

Dosimetric Comparison of Four Different Radiotherapy Planning Techniques for Adjuvant Radiotherapy of Left-Sided Breast, Axilla, and Supraclavicular Fossa

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Abstract

Purpose/Aim: Forward planned intensity-modulated radiotherapy (forward IMRT) with breath-hold (BH) technique is considered optimal by most practitioners for treating left-sided breast cancer. Regional nodal irradiation including axilla and supraclavicular fossa (SCF) increases can increase dose-to-organs at risk (OAR) especially lung. This study was done to assess the potential of inverse planned IMRT (inverse IMRT) to achieve significant reduction in dose to OAR. **Materials and Methods:** Ten patients with left-sided breast cancer treated with Active Breath Co-ordinator BH technique were included in the study. Forward IMRT plans were generated in both BH and free breathing (FB) scans. Inverse IMRT plans were generated in FB scan using Tomotherapy-Direct and Tomotherapy-Helical techniques. Contouring was done as per the ESTRO consensus contouring guidelines. The dose prescribed was 40 Gy in 15 fractions. Statistical significance was tested using one-way ANOVA for parametric data and Kruskal–Wallis test for nonparametric data. Multiple comparison tests were done by using Bonferroni test. $P < 0.05$ was considered to denote statistical significance. **Results:** Inverse IMRT plans achieved superior homogeneity index compared to forward IMRT with BH. Tomotherapy-Direct reduced dose to ipsilateral lung, compared to the forward IMRT with BH while achieving similar doses to other OAR. Tomotherapy-Helical plans achieved significantly better conformity index and reduced maximum dose to left anterior descending artery compared to forward IMRT plans, but low dose to other OAR was significantly worse. **Conclusion:** For left-sided breast, axilla, and SCF radiotherapy, inverse IMRT with Tomotherapy-Direct plan achieved better homogeneity index and reduced dose to ipsilateral lung compared to forward IMRT with BH.

Keywords: Breast cancer, IMRT, radiotherapy, tomotherapy

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INTRODUCTION

Breast cancer is the most common cancer in women, representing nearly a quarter of all cancers worldwide. It is also the leading cause of cancer mortality in women. In India, with 162,468 newly diagnosed cases and 87,090 deaths, breast cancer ranks 1st among cancers in women in terms of incidence and mortality.^[1]

Adjuvant radiotherapy in breast cancer improves local control and distant relapse-free survival and reduces breast cancer mortality rate.^[2] Radiation-induced cardiac events and pneumonitis are the major late effects associated with dose to heart and lungs. This decreases the overall survival benefit patients can have with radiotherapy.^[3,4] Breast fibrosis and pain also affect quality of life, and this increases with inhomogeneous

high-dose distribution in the standard bitangential field radiotherapy.^[5,6] Dose-to-organs at risk (OAR) has reduced with adoption of cardiac sparing breath-hold (BH) technique with forward planned intensity-modulated radiotherapy (forward IMRT).^[7]

Regional nodal irradiation including axilla in the target volume is usually indicated in the setting of inadequate axillary dissection or sentinel node positivity without axillary

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clearance and in selected high-risk patients.^[8-10] Axilla and supraclavicular fossa (SCF) radiation can increase the dose to lung. Inverse planned IMRT (inverse IMRT) has the potential to further reduce dose to the OAR in this setting.^[11]

This study is a dosimetric comparative study between four different external beam radiation therapy techniques namely forward planned IMRT with and without BH, and inverse planned IMRT using Tomotherapy-Direct and Tomotherapy-Helical. The aim of the study is to establish the merits and demerits of each technique and assess the ideal technique for treating left-sided breast with regional nodal irradiation including axilla.

MATERIALS AND METHODS

Ten patients who underwent forward planned IMRT with tangential fields and BH technique for left-sided breast, axilla, and supraclavicular radiotherapy were included. At the time of simulation, computed tomography (CT) scans were obtained both in free breathing (FB) and moderate deep inspiratory BH (mDIBH) with active breath coordinator (ABC).

