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Incidental dose to internal mammary nodes in adjuvant radiation of post mastectomy patients

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► ***Short Report***

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ABSTRACT

Background: The elective irradiation of internal mammary nodes (IMN) has not been preferred, attributable to the low incidental doses delivered and the effect of systemic therapies. This study analyzed the incidental dose delivered to IMN using routine planning techniques. ***Materials and Methods:*** Twenty post-MRM patients who received adjuvant radiotherapy were selected. The CTV included the chest wall with axillary/supraclavicular lymph nodes if indicated, and a 5mm expansion was taken (PTV-planning). For study purposes, IMRT and 3DCRT plans were generated for each patient. Retrospectively, IMN was delineated, and a margin of 5 mm was taken (PTV-IMN). The dosimetry of the two techniques was compared. ***Results:*** An average of 65.03% (SD - 12.45) volume of the PTV-IMN was overlapping with PTV_planning. No significant difference between 3DCRT and IMRT was found in any of the dose parameters of PTV-IMN. The volume of PTV-IMN included inside the PTV_planning had a significant correlation with the mean dose of PTV-IMN for both 3DCRT (r=0.46, p=0.04) and IMRT (r=0.62, p=0.004). A weak positive correlation was observed between the Dmean of PTV-IMN and PTV-planning (r=0.025) and the Dmean of PTV-IMN and heart (r=0.33). The IMRT technique led to improved coverage of PTV-planning, while the heart dose favoured the 3DCRT technique. ***Conclusion:*** The treatment technique did not impact the incidental IMN doses. The IMRT led to better coverage of target volume, as reflected by a few of the dose parameters, but this did not impact the IMN doses.

INTRODUCTION

Regional nodal irradiation in breast cancer, particularly elective treatment of internal mammary nodes (IMN), remains an area of long-standing controversy among radiation oncologists, with wide variation in opinion and practices. The prophylactic irradiation of IMN has been refrained because of the risk of associated rare but serious cardiac morbidity and mortality, particularly with conventional techniques [1]. Recent evidence in the era of conformal techniques showing a reduction in relapses and risk of death renewed the interest in IMN irradiation [2]. However, the adoption of IMN irradiation is still unclear, and it requires balancing the reduction in regional relapse and an improvement in survival rates against the risk of long-term cardiotoxicities. To mitigate the risk of cardiotoxicity, technological advances like deep inspiration breath holding with optimal inflation of lung have been adopted [3, 4]. It has been postulated that this region is at low risk of regional relapses due to the effect of systemic therapies and the incidental radiation dose [5, 6]. This study aimed to compare the incidental doses being delivered to the IMN with three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) and study the correlation with the doses to heart and the target volume. Analyzing the incidental dose delivered and its correlations will provide an insight regarding the adequacy of doses delivered routinely in radiation planning and address the ambiguity on its elective irradiation.

MATERIALS AND METHODS

This retrospective study included 20 post-modified radical mastectomy (MRM) patients who received adjuvant radiotherapy to the chest wall and regional nodes other than IMN were selected for this study. For patients treated by the 3DCRT technique, an IMRT plan was generated, and vice versa (n = 40 plans). The Shri Ram Murti Institute of Medical Sciences (SRMS-IMS) Institutional Ethics Committee approved the study.

Simulation

These patients underwent simulation in the supine position on a breast board with both arms

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overhead flexed at the elbow joint, abducted, and externally rotated. Radio-opaque wires were kept at the level of the opposite inframammary fold, mid-axillary line, and over the scar mark. A contrast-enhanced CT scan of 3 mm slice thickness was obtained.

Delineation

The delineation was done as per the Radiation Therapy Oncology Group's (RTOG) Breast Cancer Atlas. The clinical target volume (CTV) included the chest wall and regional lymph nodes. A Planning Target Volume (PTV_planning) expansion of 5 mm was taken from the CTV and cropped 3 mm from the skin. The organs at risk (OAR's) delineated were the ipsilateral and contralateral lung, spinal cord, contralateral breast, oesophagus, heart, and spinal cord. A Planning Risk Volume (PRV) expansion of 5 mm was taken for the spinal cord and oesophagus.

