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DOSIMETRIC ANALYSIS OF INCIDENTAL AXILLARY IRRADIATION IN BREAST CANCER USING TANGENTIAL FIELDS TREATED BY 3DCRT TECHNIQUE

Oncology/Radiotherapy

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ABSTRACT

Introduction Radiotherapy is an important aspect of treatment for multimodality approach in cancer breast. Inclusion of axillary nodes in radiotherapy tangential fields remains a long-standing controversial issue. It is considered that axillary nodes receive incidental radiation through tangential beams of chest-wall. The benefit of decreasing regional recurrences with axillary nodal irradiation needs to be weighed against the risk of chronic lymphedema and its impact on quality of life. The following study was done to analyze the incidental dose received to axillary region and whether the addition of radiotherapy to axillary region will be useful. **Material and methods** Twenty post Modified Radical Mastectomy (MRM) patients who had received adjuvant radiotherapy from 2018-2021were retrospectively selected. Planning was a done with Field in Field–Forward planned–3DCRT with mono-isocentric technique. Dose prescribed was 50Gy/25 fractions. Axillary Lymph nodes were contoured according to RTOG guidelines. Various parameters of PTV(V95,D90, D95, Dmax, Dmean, Homogeneity Index(HI), Conformity Index (CI), Volume of PTV), Axillary Lymph nodes I, II, III and SCF (Dmean,V95, V90, Volume) and BMI were evaluated. Correlation was done among these parameters and Statistical analysis was done using Pearson-Correlation coefficient. **Results** The mean dose to axillary Lymph node level I, II, III were 45.75Gy, 31.80Gy and 25.83Gy respectively. The V90% and V95% of Axillary level–III also received a dose of 32.97Gy and 22.73Gy respectively. The combined volume of I and II received a mean dose of 40.85Gy and all three levels received 39.44.Gy. There is a weak correlation of SCF dosimetry with axillary nodal volumes although PTV volumes and BMI had positive correlation with axillary lymph nodal irradiation. **Conclusion** Axillary levels I and II received substantial amount of incidental radiation by the tangential field 3DCRT technique. Our small sample size may have impacted a more detailed analysis of the correlation among variables. However more prospective clinical studies addressing this issue may help in understanding the risks versus benefits of axillary lymph nodal irradiation.

KEYWORDS

Breast cancer, Tangential Breast radiotherapy, axillary nodal irradiation, Breast radiotherapy, Dosimetric study in breast

BACKGROUND:

Radiotherapy is an important aspect of treatment for multimodality approach in cancer breast helping in potentially eliminating microscopic tumour foci after surgery. Adjuvant nodal irradiation is usually indicated in patients with high-risk features. There is an increased risk of lymphedema with full axillary radiation following dissection that may result in subsequent lymphedema resulting in poor quality of life. There-fore inclusion of axillary nodes in radiotherapy fields remains a long-standing controversial issue[1].

The benefit of decreasing regional recurrences with axillary nodal irradiation needs to be weighed against the risk of chronic lymphedema and its impact on quality of life. Surgeons have migrated towards limited sentinel nodal dissection due to this morbidity[2-4]. Similarly, the concept of axillary nodal irradiation even in high-risk case is not uniformly embraced by radiation oncologists. More-over it is considered that axillary nodes received incidental radiation through tangential beams of chest-wall although the dose depends on various factors like patient anatomy and the technique utilized.

The following study was done to analyze the incidental dose received to axillary region and whether the addition of radiotherapy to axillary region will be useful.

MATERIALS AND METHODS:

Twenty post Modified Radical Mastectomy (MRM) patients who had received adjuvant radiotherapy from 2018-2021 were retrospectively selected.

For Simulation, patients were made to lie down in supine position on breast board with arms over and above head abducted and externally rotated. The delineation was done according to RTOG Breast Cancer Atlas. The Clinical Target Volume (CTV) was inclusive of chest-wall and Supra-clavicular lymph nodes (SCF) if indicated. A PTV margin of 5 mm was given according to institutional protocol. Treatment was delivered using 6 MV or 16 MV photons using Eclipse treatment Planning system LINAC version 13.6. Dose delivered was 50 Gy in 25 fractions with 2 Gy per fraction for 5 weeks for 5 days a week daily.

