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A comparative study evaluating the dose volume parameters in 3D conformal radiation of left sided whole breast irradiation including regional lymphnodes — a need of resource constrained countries

Surekha Goyal, Richa Tiwari, Geeta S. Narayanan, Soumya S. Narayanan

Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India

ABSTRACT

Background: The purpose of this study was to compare four 3D conformal radiation techniques in treatment of left breast cancer patients.

Materials and methods: Radiation was planned for 20 patients to the left breast and regional lymph nodes using four techniques: partially wide tangents, photon-photon mix, photon-electron mix and 30/70 photon-electron mix. All plans were evaluated for internal mammary nodes (IMN) coverage, hotspot and normal tissue constraints.

Result: The 85% of planning target volume (PTV) coverage was lesser for upper IMN than the lower IMN (below the lower border of the clavicular head) for all four techniques. The lower IMN coverage was better for partially wide tangent (80.46%) and photon-photon mix (88.88%). The lowest value of hotspot was seen in the partially wide tangent technique (112.69% ± 1.92). Hotspot is unacceptably high in both photon-electron mix and 30/70 photon-electron mix (> 120%). Left lung mean dose for all techniques on a pair-wise comparison showed no statistical difference. Left lung V20 values for partially wide tangent was 37.56% ± 8.17 and for photon-photon mix it was 40.49% ± 3.36. The mean heart dose with partially wide tangent was 9.43 ± 3.15 Gy and with photon-photon mix it was 10.10 ± 2.70 Gy. The mean heart dose for photon-electron mix was 7.56 ± 1.95 Gy and for 30/70 photon-electron mix it was 7.98 ± 2.16 Gy.

Conclusion: No single technique satisfies all the criteria. The decision should be made on a case-by-case basis, considering the anatomy of the patient, availability of electron facilities and setup accuracy and reproducibility.

Key words: left sided breast cancer; internal mammary nodes; regional nodal irradiation

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Introduction

Breast cancer is the most common cancer in women contributing to 46.3% of all cases worldwide and also the leading cause of death (13%), according to Globocan 2018 [1]. Globocan 2018 also showed breast cancer to be the most common cancer in India with incidence of 14% and with the highest mortality (12.1%). Breast cancer cases are more prevalent in developing countries as compared to developed countries. According to NCRP 2014 report, the percentage of breast cancer cases was the highest amongst females in four major cities: Bangalore (27.5%), Delhi (28.6%), Mumbai (28.8%) and Kolkata (25.4%) [2]. When the laterality of breast cancer was studied, the number of left

Address for correspondence: Surekha Goyal, Vydehi Institute of Medical Sciences and Research Centre, Radiation Oncology, Bangalore, India; e-mail: surekhagoyal16@gmail.com

sided and right sided cancers was comparable (51% and 49%, respectively) [3].

With the advent of breast conservation surgery, radiation therapy has become an important part of the treatment of early breast cancer. Along with whole breast irradiation, internal mammary irradiation is being indicated in all patients with tumors with positive axillary nodes even in early breast cancer. 15-year results of EORTC 22922/10925 though do not show improved survival, they show a significant reduction of breast cancer mortality (16.0% *vs.* 19.8%, p = 0.0055) and any breast cancer recurrence (24.5% *vs.* 27.1%, p = 0·024) by internal mammary-medial supraclavicular irradiation in stage I–III breast cancer [4].

In patients with left sided breast cancer, higher rates of cardiac toxicities are seen, which are even higher in females undergoing regional lymph node irradiation, specifically internal mammary irradiation. Rate of coronary events in breast irradiation patients increases linearly with the mean dose to the heart by 7.4% per Gray [5]. Also in these patients, cardiovascular disease, chemotherapy and antiHer2 therapies increase the absolute risk of cardiac toxicity. In order to increase the benefits of internal mammary nodes (IMN) irradiation, the dose to the heart and lungs should be reduced. Various techniques have been used to reduce the dose to the heart and lungs in the irradiation of breast cancer.

