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FULL PAPER

Use of tomotherapy in treatment of synchronous bilateral breast cancer: dosimetric comparison study

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Objective: Synchronous malignancy in both breasts is a rare incidence. The present study aims at dosimetric comparison of conventional bitangential radiotherapy (RT) technique with conventional [field-in-field (FIF)] and rotational [Helical TomoTherapy® and TomoDirect™ (TD); Accuray Inc., Sunnyvale, CA] intensity-modulated RT for patients with synchronous bilateral breast cancer (SBBC).

Methods: CT data sets of 10 patients with SBBC were selected for the present study. RT was planned for all patients on both sides to whole breast and/or chest wall using the above-mentioned techniques. Six females with breast conservation on at least one side also had a composite plan along with tumour bed (TB) boost using sequential electrons for bitangential and FIF techniques or sequential helical tomotherapy (HT) boost (for TD) or simultaneous integrated boost (SIB) for HT.

Results: All techniques produced acceptable target coverage. The hotspot was significantly lower with FIF technique and HT but higher with TD. For the organs at risk doses, HT resulted in significant reduction of the higher dose volumes. Similarly, TD resulted in significant reduction of the mean dose to the heart and total lung by reducing the lower dose volumes. All techniques of delivering boost to the TB were comparable in terms of target coverage. HT-SIB markedly reduced mean doses to the total lung and heart by specifically lowering the higher dose volumes.

Conclusion: This study demonstrates the cardiac and pulmonary sparing ability of tomotherapy in the setting of SBBC.

Advances in knowledge: This is the first study demonstrating feasibility of treatment of SBBC using tomotherapy.

Breast cancer is the most common malignancy amongst females in the world, including Indian females. $¹$ $¹$ $¹$ Cancer in</sup> both breasts is an uncommon presentation. Incidence of bilateral breast cancer (BBC) has been reported in the range of 1.4–11.8% with the majority being metachronous cancer. 2,3 2,3 2,3 Depending upon various definitions adopted by authors, synchronous BBC (SBBC) accounts for approximately 0.4–2.8% of all breast cancers. $4,5$ Whether bilaterality confers worse prognosis or similar prognosis is yet to be conclusively determined. Some studies have indicated that there is no difference in survival between the unilateral vs BBC patient groups, while other studies claim that bi-lateral carcinoma significantly reduces survival.^{[6,7](#page-12-0)} Treatment in patients with BBC is similar to that in patients with unilateral breast cancer wherein adjuvant radiotherapy (RT) forms an integral part of the breast conservation algorithm. The safety of breast conservation surgery (BCS) for SBBC has been documented in literature.^{[8](#page-12-0),[9](#page-13-0)} Adjuvant RT for breast cancer typically includes whole breast

irradiation after lumpectomy or chest wall irradiation after mastectomy with or without regional nodal irradiation. This is accomplished using conventional bitangential portals that include part of the anterior chest wall adjacent to the RT target.^{[10](#page-13-0)–[12](#page-13-0)} RT delivery in cases of SBBC is even more complex owing to multiple field junctions, which results in heterogeneous dose distributions as well as significantly higher irradiation volume of organs at risk (OARs) such as the lungs and heart.

The reported incidence of radiation pneumonitis (RP) varies from 0% to 80% depending upon the radiation technique, length of follow-up, imaging modality used and the end point chosen.^{[13](#page-13-0)–[16](#page-13-0)} Although symptomatic RP is a rare clinical complication for unilateral breast cancer, it has a potential detrimental effect of reducing the normal functional reserve and should be taken into consideration given the long life expectancy of patients and higher volume of irradiation owing to bilaterality in

patients with SBBC. The risk and severity of RP is influenced by various therapy-related (volume of incidentally irradiated lung, region of irradiated lung, radiation dose, fractionation and concomitant use of systemic agents, particularly paclitaxel) and patient-related factors (age, pre-existing lung disease, poor pulmonary function, smoking habits, genetic predisposition). The most significant amongst these include patient age, locoregional RT, reduced pre-RT pulmonary reserve and concomitant tamoxifen use with adjuvant RT .^{[17](#page-13-0)-[19](#page-13-0)} These factors correlate with various dosimetric indices $[V_{20}, D_{25}]$, mean lung dose (MLD)] that predict the risk of RP^{20} RP^{20} RP^{20}

