in 15 fractions over three weeks using 6 MV photons.

For statistical analysis, chi–square tests were used to compare categorical variables, while continuous variables and correlations between dosimetric parameters were evaluated using the two–tailed, dependent Student's t–test. A p–value of less than 0.05 was considered statistically significant.

Results

This study conducted a thorough dosimetric analysis of the planning target volume (PTV) and the internal mammary lymph nodes (IMN) in 36 patients with left–sided breast cancer treated with intensity–modulated radiation therapy (IMRT). This study provides valuable

insights into the extent of incidental IMN irradiation and underscores the need to balance the benefits of such exposure against the risks of cardiopulmonary toxicity, informing the ongoing debate about optimal lymph nodal irradiation strategies in breast cancer treatment. Figures 1(a) and 1(b) show the dose distribution over the IMLNs in axial and coronal views, respectively.

For the PTV, the dose–volume histogram (DVH) analysis revealed that the mean dose received by 95% of the PTV (D95) was 38.47 Gy, and the dose received by 90% of the PTV (D90) was 37.20 Gy. This indicates that the vast majority of the PTV was covered effectively by the therapeutic dose, with only a slight deviation from the prescribed dose of 40 Gy. The maximum dose (Dmax) observed within the PTV was 44.01 Gy, suggesting that some areas received slightly higher doses, while the mean dose (Dmean) delivered to the PTV was 40.10 Gy, closely aligning with the prescribed dose. These parameters collectively show that the PTV coverage was highly effective, ensuring adequate radiation delivery to the targeted tumor area. These values are presented in Table 1.

The analysis of the IMN dosimetric parameters highlighted significant incidental radiation exposure. The mean volume of the IMN that received at least 25 Gy (V25) was 37.95%, indicating that a substantial portion of the IMN volume received a moderate dose of radiation. Furthermore, the mean dose received by 95% of the IMN volume (D95) was 8.49 Gy, while 50% of the IMN volume (D50) received 21.59 Gy. This suggests that incidental radiation exposure was non–uniform, with half of the IMN volume receiving more than half of the prescribed PTV dose. The maximum dose (Dmax) to the IMN was 38.14 Gy, close to the maximum dose observed in the PTV, indicating that some areas of the IMN were exposed to doses nearly equivalent to those intended for the PTV. The mean dose (Dmean) delivered to the IMN was 21.40 Gy, reflecting significant incidental radiation exposure. These findings are summarized in Table 2.

These findings demonstrate that while the primary goal of the radiation therapy was to target the PTV, the IMNs also received substantial incidental doses. This incidental radiation to the IMNs could potentially contribute to therapeutic effects, such as reducing the risk of recurrence in these lymph nodes. However, it also raises concerns about the potential for increased radiation–induced toxicities to adjacent organs, particularly the heart and lungs.

The dose–volume histogram (DVH) illustrates the dose distribution for the internal mammary nodes (IMN) and the planning target volume (PTV) in a radiotherapy treatment plan. The PTV, depicted by the red curve, represents the region targeted for therapeutic radiation, ensuring that it receives the prescribed dose with optimal coverage. The IMN, shown by the purple curve, is not directly targeted but still receives incidental radiation due to its proximity to the PTV. The graph indicates how much of the volume for each structure receives specific radiation doses, with the x–axis representing dose (in centigray) and the y–axis representing the percentage of the total volume. This visualization is crucial for evaluating the effectiveness of radiation delivery to the target (PTV) and assessing any unintentional exposure to IMN, which may receive

Variable	PTV (Mean)
V95 %	93.19
D90 (Gy)	37.20
D95 (Gy)	38.47

Table 1: Dose–Volume Histogram (DVH) for Planning Target Volume (PTV)

In this table, the dose received by 90% of the PTV volume is 37.20 Gy, and the dose received by 95% of the PTV volume is 38.47 Gy. These values are presented alongside the corresponding percentage of PTV volume for each DVH curve.

Variable	IMN (Mean)
V25 (%)	37.95
D95 (Gy)	8.49
D50 (Gy)	21.59

Table 2: Volume Dose Parameters of Left–Side Internal Mammary Lymph Node (IMN)

In this table, the dose received by 95% of the IMN volume is 8.49 Gy, and the dose received by 50% of the IMN volume is 21.59 Gy. These values are presented alongside the corresponding percentage of PTV volume for each DVH curve.

Variable	PTV (Mean)	IMN (Mean)	P Value	t Value
Dmax (Gy)	44.01	38.14	0.004	5.16
Dmean (Gy)	40.10	21.40	0	10.81

Table 3: Maximum dose (Dmax) and mean dose (Dmean) for PTV and IMN

The table compares radiation doses between the Planning Target Volume (PTV) and Internal Mammary Nodes (IMN). The maximum dose (Dmax) for PTV is 44.01 Gy and for IMN 38.14 Gy ($p = 0.004$). The mean dose (Dmean) for PTV is 40.10 Gy, compared to just 21.40 Gy for IMN, with a p value of 0 indicating strong statistical significance. Showed that ther is significant incidental radition exposure.