Planning Technique:

Field in Field–Forward planned–3DCRT(FiF FP 3DCRT):-

Planning was a done with a mono-isocentric technique with half beam block at the junction of tangential fields and supraclavicular field. Two open tangential fields were created in this technique in such a way that the beam entry is not passing through the opposite breast, to achieve uniform dose distribution to the PTV, minimizing hot spot regions. The 95% dose cloud in a beam's eye view projection of the treatment fields was visualised and subfields were manually designed to boost the area not included in the dose cloud. The manual iteration of subfields was done to achieve the desired dose distribution. The number of subfields varied from one to three tangential pairs. Either 6 or 10MV photons were selected for the subfields depending on separation of fields. The plans were individually optimised using Field in Field (FIF) technique with varying weightage of beams.

A single supraclavicular anterior field has been used where ever indicated.

Contouring of axillary lymph node stations:-

Axillary lymph nodes level I,II,III, were delineated separately according to RTOG guidelines and incidental dose delivered to each level was evaluated[5].

Evaluation was done using Dose- Volume Histogram (DVH). The following parameters were evaluated.

Dosimetric parameters

Variable	Parameters
PTV	V95,D90, D95, Dmax, Dmean, Homogeneity Index(HI), Conformity Index (CI), Volume of PTV
Axillary lymph nodes Level I,II,III	Dmean,V95, V90, Volume
Supraclavicular nodal level	Dmean,V95, V90,Volume

Correlation Parameters: Different Parameters were correlated

- Influence of SCF mean doses on axillary nodal mean doses,
- Correlation of PTV Volume, Body Volume with axillary nodal volumes and
- Correlation between BMI with axillary nodal volumes and mean doses.

Statistical analysis: -

Collected data was analyzed using SPSS software with parameters evaluated were Mean, Median, Standard Deviation (SD), Interquartile range (IQR). Pearson Correlation coefficient has been used to establish

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a relation between either of evaluated parameters. Level of significance using "p" value of < 0.05 was considered statistically significant.

RESULTS

Dosimetric Parameters of Planning Target volume (PTV), Axillary Lymph nodal volumes and mean doses and SCF mean doses.

The Dose-Volume Histograms evaluated for PTV were given in the **Table-1**.

Table 1– Table showing Dosimetric parameters of PTV, volume in percentage Dose in Gray

Variable	Mean
V95	76.40
D90	42.97
D95	36.83
Dmax	54.85
Dmean	48.211
HI	0.48
CI	1.29
PTV(cc)	859 cc

The dose received by 90% of volume of PTV was 42.97 Gy and the dose received by 95% of volume was 76.4%. The Homogeneity Index and Conformity Index was 0.48 and 1.29 respectively. The mean volume of PTV was 859 cc.

The mean dose to axillary Lymph node level I, II, III were 45.75Gy, 31.80Gy and 25.83Gy respectively. Other dosimetric parameters including V90% and V95% can be observed in **Table 2**. It can be observed that V90% and V95% of Axillary level–III also received a dose of 32.97Gy and 22.73Gy respectively.

Table 2 -Table showing coverage of Axillary lymph node levels, volume in percentage (mean ± SD) (median± IQR), Dose in Gray.

Axillary Lymph node Level-I		
Variable	Mean+SD	Median+IQR
Mean(Gy)	45.75 + 4.63	47.79+5.825
V90(%)	81.83 + 23.46	90.725+ 26.96
V95(%)	61.42 + 31.07	65.1+ 36.88
Axillary Lymph node Level-II		
Mean(Gy)	31.80 + 13.5	35.415+ 19.21
V90(%)	29.35 + 25.21	22.9+53.34
V95(%)	11.30 + 15.92	1.69+19.285
Axillary Lymph node Level-III		
Mean(Gy)	25.83 + 20.68	28.735+41.705
V90(%)	32.97 + 43.61	2.12+84.38
V95(%)	22.73 + 39.95	0+40.975

The combined volume dose parameters of axillary nodal volumes are given in **Table-3.** The combined volume of I and II received a mean dose of 40.85 Gy with V90% and 95% of 61.8% and 43.32% respectively. All three levels combined, reported a mean dose of 39.44 Gy. The mean Volume of combined axillary level I and II was 48.29 cc where as Level- I, II and III combined volume of 53.8 cc.