Similarly, the toxic effect of radiation on the heart has been well documented. The long-term risk of ischaemic heart disease following breast RT has been correlated with the mean heart dose, maximum heart distance and various dosimetric parameters $(V_{20}, V_{30}$ and V_{40}). Moreover, several patientrelated risk factors (body mass index, diabetes mellitus, dyslipidaemia, tobacco/alcohol consumption, prior heart disease) and systemic agents (anthracyclines, trastuzumab, tamoxifen) modify the risk of radiation-induced cardiac toxicity.^{[21,22](#page-13-0)} Patients with BBC receive a higher radiation dose to the heart (owing to scatter radiation from the right side) and would be at increased risk of radiation-induced cardiac toxicity. 23 23 23

Although techniques of delivering RT have improved considerably for various sites in past two decades, the technique of delivering RT to the breast or chest wall, unilateral or bilateral, has not changed much. Various other methods have been used to deliver RT to the breast and/or the chest wall for SBBC across the world, such as electron arc therapy, or static or rotational intensity-modulated RT (IMRT), but none has been compared with conventional bitangential RT. 24,25 24,25 24,25

Helical TomoTherapy® (HT) (Accuray Inc., Sunnyvale CA) is a radiation delivery modality that delivers an intensitymodulated fan beam using a 6-MV linear accelerator mounted on a ring gantry that rotates around the patient as he/she advances slowly through the gantry bore. 26 26 26 Dosimetric data regarding the use of HT in breast cancer treatment have resulted in equivocal results, not only in the context of target coverage and homogeneity but in the sparing of the heart and lungs as well. Although HT has been studied in the context of partial breast irradiation, whole breast irradiation and locoregional nodal irradiation, $27-30$ $27-30$ $27-30$ fewer data are available on the dosimetry and feasibility of HT in the context of SBBC requiring bilateral adjuvant radiation with or without simultaneous integrated boost (SIB) of the tumour bed (TB).

TomoDirect™ (TD) (Accuray Inc.) is a static or non-rotational extension of HT, which is also referred to as TomoTherapy®. In this application of TomoTherapy, the patient is translated craniocaudally through fixed gantry positions with simultaneous beam modulation. Up to 12 coplanar fixed beams can be used for dose optimization and target coverage. Similar to HT, dosimetric and clinical data are also available with TD in both, three-dimensional conformal RT (3DCRT) and/or IMRT mode for treatment of unilateral breast cancer treatment.[28,31](#page-13-0)–[33](#page-13-0) However, no data are available on the dosimetry and feasibility of TD in the context of SBBC.

In our study, we aimed to compare conventional bitangential RT with conventional IMRT and two techniques of tomotherapy, namely HT and TD dosimetrically in the context of SBBC.

METHODS AND MATERIALS

In this pilot study, those patients who were diagnosed with SBBC and received conventional bitangential RT to the breast and/or chest wall were identified during January 2009 to November 2013. CT planning data sets of these patients were retrieved for the dosimetric comparison. This constituted a total of 10 patients inclusive of 4 patients who had BCS on both sides, while 4 had modified radical mastectomy on both sides. Two females had mastectomy on one side (left side for both) and breast conservation on another side. All cases had a histopathological diagnosis of infiltrating ductal carcinoma (IDC) in both breasts.

Conventional planning

Conventional plans were made for each side respecting principles of conventional bitangential treatment planning consisting of two opposed tangential beams of 6- or 10-MV energies for unilateral breast RT with at least 0.7 to 1.0-cm gap between medial tangential portals of both sides. All plans were made on the treatment planning system ARIA™ (Eclipse™ v. 8.6.0; Varian® Medical Systems, Palo Alto, CA) for treatment on a Varian Trilogy®, with a 120-leaf multileaf collimator (MLC; Varian Medical Systems). 15° and 30° physical wedges in superoinferior direction were used when indicated. The heart was spared by using the MLC whenever possible without compromising target volume coverage. Bolus was not used for any chest wall planning. For five patients (including one chest wall), the 6- and 15-MV combinations were used, while for the rest, only the 6-MV combination was used. Plans were made with acceptable central lung distance (CLD; mean CLD was 1.66 cm for the right side and 1.87 cm for the left side) and maximum heart distance (MHD; mean MHD, 1.45 cm). Each side plan was summated and the sum plans were evaluated respecting the International Committee on Radiation Units and Measurements (ICRU) criteria and disregarding contours. For TB boost, electron plans of appropriate energy were generated in the same planning CT scan. Single electron boost fields were added using rectangular apertures. The gantry was angled to be perpendicular to the skin surface, and the collimator was rotated for the best fit to the planning target volume (PTV) shape. Electron energies from 6 to 20MeV were used, with the aim to put the 90% isodose at the posterior limit of the PTV boost. The dose was prescribed to the 90% isodose. Plans were calculated using the electron Monte-Carlo algorithm.