Tomotherapy-helical and tomotherapy-direct plans were generated in the FB scan. Forward IMRT plans with field-in-field technique were generated in both FB scan and mDIBH scan.

Technical information

Radiation treatment workflow

Pretreatment patient education

Informed consent was taken from all patients. Before CT simulation, all the patients underwent a 20–30-min-long training session for 2 days with the Active Breathing Coordinator R2.0 (Elekta, Stockholm, Sweden) to enhance patient compliance and to determine individual mDIBH (levels set at 75% of maximum inspiratory capacity). Verbal instructions were given during the training process to motivate the patients to achieve a constant breathing pattern. BH was practiced at moderate deep inspiration until a steady and reproducible breathing pattern is reached. Patients with a comfortable BH duration of 20–25 s were considered eligible to undergo treatment with ABC–mDIBH.

Simulation

Planning CT simulation scan was obtained using a GE Optima580WRT CT Simulator (GE Healthcare, Chicago, Illinois, USA). All patients were treated in supine position with both arms above the head, using a MED-TecM350 breast board (Civco Radiotherapy, Orange City, Iowa, USA) with an inclination of 15°–30°. Radio-opaque wires were used to outline the palpable breast tissue, visible surgical scar, midline, and the mid-axillary line to assist in target delineation. ABC device was used for assisting mDIBH. A nose clip was used to ensure breathing through the mouth only. After acquiring a steady breathing pattern, two sets of CT images were acquired for each patient with a slice thickness of 3 mm. The first scan was acquired at mDIBH with ABC system which was used for

actual treatment. This was followed by a second scan in FB. CT data were acquired superiorly from the infra-orbital margin, extending inferiorly till the L2 vertebral level.

Contouring

For consistency, all contours were done by the same physician. The clinical target volume—breast and SCF + axilla were contoured as per the ESTRO consensus contouring guidelines.^[12] A 0.5-cm margin was added around the clinical target volumes to generate the planning target volume (PTV) and were labeled as PTV-breast and PTV-SCF + axilla. PTV-combined was generated as the sum of PTV-breast and PTV-SCF + axilla. The delineated OARs included the ipsilateral and contralateral lung, heart, contralateral breast, spinal cord, esophagus, and the left anterior descending artery (LAD). The LAD was contoured using the cardiac contouring atlas for radiotherapy.^[13]

Treatment planning

For consistency, all treatment plans were generated by the same medical physicist. Tomotherapy-direct and tomotherapy-helical plans were generated using Accuray Precision Treatment Planning Station (Version 2.0.1.1; California, USA). All the plans were optimized using 2.5-cm jaw and modulation factor of 2.2. Pitch for all Tomotherapy-Helical plans was 0.26 and 0.251 for all Tomotherapy-Direct plans. The dose calculation grid size was set to “fine” and final dose resolution to “high.” The optimization parameters were kept the same initially for both calculations and changed accordingly during optimization. The number of iterations for all plans was kept between 200 and 300.

Tomotherapy-direct planning

The paired tangential angles were chosen same as those of conventional linear accelerator. The beam angles were arranged to include PTV and minimize OARs. For PTV breast, a total of six angles were used. Medial tangential angles ranged from 315 to 340°, and lateral tangential angles ranged from 110 to 130°. A flash of 2 cm was given for two main tangential fields. For SCF, four angles were given. The angles ranged from 318 to 110°. To avoid field junction hotspot, a separation of one slice thickness, i.e. 3 mm, was given during the optimization. Adequate coverage was achieved in that slice [Figure 1].

Tomotherapy-helical planning

To avoid the low-dose spillage to OARs, dose-limiting volumes for the right breast and lung were used and defined “exit only” during optimization. Unwanted spillage was avoided using a spill structure which was created by giving 1-cm margin from PTV [Figure 2].