Table 3– Table showing coverage of Axillary lymph node level I+II and I+II+III in combination volume in percentage (mean ± SD), (median± IQR), Dose in Gray, Volume in cc

Axillary lymph node level I+II		
Variable	MEAN + SD	MEDIAN+IQR
Mean(Gy)	40.85+7.1	44.11+8.88
V90(%)	61.85+21.1	71.79+28.41
V95(%)	43.32+22.8	43.51+29.6
Vol. in CC	48.29	--
Axillary lymph node level I+II+III		
Variable	MEAN + SD	MEDIAN+IQR
Mean(Gy)	39.44+7.2	41.53+8.5
V90(%)	57.7+19.75	65.28+24.69
V95(%)	40.78+20.63	43.39+25.39
Vol. in CC	53.8	--

The adequate dose to SCF is of paramount importance in terms of loco-regional relapse or recurrence. Hence optimal dose to SCF may reduce chances of failure. **Table 4** reported the dose parameters including mean dose of 43.43 Gy and V90% and V95% of 61.1% and 42.6% respectively.

Table 4– Table showing coverage of Supraclavicular nodal region, volume in percentage (mean ± SD), (median± IQR), Dose in Gray, Volume in cc

Variable	MEAN + SD	MEDIAN+ IQR
Mean(Gy)	43.43+6.66	45.45+4.9
V90(%)	61.15+16.7	68.31+19.9
V95(%)	42.61+15.5	48.42+20.53
Vol. in CC	100.55	--

Influence of mean dose of SCF on Axillary nodal mean doses.

In our study, no correlation between SCF dosimetry to that of axillary nodal irradiation has been established clearly as can be observed in following **Table-5**

Table 5– Table showing Influence of mean dose to SCF on axillary nodal mean dose.

SCF and Axillary Lymph Node III		
Variable	Pearson Correlation Coefficient(r)	P Value
Mean	-0.17	0.55
V90	-0.4054	0.16
V95	-0.3227	0.28
SCF and Combined Axillary Lymph Node I+II+III		
Variable	Pearson Correlation Coefficient(r)	P value
Mean	-0.4065	0.16
V90	-0.6173	0.02
V95	-0.3497	0.24

The Pearson Correlation co-efficient value for mean dose of r=0.17 shows that their is a weak correlation between the variable. It can observed that V90 of SCF vs Combined Axillary Lymph nodes has significant but moderate correlation with significant p value.

Correlation of PTV volume, Body Volume and BMI with Axillary nodal volumes and mean doses.

Table 6– Table showing Correlation of PTV volume, Body Volume with axillary nodal level volumes, volume in CC

PTV volume and axillary nodal level volumes		
Variable	Pearson Correlation Coefficient(r)	P value
Axillary I+II+III	0.77	.000051
Axillary I+II	0.74	.000163

It can be seen that all the PTV volume parameters have significant positive correlation with axillary nodal volumes (**Table 6**) suggesting an evidence that PTV volume also has an important role in the coverage of axillary nodes.

Table 7 – Table showing Correlation between BMI with axillary nodal level volumes and mean

BMI and Axillary Lymph Node Level I+II					
BMI	Mean	r With cc	p-Value with cc	r With mean dose	p-Value with mean dose
Total patients	27.6	0.69(1)	.005	0.599(1)	0.02
BMI < 25	21.1	0.99(2)	.0003	0.99(2)	0.0004
BMI > 25	28.68	0.52(1)	.078	0.29(3)	0.35
BMI and Axillary Lymph Node Level I+II+III					
BMI	Mean	r With cc	p-Value with cc	r With mean dose	p-Value with mean dose
Total patients	27.6	0.71(1)	0.003	0.24	0.002
BMI < 25	21.1	0.59(1)	.024	0.98(3)	0.001
BMI > 25	28.68	0.52	0.07	0.3(2)	0.33

It can be seen in above **Table-7**, we observed that BMI>25 had positive correlation with axillary volumes as well as mean doses.