In this study, we compared four 3D conformal radiation techniques, in treatment of the left sided breast cancer patients who had undergone BCS, followed by radiation to the left breast and regional nodes, in terms of IMN coverage and doses to the organs at risk: the heart, lung and contralateral breast. Though in the present era the use of advanced techniques like breath hold and IMRT are on rise, which helps in decreasing cardiac doses, we took into consideration the large number of cases being treated in resource constrained centers in developing countries like ours. Hence, we focused on evaluating simpler 3D techniques which are easier for our patients to learn and can be easily implemented on a daily basis.

Materials and methods

Inclusion criteria

20 patients were included in this study. All patients had left sided breast cancer and had undergone breast conservation surgery with axillary lymph nodal dissection, after which patients received adjuvant chemotherapy and were referred for radiotherapy.

CT simulation

Patients were positioned using a breast board with hands above the head, holding a T-bar and head turned to the right side. Three lead fiducials were placed at the level of the diaphragm, one at the midline and two on the sides. A lead wire was put around the left breast to facilitate the delineation of the breast tissue. The CT scan was acquired from the mandible to mid-abdomen in free breathing phase.

Contouring

Left breast, left supraclavicular nodal stations and internal mammary nodes on the left side were contoured according to ESTRO contouring guidelines. 5 mm PTV was given around the CTVs and clipped 3mm from the skin. Boost to lumpectomy cavity was not planned as none of our patients had high risk features for recurrence.

Planning

Treatment plans were created for 20 patients who had undergone Breast Conservative Surgery (BCS) using four different techniques. Treatment planning was performed using a 3D Treatment Planning System (Eclipse v 11.1, Varian Medical Systems). We are facilitated with Linear Accelerator Clinac 2300 C/D (Varian Medical Systems, Palo Alto, CA).

All relevant planning parameters were kept constant for all patients and plans. A dose prescription of 50 Gy in 25 fractions was employed for all cases. The choice of photon energy was 6 MeV and electron energy in some techniques depends on the depth to be covered (say, 6, 9 or 12 MeV). The electron fields were normalized to D90 so as to achieve adequate coverage. Mono isocentric technique was employed for all cases with a match line, with the superior part covering the SCF and inferior one treating the tumor bed and IMN. The SCF field was matched with the breast field using the half beam blocking technique. The whole breast target volume was planned using medial and lateral coplanar tangential beams. The SCF for all plans was planned using an anterior photon beam (6 MV) with slight angulations (approx. 10°) to limit exit dose to the