Planning

A dose of 50 Gy in 25 fractions at 2 Gy per fraction was delivered over five weeks. The planning objectives were a minimum of 90% of the dose delivered to 90% of the volume and an upper dose limit of 110% to less than 1% of the volume. Tangential beams were used in both techniques, with angles so chosen to minimize the entry dose through adjacent OARs. The dose constraints for Organs at risk (OAR's) were ipsilateral lung (V20 <25%) without nodal irradiation and <35% with nodal irradiation; heart: mean dose <10 Gy, V25 <10%; contralateral lung and breast: mean <5 Gy, V5 <5%; PRV Spinal Cord: maximum dose <50 Gy; PRV Esophagus: mean <34 Gy, V35 < 50%.

3DCRT planning

The planning was done using the monoisocentric technique, using two tangential fields for the chest wall and a single supraclavicular field for nodal irradiation. The plans were optimized using varying weightage of beams, Field in Field (FiF), and enhanced dynamic wedges. A sample 3DCRT planning is shown in figure 1.

IMRT planning

In the IMRT technique, inverse planning was done, and five to seven tangential fields were used. The tissue inhomogeneities were considered using a progressive resolution optimizer algorithm. The calculation was performed using the analytical anisotropic algorithm. The maximum iteration limit was 1,000, and the iteration time given was 1,000 seconds with a resolution of 2.5 mm. The normal tissue objective was modified for these plans. The plans were calculated using a dynamic multileaf collimator and jaw-tracking tools. A sample IMRT planning is shown in figure 1.

IMN delineation and data analysis

For calculating the incidental dose in the treated patients, IMN nodes were delineated based on the volume encompassing the internal mammary vessels in the first three intercostal spaces. An isotropic PTV margin of 5 mm was taken (PTV-IMN). The following dose-volume parameters of PTV-IMN, PTV planning, and heart were analyzed and compared among the two conformal techniques.

PTV_planning: Dmean, D95, D90, V95, V30
PTV_IMN: Dmean, D95%, D90%, V95%, V60%
Heart: Dmean, V25Gy

Overlap index- the percentage of the absolute volume of PTV_IMN overlapping with PTV_planning and the absolute volume of PTV_IMN

Statistical analysis

The distribution of data was analyzed using the Kolmogorov-Smirnov test of normality. Statistical analysis was done using a paired t-test for data with a normal distribution and a Wilcoxon signed rank test for data with a skewed distribution. A p-value of less than or equal to 0.05 was considered statistically significant. The correlation between variables was calculated using Spearman's rho correlation test.

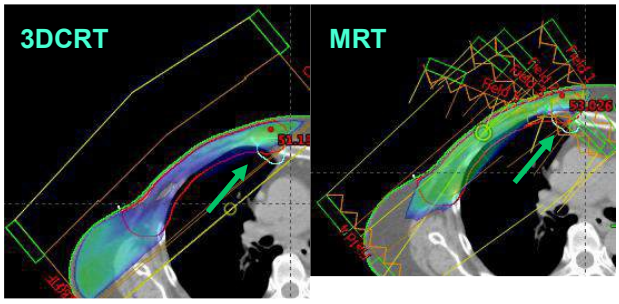

Figure 1. Beam arrangement and dose color wash in 3DCRT and IMRT plans. PTV_planning – Red, PTV_IMN- blue (green arrow).

RESULTS

The population mean age was 47±3.5 years and 70% had right sided breast cancer. An average of 65.03% volume (SD - 12.45) of the PTV-IMN was overlapping with the PTV-planning. The PTV coverage and conformity index were better with the IMRT technique, while the PTV-IMN coverage was comparable amongst both techniques. In both arms, on average, half of the volume received 95% of the planned dose, and nearly 85% of the volume received 60% of the planned dose. A weak positive correlation was found between the mean PTV_IMN dose to that of the mean PTV-planning dose (r_s=0.025; p=0.88) and the mean heart dose (r_s=0.33; p=0.15). The overlap index had a significant correlation with the mean dose of PTV_IMN for 3DCRT (r_s=0.46; p=0.04)

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and IMRT technique (r_s=0.62; p=0.0039) (table 1). A relative of 90% of the prescribed dose was received by PTV-IMN in only 35% of plans in the 3DCRT technique and 30% of plans in the IMRT technique. A mean of 85% of the prescribed dose was delivered to the PTV-IMN in most plans, but that is in the subtherapeutic range. In comparison to the heart dose, the mean dose was significantly lesser with the 3DCRT technique (table 1). The PTV coverage (D90, D95), Homogeneity and Conformity index were significantly better in the IMRT technique, but the Dmean and D50 were comparable (table 2).