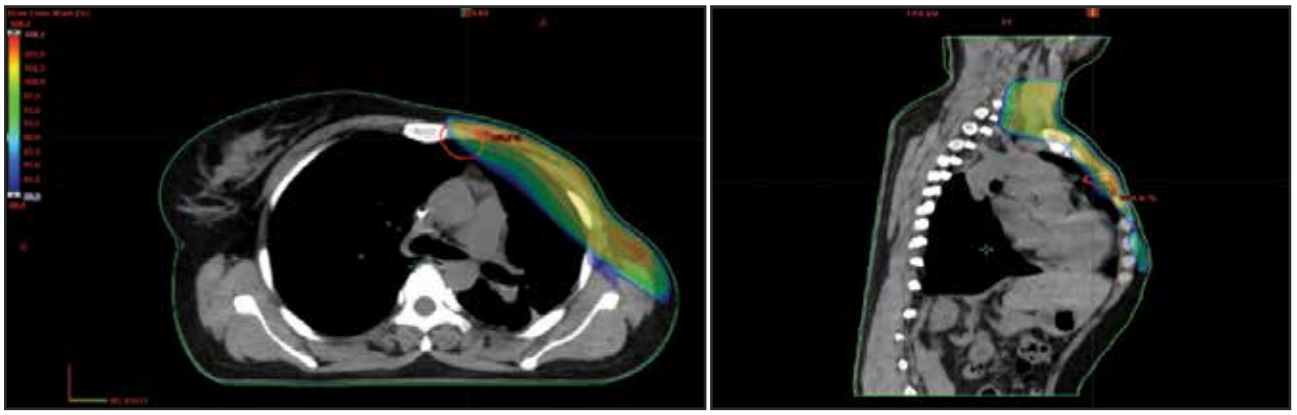


Figure 1(a) and 1(b), the color intensity illustrates the radiation dose distribution within the patient's thoracic region and internal mammary lymph nodes (Red outlined region showed IMLN) 1(a) axial and 1(b) coronal section

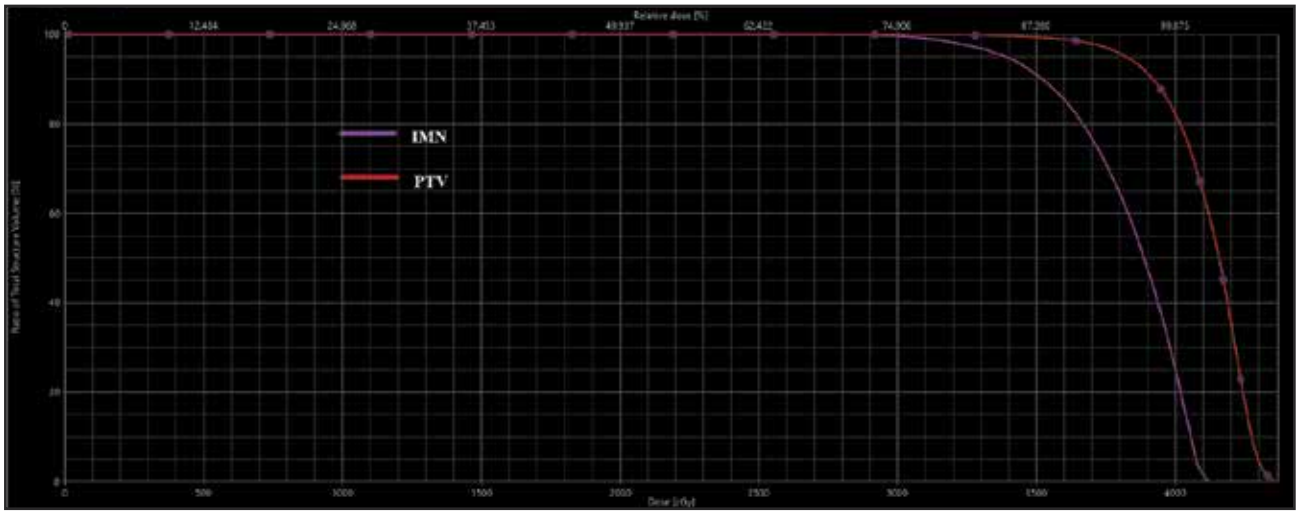


Figure 2: Dose–Volume Histogram (DVH) showing the dose distribution for the Internal Mammary Nodes (IMN) and the Planning Target Volume (PTV) in a radiation treatment plan

a lower but notable radiation dose. Understanding this distribution is important for optimizing treatment plans to maximize target coverage while minimizing exposure to surrounding tissues.