Forward IMRT planning

Three-dimensional conformal plans with forward IMRT field-in-field technique were generated in XIO planning station (version v. 5.10.02) (Elekta, Stockholm, Sweden). Tangential fields (medial tangent MT and lateral tangent LT) were given with photon energy ×6, while SCF fields which are given anteroposterior beams were a combination of ×6

and $\times 15$. The weightages of the said beams were chosen such that lung doses were minimized and optimal coverage was achieved. One field-in-field beam (MT subfield) helped to reduce the hotspots and heart dose. Both set of beams were matched at the lower end of the head of clavicle. A dose of 40 Gy in 15 fractions was prescribed for each dose reference point for PTV breast and SCF [Figure 3].

Statistical analysis

Statistical analysis was done using IBM SPSS 20.0 (SPSS Inc., Chicago, USA). To test the statistically significant comparison of parameters among the different external beam radiation therapy techniques, one-way ANOVA was applied for parametric data and Kruskal–Wallis test was applied for

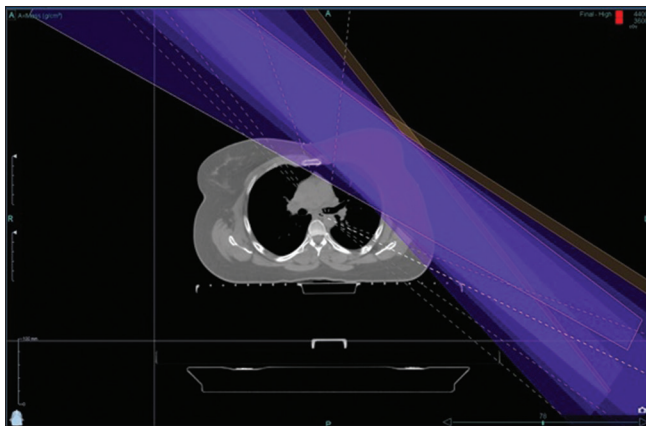


Figure 1: Beam orientation in tomotherapy-direct plan



Figure 2: Dose distribution in tomotherapy-helical plan

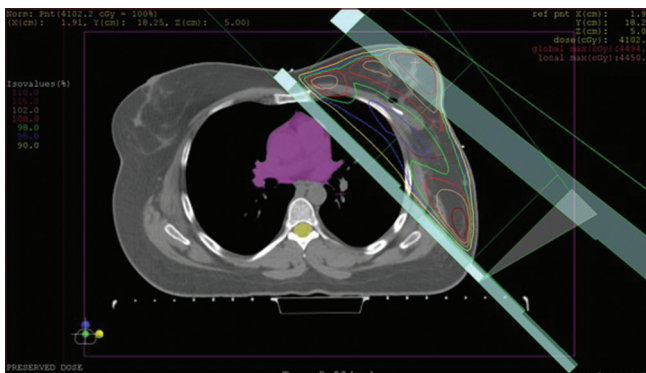


Figure 3: Forward IMRT plan with field-in-field technique in breathhold

nonparametric data. Multiple comparison tests were done by using Bonferroni test. $P < 0.05$ was considered to denote statistical significance.

RESULTS

The mean dosimetric parameters of the four techniques of radiation planning namely forward IMRT, forward IMRT with BH, tomotherapy direct, and tomotherapy helical for the ten patients are summarized in Tables 1 and 2.

Target volumes

Target coverage was given priority during planning and hence the coverage was not different among the four techniques. Conformity index was calculated using the following formula: volume of reference isodose (95%) divided by the PTV volume, and homogeneity index was calculated using the RTOG formula of ratio of maximum isodose to reference isodose and the ICRU formula of $D_{2\%} - D_{98\%}$ divided by $D_{50\%}$.^[14,15] There was a significant difference in conformity index for “PTV COMBINED” among the four groups ($P \leq 0.001$). Tomotherapy-Helical had a better conformity index compared to that of forward IMRT with BH ($P = 0.001$) and forward IMRT ($P = 0.010$). The homogeneity index was similar between the tomotherapy plans, and both were statistically superior over both the forward IMRT plans.