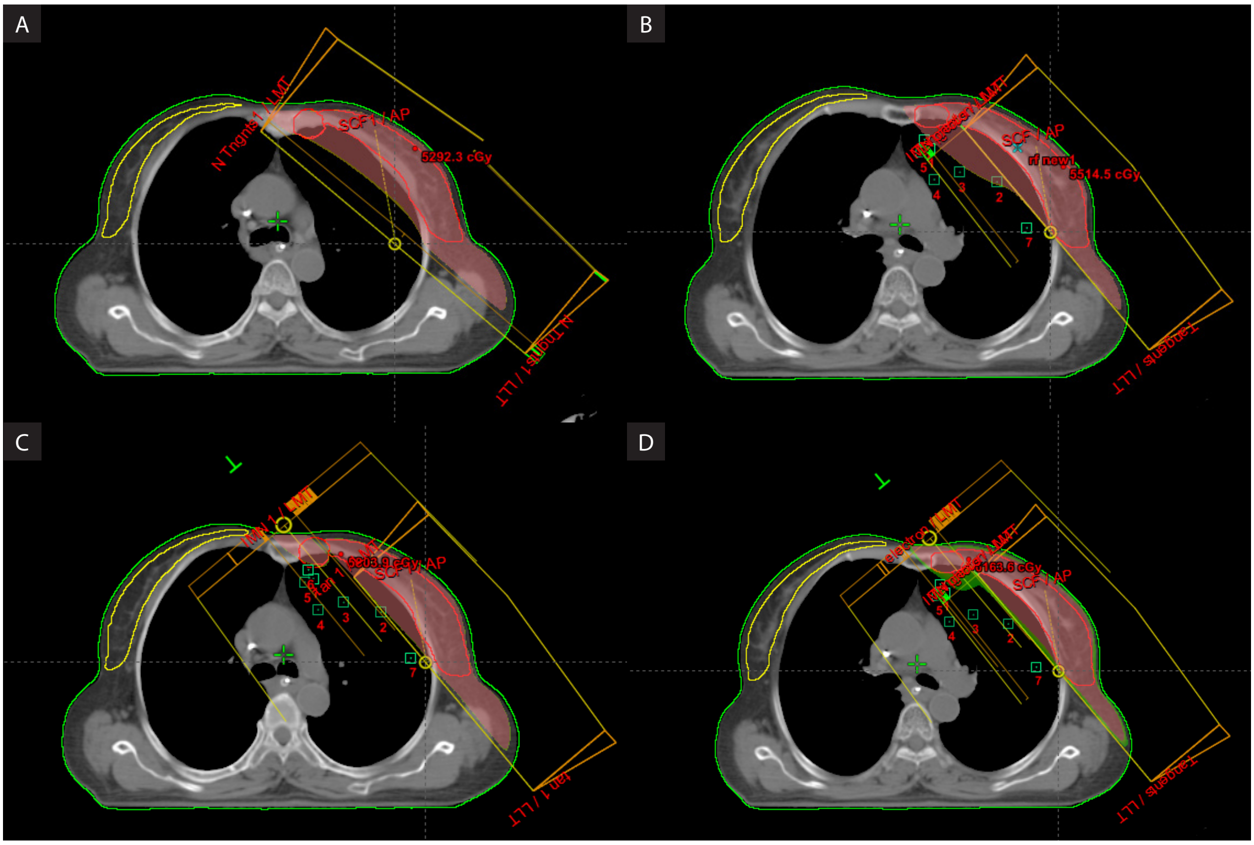

Figure 1.A. Partially wide tangent; **B.** Photon-photon mix; **C.** Photon electron mix; **D.** 30/70 Photon-electron technique

spinal cord. All field junctions were matched by asymmetric jaws. Dynamic wedges were used for tangential beams (if required) to reduce the hotspot and to improve homogeneity. All plans were generated with the heterogeneity correction ON, and AAA as the dose calculation algorithm.

We chose four techniques for planning these cases, which included only photon beams or photon and electron beams in different combinations to cover the IMN volume. The techniques used for planning IMN are discussed below:

1. Partially wide tangents (PWT) (Fig. 1A): This plan was generated with the explicit use of 3D-TPS to identify and treat the whole breast and IMNs together using Medial and Lateral coplanar tangential beams with 6 MV photons. The shielding of the lung and heart from deep tangents and the sparing of contralateral breast from stochastic doses were a major concern. The suitable gantry angles were chosen for tangents in order to achieve the coverage.
2. Photon-photon mix (Fig. 1B): This technique uses a medial and lateral coplanar tangential beams of 6 MV photons to cover the whole breast with minimum dose to the lung and heart. The IMN volume is covered using a single anterior — oblique photon beam of 6 MV using the same gantry angle and isocentre.
3. Photon-electron mix (Fig. 1C): The single anterior photon beam in Photon-photon mix is replaced by an electron beam, with an intention to reduce dose to the lung and heart. The photon-electron junction in this method is of serious concern, as it gives rise to significant hotspot. To reduce the hotspot, a margin in millimeter (mm) is given between the photon-electron fields, without compromising the target coverage. The electron field was treated with extended SSD, because applicator-patient collision seemed to occur at nominal SSD.
4. 30/70 Photon-electron mix (Fig. 1D): The whole breast was treated using tangential beams as in partially wide tangents. The IMN region is covered using anterior oblique beams of photon and electron with differential weightage, i.e. 30% dose by photon beams and 70% dose by electron beams.

Table 1. Comparison of variables in various techniques by one-way ANOVA

	PTV coverage (%)	Upper IMN coverage (%)	Lower IMN coverage (%)	Hotspot (%)	Left lung mean dose [Gy]
Partially wide tangents	94.24 ± 1.44	27.84	80.46	112.69 ± 1.92	15.86 ± 3.26
Photon-photon mix	94.87 ± 1.41	31.05	88.88	113.87 ± 1.60	19.58 ± 3.11
Photon-electron mix	92.35 ± 1.61	28.64	61.40	132.16 ± 4.65	15.27 ± 2.67
30/70 photon-electron mix	92.03 ± 1.65	28.95	60.81	125.32 ± 4.90	15.95 ± 2.40