Table 1. Comparison of the dosimetric parameters of PTV-IMN and heart in 3DCRT and IMRT plans.

Parameter	3DCRT (n=20) Mean (SD)	IMRT (n=20) Mean (SD)	P value
	PTV-IMN		
D mean (Gy)	42.55 (5.65)	42.92 (4.02)	0.67
D95% (Gy)	22.51 (14.92)	24.40 (9.00)	0.41
D90% (Gy)	27.97 (14.77)	28.29 (9.59)	0.76
V95% (%)	45.46 (20.62)	47.80 (18.55)	0.63
V60% (%)	86.82 (13.34)	87.02 (10.44)	0.92
	Heart		
D mean (Gy)	4.05 (4.52)	7.32 (5.78)	0.0003
V25 Gy (%)	5.23 (8.98)	6.35 (9.71)	0.35

Dx% denotes dose in Gray received by X % of the volume, Vx% - volume in percentage receiving X dose in Gray.

Table 2. Comparison of the dosimetric parameters of PTV_planning in 3DCRT and IMRT plans.

Parameter	3DCRT Mean (SD)	IMRT Mean (SD)	P value
PTV_planning			
Dmean (Gy)	49.60 (0.64)	49.99 (0.97)	0.14
D50% (Gy)	50.11 (0.69)	50.04 (0.42)	0.68
D90% (Gy)	45.83 (0.77)	48.04 (1.30)	<0.0001
D95% (Gy)	44.08 (1.45)	46.83 (3.32)	<0.0001
Homogeneity index	0.28 (0.10)	0.14 (0.07)	<0.0001
Conformity index	1.28 (0.18)	1.16 (0.18)	0.03

Dx% denotes dose in Gray received by X % of the volume, Vx% - volume in percentage receiving X dose in Gray.

DISCUSSION

The present study showed that the incidental IMN doses were comparable among both techniques. It was primarily due to a major proportion of the PTV-IMN region overlapping with the PTV-planning with an overlap index of 65%, as a strong correlation was established between the overlap index and the incidental dose received. The better coverage of PTV-planning in the IMRT technique did not impact the PTV-IMN dose. The probable reason is that the regions of PTV-planning that had improved coverage with the IMRT technique were at the junction of the supraclavicular field and tangential, deeper aspects of the supraclavicular nodal region and the superficial buildup region of the chest wall, while the PTV-IMN region was not observed to be affected (figure 1).

In a study by Suryadevara *et al.* (n=56) having 39 post-MRM patients, the incidental relative mean dose to the PTV-IMN was 60% and the D95 of only 12% [7]. A relatively higher PTV margin of 10 mm from the vessels in their study possibly explains the lesser incidental dose compared to our study. In another study by Wang *et al*. (n=138) in post-MRM patients where the IMN was delineated in the first three intercostal spaces, an expansion of 5 mm was given for the PTV-IMN found no significant difference in the PTV-IMN doses amongst the 3DCRT (mean-33.80 Gy), forward IMRT (mean – 29.65Gy), and inverse IMRT (mean-32.95 Gy) techniques. Also, their study established moderately positive correlations between the incidental mean doses to PTV-IMN and mean heart dose in 3DCRT plans (r=0.338; p=0.01) and the V20 of lungs (r=0.250; p=0.086) and mean lung dose (r=0.271; p=0.062) for forward and inverse IMRT plans [8]. Wang *et al*. found that a lower body weight, a higher ratio of transverse and anteroposterior thoracic diameter, and a higher volume of IMN included in the PTV were significant correlative factors affecting the IMN dose. In their study, the mean dose for the PTV-IMN was 32.85 Gy (range- 2.76 Gy to 50.93 Gy). Adequate coverage of the PTV-IMN, that is, 90% of the prescribed dose (≥45 Gy), was achieved in only 7.25% of the patients [9].