The mean values of $V_{107\%}$ in forward IMRT with BH, forward IMRT, Tomotherapy-Direct, and Tomotherapy-Helical were 4.005 ± 2.577 , 4.054 ± 4.432 , 0.050 ± 0.108 , and 0.190 ± 0.567 , respectively, indicating lesser “hot” in the tomotherapy plans. Both inverse IMRT plans showed a significant difference compared to that of forward IMRT plans.

Organs at risk

Heart

The mean dose to the heart was 383.40 ± 151.341 cGy in forward IMRT with BH, 488.80 ± 165.611 cGy in forward IMRT technique, 348.20 ± 139.335 cGy in tomotherapy-direct, and 599.90 ± 78.720 cGy in the tomotherapy-helical. The comparison shows a statistically significant difference with $P = 0.001$. The mean dose to the heart was greater in the tomotherapy-helical group and showed a statistically significant difference when compared to forward IMRT with BH ($P = 0.001$) and tomotherapy-direct ($P = 0.007$).

Combined lung

The tomotherapy-direct plan had the lowest $V_{20\text{Gy}}$ dose to combined lung. $V_{20\text{Gy}}$ of $14.263 \pm 1.467\%$ in forward IMRT with BH, $V_{20\text{Gy}}$ of $16.109 \pm 2.531\%$ in forward IMRT, $V_{20\text{Gy}}$ of $10.20 \pm 1.289\%$ in tomotherapy-direct, and $V_{20\text{Gy}}$ of $14.190 \pm 2.487\%$ in the tomotherapy-helical technique. The comparison shows a statistically significant difference with $P < 0.001$.

Contralateral breast

The tomotherapy-helical plan had the highest dose to the contralateral breast. The mean dose to the contralateral breast among the different external beam radiation therapy

Table 2: Dosimetric parameters of organs at risk

Structure	Metric	Mean±SD				P					
		FI	FID	TD	TH	FI versus FID	FIF versus TH	FID versus TD	FID versus TH	TD versus TH	
Contralateral breast	Dmax (cGy)	236.20±131.871	772.5±1041.917	716.20±399.489	901.40±156.42	0.433	0.021	<0.001	1.000	0.098	1.000
	Dmean (cGy)	20.2±40.77	25.7±9.581	50.50±19.896	267.80±36.54	1.000	1.000	<0.001	1.000	<0.001	<0.001
	V5Gy (%)	0.050±0.104	0.631±0.839	3.890±4.379	60.560±17.736	1.000	1.000	<0.001	1.000	<0.001	<0.001
Ipsilateral lung	Dmean (cGy)	1385.50±163.463	1258.0±113.173	1009.30±87.271	1607.70±756.235	1.000	0.236	1.000	0.996	0.327	0.010
	V15Gy (%)	38.165±4.279	33.642±2.914	25.960±2.562	44.750±3.339	0.027	<0.001	0.001	<0.001	<0.001	<0.001
	V18Gy (%)	36.114±4.430	31.745±2.942	23.090±2.456	37.020±4.139	0.059	<0.001	1.000	<0.001	0.014	<0.001
	V20Gy (%)	34.771±4.536	30.539±2.956	21.480±2.393	30.320±4.321	0.084	<0.001	0.061	<0.001	1.000	<0.001
Contralateral lung	Dmean (cGy)	29.80±4.826	28.20±3.458	42.80±5.073	44.02±345.46	1.000	1.000	<0.001	1.000	<0.001	<0.001
	V2.5Gy (%)	0.058±0.112	0.166±0.184	0.130±0.241	54.410±8.719	1.000	1.000	<0.001	1.000	<0.001	<0.001
	V4Gy (%)	0.019±0.043	0.066±0.088	0.010±0.032	26.430±9.166	1.000	1.000	<0.001	1.000	<0.001	<0.001
Combined lung	V20Gy (%)	16.109±2.531	14.236±1.467	10.20±1.289	14.190±2.487	0.293	<0.001	0.246	<0.001	1.000	<0.001
	Dmean (cGy)	488.80±165.611	383.40±151.341	348.20±139.335	599.90±78.720	0.575	0.171	0.479	1.000	0.007	0.001
Heart	V2Gy (%)	24.446±6.395	24.229±6.187	21.850±8.841	95.650±4.451	0.529	0.091	<0.001	1.000	<0.001	<0.001
	V8Gy (%)	14.242±5.243	11.215±5.342	10.690±5.597	22.22±5.738	1.000	1.000	<0.001	1.000	<0.001	<0.001
	V10Gy (%)	12.944±5.083	10.114±5.130	9.650±5.374	13.520±4.421	0.231	0.467	<0.001	1.000	<0.001	<0.001
	V25Gy (%)	7.942±4.321	5.306±3.484	4.240±2.852	1.730±0.519	0.467	0.720	<0.001	1.000	0.090	0.489
	Dmax (cGy)	3744.00±186.351	3595.50±589.145	3231.50±688.427	2908.00±248.503	1.000	0.132	0.002	0.587	0.017	0.838
Esophagus	Dmean (cGy)	2506.30±605.498	2110.80±690.602	1767.40±780.388	1673.60±346.135	1.000	0.074	0.032	1.000	0.766	1.000
	Dmax (cGy)	3084.00±525.980	2841.50±481.924	3622.90±478.568	3409.80±549.525	1.000	0.142	0.970	0.009	0.105	1.000
	Dmean (cGy)	447.20±220.490	338.30±161.862	323.80±102.170	835.10±94.837	0.728	0.484	<0.001	1.000	<0.001	<0.001
Cord	Dmax (cGy)	1344.20±422.04	1082.00±359.028	1365.10±397.112	2227.10±111.765	0.759	1.000	<0.001	0.599	<0.001	<0.001