PTV — planning target volume; IMN — internal mammary nodes

Evaluation of plans

After planning was done, for each technique, 85% coverage for the planning target to internal mammary nodes was evaluated. We separated the upper IMN volume from the lower IMN volume at the lower border of the clavicular head. This was done as the upper IMN is located at a higher depth than the lower IMN, and so coverage is not uniform for both. Hotspot was defined as 107% of the total prescribed dose. Hotspot was seen for each plan. For organs at risk, mean heart dose and volume of the heart receiving more than 30 Gy (V30) was obtained using dose volume histograms. Similarly, left lung mean dose and the volume of the lung receiving more than 20 Gy (V20) was obtained, as these two parameters are predictive of radiation pneumonitis. Mean dose received by opposite normal breast was obtained. Mean right lung dose was also evaluated.

Statistical analysis

The data collected were entered into Statistical Package for the Social Sciences version 11.5 (SPSS Inc., Chicago, IL) software and descriptive statistics was performed to determine the mean and standard deviation of various parameters. The statistical differences between the techniques were compared using one-way ANOVA and later compared by post-hoc analysis. The level of significance was kept below 0.05.

Results

All the patients included in the study were left sided breast cancer patients who had undergone breast conservation surgery and axillary lymph node dissection followed by chemotherapy. Adjuvant radiation with a dose of 50 Gy in 25 fractions was planned to the left breast, supraclavicular fossa and internal mammary nodes.

IMN coverage

The 85% PTV coverage of Internal Mammary Node was evaluated. The upper IMN was contoured up to the caudal border of the clavicular head. Below that the lower IMN was contoured. The 85% PTV coverage was lesser for the upper IMN than the lower IMN for all four techniques, this was because the upper IMN was situated at a greater depth as compared to lower IMN. The upper IMN coverage was the highest for photon-photon mix. The lower IMN coverage was better for partially wide tangents (80.46%) and photon-photon mix (88.88%) as compared to photon electron mix and 30/70 photon-electron Mix (as shown in Tab. 1).

PTV coverage

The PTV coverage of the left breast, supraclavicular nodes and IMN for all techniques was compared by one-way ANOVA, which was followed by pair-wise comparison. Partially wide tangents technique and photon-photon mix technique had a higher coverage (94.24% ± 1.44 and 94.87% ± 1.41, respectively), and the difference between these two techniques on post-hoc analysis was not significant. The coverage of the photon-electron mix and the 30/70 photon-electron mix was lower, 92.35% ± 1.41 and 92.03% ± 1.65, respectively (as shown in Tab. 1).

Hotspot

When all the techniques were compared for hotspots, the least value of hotspot was seen in the partially wide tangents technique (112.69% ± 1.92). The hotspot for photon-photon mix was 113.87% ± 1.60. Hotspot is unacceptably high in both photon-electron mix and 30/70 photon-electron mix (as shown in Tab. 1).

Left lung

Pair-wise comparison for the left lung mean dose showed that partially wide tangents (15.86 ± 3.26 Gy),

Table 2. Comparison of variables in various techniques by one-way ANOVA

	Right lung mean dose [Gy]	Right breast mean dose [Gy]	Left lung V20 (%)	Heart V30 (%)	Heart mean dose [Gy]
Partially wide tangents	0.55 ± 0.20	0.91 ± 0.78	37.56 ± 8.17	5.98 ± 8.70	9.43 ± 3.15
Photon-photon mix	0.43 ± 0.16	0.53 ± 0.49	40.49 ± 3.36	6.54 ± 5.80	10.10 ± 2.70
Photon-electron mix	0.85 ± 0.25	1.00 ± 0.60	30.70 ± 8.32	5.13 ± 1.88	7.56 ± 1.95
30/70 photon-electron mix	0.58 ± 0.15	0.71 ± 0.52	31.64 ± 5.90	5.75 ± 2.82	7.98 ± 2.16

photon-electron mix (15.27 ± 2.67 Gy), and 30/70 photon-electron mix (15.95 ± 2.40 Gy) had no statistical difference. Higher values were seen in photon-photon mix (19.58 ± 3.1 Gy) (as shown in Tab. 1).