Discussion

Our study investigates the incidental radiation dose to the internal mammary lymph nodes (IMLNs) in breast cancer patients treated with forward planning intensity–modulated radiation therapy (IMRT). The results reveal that IMLNs receive a significant incidental radiation dose, even when they are not the primary target of irradiation. The primary dosimetric findings include a mean dose (Dmean) to the IMLNs of 21.40 Gy and a dose received by 95% of the IMLN volume (D95) of 8.49 Gy. These findings suggest that IMRT, while focused on the PTV, also provides incidental coverage to the IMLNs, which may contribute to therapeutic effects and reduce the risk of recurrence in these nodes. These findings are consistent with previous studies, such as those by Govardhan et al. (Journal of Radiation Oncology, 2021) and Leite et al. (Radiotherapy and Oncology, 2022), which reported similar incidental doses to the IMLNs using the FIF–IMRT technique . The slightly lower dose parameters (D_95 and D_90) in our study indicate more conformal plans with FIF–IMRT, comparable to the literature[14,15]. Jagsi et al. reported substantial incidental radiation exposure to IMLNs in breast cancer treatments not specifically targeting these nodes [16]. Poortmans et al. also observed that incidental irradiation of the IMLNs is common in breast cancer radiotherapy[5], highlighting its prevalence and clinical relevance. This is consistent with the low recurrence rate of isolated IMLN reported in the literature[9]. The dose distribution images (Figures 1(a) and 1(b)) and the dose–volume histogram (DVH) tables (Tables 1 and 2) provide a comprehensive view of the dose delivery to the PTV and IMLNs. The PTV received an effective therapeutic dose, with the majority of the volume receiving between 95% and 107% of the prescribed 40 Gy. However, the IMLNs received substantial incidental doses, which could potentially enhance local control but also pose a risk for increased toxicities.

The incidental radiation to the IMLNs might offer therapeutic benefits, particularly in controlling microscopic disease within these nodes. Budach et al. have noted that incidental irradiation of regional lymph nodes could contribute to improved local control and potentially enhance survival rates[17]. This finding is corroborated by Hennequin et al., who discussed the potential advantages of incidental irradiation of IMLNs, particularly in patients with a higher nodal burden[18]. Such incidental doses might inadvertently contribute to a more comprehensive treatment of subclinical disease, possibly reducing the risk of regional recurrence. However, the potential benefits of incidental IMLN irradiation must be weighed against the associated risks. Studies by Darby et al. and Taylor et al. have demonstrated an increased risk of ischemic heart disease and pulmonary complications due to radiation exposure to adjacent organs [8,19]. These risks underscore the need for careful planning and execution of radiotherapy to minimize unintended exposure to critical structures. Techniques such as Deep Inspiration Breath Hold (DIBH) and advanced IMRT approaches are crucial in mitigating these risks. Wang et al. showed that DIBH significantly reduces heart doses in patients undergoing left–sided breast radiotherapy[20]. Similarly, McGale et al. emphasized the importance of minimizing cardiac doses to reduce long–term cardiac risks[21].

The incorporation of advanced imaging and treatment techniques can optimize dose distribution and reduce normal tissue exposure. Whelan et al. and Poortmans et al. suggest that integrating these techniques into treatment planning can enhance outcomes and reduce unnecessary radiation to non–target areas[4, 5]. Adaptive radiotherapy, as discussed by Yan et al., allows for real–time adjustments based on anatomical changes during treatment, which improves precision and effectiveness[22]. Furthermore, Marks et al. highlight the critical role of quality assurance in optimizing radiotherapy, ensuring that therapeutic benefits are maximized while minimizing potential risks[23]. Long–term follow–up studies and clinical trials are necessary to definitively assess the impact of incidental IMLN irradiation on patient outcomes and toxicity. Research from the EBCTCG meta–analysis and Offersen et al.'s study on regional nodal irradiation emphasizes the need for continued investigation into the benefits and risks of such incidental irradiation [4,24]. The EBCTCG meta–analysis provides valuable insights into the broader context of radiotherapy's impact on breast cancer treatment, while Offersen et al.'s findings offer specific data on the effects of internal mammary and medial supraclavicular lymph node irradiation. These studies underscore the importance of ongoing research to refine treatment protocols and enhance patient care.

Conclusion:

In conclusion, while incidental irradiation of the IMLNs in forward–planned IMRT for left–sided breast cancer may offer potential therapeutic benefits, it is crucial to balance these with the associated risks. Advanced techniques and careful planning are essential to optimize treatment outcomes and minimize adverse effects. Continued research and clinical trials will be vital in guiding future radiotherapy practices and ensuring that the benefits of incidental IMLN irradiation are maximized while safeguarding patient health.

Authors Contribution:

1. Dr Vishwadeep Mishra– Concepts, Design, Literature search, Data analysis
2. Dr Shashank Shekhar – Incorporated thoughts in methodology and editing
3. Dr Sudeep Bisht– Data analysis
4. Dr Rachita Chatterjee– Manuscript review, Statistical analysis
5. Dr Laxman Pandey– Manuscript preparation, Manuscript editing
6. Archana Pandey– Data acquisition

Additional Information

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