DISCUSSION

The advantage of Tangential field breast irradiation in local control of breast cancer is undeniable but has implications in quality of life and also its impact in reducing axillary recurrences is still considered controversial. Literature have shown better long-term axillary control with breast irradiation but higher nodal recurrence if breast irradiation is skipped[6].

Since the developing years of radiotherapy in breast cancer, the clinicians are particularly concerned with the chances of developing lymph edema which is proven to occur due to axillary irradiation mostly. How-ever, as noted in the literature, the clinically negative axilla harbors subclinical microscopic disease in up to 40% of patients with early-stage operable breast cancer and both axillary dissection and axillary radiation result in high rates of regional nodal control[7-8].

Krasin et al. (2000) were the first to review the issue of addressing the axillary lymph nodes in a dosimetric way. They noted that patients treated with tangential fields had adequate coverage of axillary level I. In contrast, levels II and III, and internal mammary chain lacked adequate dose for treatment[9]. **Donker et al.** (2014) showed that nodal irradiation and axillary node dissection produce comparable axillary control for patients with tumors < 5cm and positive sentinel node[10]. The Dosimetric parameters of the axillary lymph nodal stations in our current study showed that it received significant amount of incidental radiation with mean doses to level I, II, III were 45.75Gy, 31.80Gy and 25.83Gy respectively as can be seen in the tabulated format in **Table 2**. In a study by **T.Kataria** et al., the incidental mean doses to all the the three axillary lymph nodal levels were evaluated by IMRT, 3DCRT and Standard Tangential field techniques. It is observed in this study that Standard tangential field technique delivered maximum dose to axilla. Level I received 87%, Level II-65% and Level III-41%[11]. In another study **by Reznik** et al. analyzed axillary dose-volume data with Standard Tangential fields in 35 patients. The average doses delivered to levels I, II and III were 66%, 44% and 31%, respectively[12]. Similar findings were reported in our study also with mean doses to axillary level I, II, III are 91%(45.7Gy), 63%(31.8Gy), 51%(25.8Gy) respectively.

In a RTOG multi-institutional and multi-observer study by **Li XA** et al. on delineation variation in axillary volumes in breast cancer, wide inter-observer variability was seen, the structure overlaps were as low as 10% and volume variability had a standard variation up to 60%[13]. Individual patient factors may play a role in higher SD values as seen in our study also. In a dosimetric study by **Araújo et** al. V45 volumes were evaluated for axillary level I and II with mean V45 doses reported as 43.2Gy and 17.5Gy respectively[14]. Our study had comparable findings with V45 received was 40.9Gy and 14.07Gy.

It can be inferred from the above discussion that incidental doses delivered to the axillary lymph nodes were consistent with contemporary literature and question of optimum and adequate dose to axilla needs to be further evaluated clinically. There-fore interpretation upon clinical significance of our axillary doses needs to be further validated with adequate clinical follow up.

The mean dose to axillary Lymph node level I, II, III were 45.75Gy, 31.80Gy and 25.83Gy respectively. The combination of Axillary Level I and II recieved the mean dose of 40.85 Gy with V90 and V95 doses are 30.9Gy (61.85%) and 21.6 Gy (43.32%) respectively (**Table 3**). It can be observed that all III levels dosimeteric data had received significant incidental dose. Even the Level-III has received a mean dose of 25.8Gy.

Relationship of axillary nodal volumes with various parameters.

The dose to axillary lymph nodes especially Level-III had been historically influenced by SCF nodal irradiation which is in close proximity. Several literatures are of opinion that SCF irradiation increases the dose coverage of axillary lymph nodes in the tangential field plans. The coverage of SCF in the tangential field irradiation of our recruited breast cancer patients shows that mean dose to SCF was 43.4Gy (86%) and the median as 45.4 Gy (90.8%) with V90% and V95% reported as 61.1% and 42.61% respectively (**Table 4**).