^aForward IMRT, ^bForward IMRT with DIBH, ^cTomo-direct inverse IMRT, ^dTomo-helical inverse IMRT, ^eIMRT: Intensity-modulated radiotherapy, DIBH: Deep inspiratory breath hold, SD: Standard deviation, FI: Forward IMRT, FID: Forward IMRT with Deep Inspiration Breath Hold, TD: Tomo-Direct inverse IMRT, TH: Tomo-Helical inverse IMRT, LAD: Left anterior descending

with a risk reduction of skin telangiectasia and superior overall cosmesis.^[20] A thorough literature search by Ratoso *et al.* demonstrated that inhomogeneity and excessive radiation dose (hotspots) in the planning of target volume contributed to a higher rate of acute adverse events and suboptimal final cosmetic outcome in adjuvant breast cancer radiotherapy, regardless of the fractionation schedule, and improved homogeneity leads to a lower rate of \geq Grade 2 toxicity.^[21]

Radiation pneumonitis is a concern in women receiving radiation therapy to the breast. In the current study, the volume of ipsilateral lung receiving 5 Gy was similar to that in tomotherapy-direct and forward IMRT with BH but had significantly superior dose suppression as compared to that of tomotherapy-helical and forward IMRT plan. The mean dose to the ipsilateral lung was significantly less in tomotherapy-direct as compared to that of tomotherapy-helical. V_{20} was also significantly lesser in tomotherapy-direct arm compared to that of the other techniques. The mean dose to the contralateral lung was highest in the tomotherapy-helical arm as well as the $V_{2.5}$, V_4 , and V_5 , thereby highlighting that low dose spill to OARs is seen maximally with tomotherapy-helical. The V_{20} of the combined lung was significantly the least in tomotherapy-direct. These findings were consistent with those of Takano *et al.*, which showed a significant difference between tomotherapy-direct and 3DCRT in terms of mean dose to the combined lung, ipsilateral lung, and contralateral lung.^[17] The low dose spill was highest in tomotherapy-helical arm. The findings were also similar to the study conducted by Zhou *et al.* Tomotherapy-direct had superior dosimetry in high-dose region of ipsilateral lung.^[19] Low-dose spread also affects the induction of second primary cancers. Santos *et al.* estimated the risk of second primary cancer following postoperative radiation therapy for breast cancer and concluded that the lungs and contralateral breast had high life-attributed risk estimates.^[22]