When left lung V20 values were compared, the value obtained for partially wide tangents was 37.56% ± 8.17 and for photon-photon mix it was 40.49% ± 3.36. Pair-wise comparison showed photon-electron mix (30.70% ± 8.32) and 30/70 photon-electron mix (31.64% ± 5.90) had no statistical significance and had lower values.

Heart

The mean heart dose with partially wide tangents was 9.43 ± 3.15 Gy and photon-photon mix was 10.10 ± 2.70 Gy. The mean heart dose for photon-electron mix was 7.56 ± 1.95 Gy and 30/70 photon-electron mix was 7.98 ± 2.16 Gy, and the difference between the two was not significant on pair-wise comparison. The mean heart dose was significantly lesser for photon-electron mix was when compared to these two techniques. (As shown in Tab. 2).

When comparing heart V30, the values were not statistically significant between all 4 techniques on pair-wise comparison.

Right breast

The mean dose to the right breast for partially wide tangents was 0.91 ± 0.78 Gy, and in photon-photon mix it was 0.53 ± 0.49 Gy. It was maximum in the photon-electron mix technique (1.00 ± 0.60 Gy). The mean dose for photon-photon mix was significantly lesser than for the photon-electron mix technique. (As shown in Tab. 2)

Right lung

The mean dose to the right lung was maximum in photon-electron mix (0.85 ± 0.25 Gy) which was significantly higher than all other techniques on pair-wise comparison (as shown in Tab. 2).

Discussion

In this planning study, we compared the IMN coverage and doses to organs at risk for four different plans done for left breast cancer patients who had undergone breast conservation surgery followed by chemotherapy and adjuvant radiation to the left breast, supraclavicular nodal station and internal mammary nodes. We saw that the standard partially wide tangents had better PTV coverage than the other techniques, and was in the acceptable limits of coverage (> 93%). 80% coverage of IMN was achieved by partially wide tangents. The value of mean dose and V30 to the heart for partially wide tangents was comparable to other techniques. The dose to the opposite breast was also comparable. We observed that the techniques including electron beams had unacceptably high hotspots and also lower IMN coverage was lesser with them. The photon-photon mix, photon-electron mix and 30/70 techniques were difficult to execute, reproduce daily and were cumbersome for patients as they had to lie for longer times.

Similar to our study, in a study done by Severin et al. [6] where they compared the partially wide tangents (PWT) technique of breast and internal mammary chain irradiation with photon/electron (P/E) and standard tangent (ST) techniques, they showed that the mean dose for the left breast volume with the photon- electron and PWT techniques was 98.4%, and 96.5%, respectively. They showed that the internal mammary chain volume was most consistently treated with the partially wide tangents (mean dose 99%) *vs.* P/E (86%) and ST (38.4%) techniques. In a study done by pierce et al. [7[, where they compared the chest wall coverage and dose to organs at risk with various techniques, the chest wall coverage with the partially wide tangents technique was adequate with the mean dose in the range of 49.30 ± 2.34. They found that all four techniques had similar mean dose with no statistical difference.

We found that the partially wide tangents technique, along with better coverage, had the least hotspots as well. We observed that the hotspot in the photon-electron mix and 30/70 techniques were unacceptably high (> 120%). These high values of hotspot were observed on the junction of the photon and electron fields and were caused by the overlap of the electron field and the photon field. Similar findings were seen in a study by Severin et al. [6], where the hotspot in the photon-electron field was in the range of 136.3%, which was much higher than the partially wide tangents technique.

The most common complications seen in the left breast irradiation with IMN treatment is cardiac and lung toxicity. Radiation pneumonitis is expected in 1–5% of patients with breast cancer irradiation [8]. Graham et al. [9] reported that patients receiving 20 Gy to 25% of the lung were at lower risk of pneumonitis. Ischemic heart diseases are another long term complication.