A study by **Schmitt M et al**. showed that the dosimetric coverage of axillary Lymph node levels I, II, and III was higher in cases of SCF irradiation than that in the absence of supraclavicular lymph node irradiation. It is likely that a significant part of the dose delivered to level IV contributes to the dose delivered to the other volumes and, in particular, to level III because of the proximity of these volumes and higher doses to level III in our study is explained possibly by SCF nodal irradiation done in almost all the patients[15].

Hence it can be postulated that dose to SCF was considered adequate and further its influence on axillary lymph nodes dosimetry based on above findings are suggestive that SCF has some correlation with axillary lymph nodes and clear relation may not be evident owing to other factors like patient's anatomy including Body Mass Index (BMI), dose coverage of PTV which may play a role in dose statistics of SCF as well as axillary nodes.

Many other factors may influence the dose coverage of axilla. In our study their was a strong positive correlation with PTV in terms of volume in cubic-centimeters (cc) to that of axillary lymph node volumes.

A retrospective study by **Araújo** et al tried to establish relationship of various factors on axillary coverage. In this study, no correlation was established between CTV volume and V45[14]. However another study by **Russo et al.** (2011) reported that the axillary coverage increases with the delineation of expander's volume of CTV. This difference in correlation in literature between the CTV parameters with axillary nodal irradiation is hugely influenced by individual user variation in creating a CTV expanders volume and Planning Target Volume[16].

Another important parameter that was evaluated in our study was BMI. Different groups of Body Mass Index (BMI<25 and BMI ≥ 25) as per the WHO classification for normal versus overweight/ obese has been evaluated in our study with relation to axillary dose parameters[17]. It can be observed that that the BMI of our cases was found to be 27.6 on average, which shows that most of the patients are obese/overweight.

All the parameters of BMI had significant impact on dosimetry of axilla as can be observed in Table 7. It can be observed that the category of patients with BMI<25 had a strong positive pearson correlation coefficient suggesting that BMI with <25 patients may have profound impact on coverage of axillary nodal volumes, although this needs to be confirmed on such a study with larger population group. **Araújo et al** stated that patients with BMI>25 received significant higher dose at level I (p=0.026) on a univariate analysis. It can be observed that in this study, the maximum number of patients had BMI>25[14]. Similar data conducted at MD Anderson Cancer Center showed similar correlation with Obese patients received higher dose at level I, although, this dose remained sub-therapeutic[18].

In our study also, we observed that BMI>25 had positive correlation with axillary volumes as well as mean doses. But contrary to above mentioned literature, our study showed stronger correlation in BMI<25 than BMI ≥ 25 which can be explained by few limitations of our study including retrospective nature as well as smaller study group that may have influenced these results. It is suggested that BMI correlation in our study doesn't impact hugely on the axillary volumes or doses and shouldn't be a concern while deciding the axillary nodal irradiation.

It can be observed from the above discussion that axillary nodes were irradiated in tangential beam 3DCRT incidentally and our study showed that significant and considerable amount of dose was delivered in Axillary level-I and II along with ample dose to Level-III. Also various parameters of SCF, PTV and Body volume and BMI have some influence over axillary nodal coverage which were explained to some extent in our study. How-ever our small sample size may have impacted a more detailed analysis of the variables. Although, in our opinion, the variables are well documented and the fact that it is a retrospective study with limited number of patients with wide variation in patient's anatomy that may have unknowingly introduced bias.

CONCLUSION

Axillary levels I and II received substantial amount of incidental radiation by the tangential field 3DCRT technique that may help in controlling micro-metastases or isolated tumor cells. More prospective clinical studies addressing this issue may help in understanding the risks versus benefits of axillary lymph nodal irradiation.

The treating oncologist may choose to give constraints to axilla if lymphedema is a concern or may include axilla as a target with possibly lower dose prescription than the breast tissue depending on a given clinical situation.

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