In a study of women who received radiation therapy for breast cancer between 1985 and 1999, Stovall *et al.* showed that the risk of secondary breast cancer in the contralateral breast increased in women younger than 40 years who received >1.0 Gy maximum dose to the breast tissue.^[23] These results suggest that low-dose spread should be avoided as much as possible. In the current study, the mean dose to the breast was least in the forward IMRT and tomotherapy-direct but significantly higher in the tomotherapy-helical arm. A study by Takano *et al.* also showed lower doses to the opposite breast with tomotherapy-direct as compared to 3DCRT and tomotherapy-helical techniques.^[17] The low dose spill to contralateral breast was controlled in the current study by defining it as exit only for optimization and also unwanted spillage was controlled by a spill structure 1 cm around PTV.

According to a population-based, case-control study by Sarah Darby, from the University of Oxford, the rate of major

coronary event increases by 7.4% for every increase of 1 Gy.^[24] The update of adjuvant breast radiation by the Early Breast Cancer Trialists Collaborative Group analyzed over 30,000 women followed up for up to 20 years, and there is a clear evidence that radiation-related heart disease (RRHD) increases by 3% per Gy.^[25]

Correa *et al.* in a retrospective review of cardiac morbidity in postirradiation patients of breast cancer had found out that coronary stenosis especially in the LAD was the most common cause of RRHD.^[26] In a previous study by Meyer *et al.*, it was demonstrated that tomotherapy-direct reduces mean dose by 40% compared to non-BH technique and noninferior to BH technique in breast-alone radiotherapy.^[27] In the current study, the mean dose to the heart was similar between forward IMRT with BH and tomotherapy-direct, however significantly lesser compared to tomotherapy-helical. On review of the plans, it was seen that the BH was not ideal in three elderly patients, which resulted in significant mean dose reduction with tomotherapy-direct plan. Hence, this finding may not be considered significant in an ideal DIBH scenario. The maximum dose to the LAD artery was significantly lowest in tomotherapy-helical compared to that of the forward IMRT plans. The mean dose to the LAD was lowest in tomotherapy-helical arm but statistically different from that of forward IMRT plan alone.

The present study demonstrates that for adjuvant radiotherapy in left-sided breast, axilla, and SCF, inverse IMRT with tomotherapy-direct achieved better homogeneity and lung constraint, compared to that of the forward IMRT with BH technique while achieving safe doses to other OAR. Both tomotherapy techniques achieved a significantly superior homogeneity index. Tomotherapy-helical plans achieved significantly better conformity indices, and maximum dose to LAD compared to 3D plans. However, other OAR doses were significantly worse in tomotherapy-helical plans. Based on these dosimetric parameters, tomotherapy-direct can be considered the complementary technique to forward IMRT with BH technique for better lung sparing. However, larger clinical prospective series is needed to identify whether a certain subgroup of patients should be routinely offered tomotherapy-direct planning.

Limitations of the study

This study included contouring of target volumes and OAR in two study sets. Despite all contours being done by the same physician, certain degree of intra-observer variation is expected.

The study highlights dosimetric quality of different techniques but does not incorporate use of radiobiological parameters such as tumor control probability and normal tissue complication probability based on clinical outcome.

As this was a proof-of-concept study, the sample size was small, limiting definite conclusions. Larger studies exploring inverse IMRT using tomotherapy must be done to identify subgroup of patients benefitting with appropriate techniques.

CONCLUSION

For left-sided breast, axilla, and SCF radiotherapy, inverse IMRT with tomotherapy-direct plan achieved better homogeneity index and reduced dose to ipsilateral lung compared to forward IMRT with BH. The mean dose to heart was not significantly reduced, and most patients with an ideal BH might still benefit with BH technique.

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Conflicts of interest

There are no conflicts of interest.

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