Graham et al. [9] found V20 to be the most useful parameter for predicting the risk of RP. When we analyzed the doses to the organs at risk, we found out that partially wide tangents delivered a lower mean dose to the left lung (15.86 ± 3.26). Though when lung V20 was compared, it was found that volume of the lung receiving 20% of dose for partially wide tangents was significantly higher (37.56 ± 8.17) than other techniques. Lower values of lung V20 were seen for the techniques with electron beams, i.e. photon electron mix and 30/70 techniques. Similar results were seen in a study done by Thomson et al. [10] which showed that the ipsilateral lung V20 values were in the range of 28.2–43.6% and Dmean in the range of 14.4–21.3 Gy for the partially wide tangents technique in post-mastectomy radiotherapy patients. Severin et al. [6] did not find any statistical significance in the volume of the lung irradiated by the photon wide tangents and hoton/electron techniques. However, the lung dose with partially wide tangents was higher. Marks et al. [11] reported a 2.6% risk of clinical pneumonitis in patients treated primarily with partially wide tangents, out of whom only 0.5%, however, had persistent symptoms. In the data published by Arthur et al. [12], the mean lung V20 was 30%, and 28% for partially wide tangents, and photon/electron techniques, respectively.

For pericarditis, QUANTEC guidelines state for partial heart irradiation a "V25 Gy < 10% will be associated with a < 1% probability of cardiac mortality" in long-term follow-up after RT [13]. In our study, comparison of heart mean doses showed that they were significantly lower for the photon electron-mix technique (7.56 ± 1.95) and 30/70 technique (7.98 ± 2.16) than for partially wide tangents (9.43 ± 3.15). However, the differences in the V30 values for the heart did not reach statistical significance for all 4 techniques and was the lowest for photon-electron mix (5.13 ± 1.88). Similar results were obtained in a study done by Vander Laan et al. [14], where they compared 4 different techniques for patients undergoing breast irradiation with IMN inclusion. They used the para mixed technique by a widened medio-lateral tangential photon beam and an anterior electron beam, with the patched technique by an anterior electron beam, with the standard technique by an anterior photon and electron beam, and with the partially wide tangents technique by partially wide tangential beams. They found that the mean heart dose for para mixed technique was (8.7 ± 3.5) and for the patched technique it was (7.5 ± 2.6), which was significantly lower than partially wide tangents (11.1 ± 4.4). The heart V30 value was the lowest for the patched technique in their study (7.1 ± 2.6) and was higher for partially wide tangents (16.0 ± 9.2). However, Severin et al. [6] found in their study that the mean heart dose for partially wide tangents (10.3Gy was significantly lower than the photon/electron techniques (19 Gy) ($p < 0.05$). Similar to our study, the difference in heart volume decreases with greater doses because of steep fall-off in the electron beam doses with depth in the study done by Severin et al. [6]. Another study done by Pierce et al. [8], which compared 7 different techniques for post-mastectomy patients, showed that PWTFs resulted in the least volume of heart irradiated to 30 Gy compared with the 30/70 technique.

Keeping in view the stochastic effect of radiation on the opposite breast, we compared the mean radiation dose values to the right breast for all the patients. The partially wide tangents technique was seen to deliver higher dose to the opposite breast (0.91 ± 0.78) as compared to the photon electron mix technique. In the study done by Thomson et al. [11] the highest mean dose to the opposite breast was also seen for the partially wide tangents technique which was nearly 4.8 Gy. Similar results were seen for doses received by the opposite lung, which was lesser for the photon-electron mix technique. Similar results were seen by Severin et al. [6], the partially wide tangents technique treated the greatest amount of contralateral breast (mean dose 5.8%) *vs.* P/E (2.8%).

We comprehend that the major drawback of our study is that we have not used more recent techniques like Breath hold techniques and IMRT which have shown improved outcomes in reducing cardiac toxicities in the left sided breast cancer with internal mammary node coverage. Our study is more applicable in developing nations where all centers are not equipped with recent technologies and where patients are not educated enough to be trained for breath hold techniques.

Conclusion

In conclusion, we came to the understanding that no single technique satisfies all the criteria. Photon wide tangent and photon-photon mix are better in terms of coverage and hotspot, but deliver higher doses to organs at risk. When electron beams are combined with the photon beams, though the combination reduces the doses to the organs at risk, it comes at a cost of reduced PTV coverage and unacceptably high hotspot. Thus, there is no clear answer as to the choice of the technique for breast cancer patients and the decision should be made on a case-by-case basis, considering various other things, like the anatomy of the patient, availability of electron facilities and setup accuracy and reproducibility.

Conflict of interest

None declared.

Funding

None declared.

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