A study by Govardhan B *et al*. (n=20), comprising both post-BCS and post-MRM patients, compared the incidental doses to axilla and IMN in conventional, 3DCRT, and IMRT techniques by generating three sets of plans for each patient. The IMN was delineated in the first four intercostal spaces, and an expansion of 7 mm was made for PTV. A significant reduction was demonstrated in the V50%, and Dmean of the PTV-IMN with the IMRT technique compared to the 3DCRT technique, but the higher isodose volumes of V95% and V80% were comparable [10].

Although various studies and our findings also have shown variation in the dosimetric properties of PTV and OARs amongst 3DCRT and IMRT techniques [11, 12], in comparison of IMN doses, only one study showed significant differences in the IMN incidental doses [10]. The incidental dose received by the IMN region is quite variable (table 3), attributable to the variability in anatomical factors, delineation, and planning objectives. All the studies described here [7-10] used RTOG contouring guidelines, where the posterior boundary of CTV is at the rib-pleural interface [13]. However, the ESTRO guidelines that have been increasingly adopted in recent years restrict the posterior border of CTV to the anterior limit of the pectoralis major and intercostal muscles [14]. This is expected to reduce the incidental dose to the IMN region; therefore, its inclusion needs additional attention. Also, there is some evidence suggesting an increase in the incidence of regional failures with the volumes proposed by ESTRO guidelines [15].

In retrospective series without inclusion of IMN in the target region, recurrences in this region have

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been reported in less than 2% of patients [16]. These studies led to a subtle drift from IMN irradiation, but with improved survival outcomes, it has again been recognized as a possible site of relapse. In the series by Chen *et al*. of 133 patients with IMN recurrence, it presented as the first site of relapse in 91% of patients [17].

Table 3. Table summarizing the literature and present study's findings.

Author (year)	Sample size	Incidental IMN dose	3DCRT	IMRT	P value
Govardhan B et al. (2017) [10]	20	V95%	40 %	43 %	0.43
		V80%	55 %	49 %	0.09
		V50%	82%	75%	0.01
		Dmean	77%	61%	<0.05
Wang W et al. (2019) [9]	138	V50Gy	17.54%	22.10%	-
		Dmean	33.80 Gy	32.95Gy	0.299
Present study	20	V95%	45.46%	47.80%	0.63
		V60%	86.82%	87.02%	0.92
		Dmean	49.60 Gy	49.99 Gy	0.67

Large-scale evidence has also highlighted its benefit in improving survival outcomes [2, 3]. Based on the existing literature and our findings, the incidental doses for IMN are in the subtherapeutic range, pointing towards elective inclusion in patients at high risk of involvement. One concern of IMN inclusion is the remote risk of cardiotoxicity, even at small dose increments to the heart [18]. Low doses can also induce anti-inflammatory response, fibrosis, and resultant cardiac damage [19]. The risk of IMN involvement can be quantified by nomogram based on pathological features that can help guide the decision-making of IMN inclusion [20].

Our study had a few limitations. Firstly, the limited sample size and other the impact of anatomical factors could not be accounted for. Nevertheless, this study provides insight into the range of variable incidental doses delivered, emphasizing the importance of quantifying the doses to the IMN region and its elective inclusion. The strength of our study is the inclusion of a similar set of patients in both arms so that the findings are not biased by anatomical variation.

CONCLUSION

In our series, the IMN doses were slightly lesser than the therapeutic range, with no significant difference between the two conformal techniques. The major determining factor of incidental dose was the volume of IMN overlapping with the PTV. The IMRT technique significantly improved the coverage of the PTV, but it did not impact the incidental dose to IMN.

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***Ethical consideration*:** This study involved dosimetric analysis that poses no known ethical risk.

***Author contribution*:** A.M., Data collection, manuscript drafting; P.K., study design, manuscript finalization; N.S.S. and S.N., manuscript drafting.

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