A composite plan was produced by summing the boost plan and the whole breast plan of both sides (whenever applicable).

Contouring

The clinical target volume (CTV) for the breast and/or chest wall was contoured with the help of a wire placed on the patient during planning CT scan. A 5-mm margin was grown to this volume to form the PTV. The PTV was cropped from the skin by 5 and 3 mm in case of post-breast conservation surgery and post-mastectomy RT, respectively. OARs such as the lung on

each side and the heart were contoured. Both lungs were delineated with automatic segmentation. The heart was contoured from the level of the pulmonary trunk to the apex and included the pericardium but not the major vessels. In cases of BCS, the TB was delineated with the help of seroma or surgical clips, if present, or with a metal wire placed over the scar. A margin of 1 cm was given in all directions to form CTV boost. Volume of CTV boost was modified so as to be confined within the breast volume. Furthermore, a 5-mm margin was given to make PTV boost, to be confined within PTV breast volume (Figure 1).

PTV modification

PTVs were modified according to the volume covered in conventional portals so as to keep comparable targets for all treatment plans. For the breast and chest wall RT, the volume covered by 95% and 90% of the prescription dose was taken as the reference volume created with the help of the tool "convert isodose to contour" in ARIA. In three instances with breast $\frac{1}{2}$ conservation \leq 95% isodose (90% isodose in two instances, 93%) in one instance) was taken as the reference volume to achieve adequate coverage of boost volume. The volume common to the reference volume and PTV was created and termed as "TREAT PTV". These contours were used for planning other treatment techniques (Figure 2).

Field-in-field intensity-modulated radiotherapy planning

Field-in-field (FIF) plans were made for each TREAT PTV on

treatment planning system (TPS) (Eclipse). In the FIF technique, an initial calculation was performed first with two open tangential photon beams without any beam modifiers. After achieving dose distribution, hotspot volumes (volume receiving $>$ 107%) were created as structures by TPS, and for these hot spot volumes, blocking subfields (average three subfields for

Figure 1. Target volume delineation [note: metal wires are used to mark extent of breast clinically. Planning target volume (PTV) whole breast; volume covered by 95% isodose using conventional bitangential technique; TREAT PTV; tumour bed cavity; clinical target volume (CTV) tumour bed; PTV tumour bed]. TREAT PTV, term for volume common to reference volume and PTV.

each side) were then determined in order to improve the dose homogeneity for the PTV in a stepwise manner. Precaution was taken that none of the subfields should contribute \leq 5 cGy or .20 cGy to the final plan. The heart was spared by using the MLC whenever possible without compromising target volume coverage. The main field and the subfields were merged into one portal, including several MLC segments for sequential irradiation. Boost plans were generated same as those for conventional plan.

Tomotherapy planning

Each TREAT PTV was planned on Helical TomoTherapy Hi-Art® system (TomoTherapy Inc., Madison, WI), TomoPlan (TomoTherapy planning system) v. 4.2.0 for HT-IMRT and TD with 3DCRT (TD-3DCRT) and IMRT (TD-IMRT) separately. Helping structures were created within the body volume outside the PTV where significant hotspots were likely to occur. In addition, a horizontal dummy along the posterior part of the body was used for blocking the entry of the beamlets (Figure 2).

For each plan, the treatment field width (FW), pitch (defined as the ratio of the distance travelled per rotation to the axial FW

Figure 2. Dose distribution with TomoDirect™ (TD) (Accuray Inc., Sunnyvale, CA) intensity-modulated radiotherapy (IMRT) and helical tomotherapy (HT) IMRT (whole breast only). Dose volumes are given with reference to prescription dose. 55 Gy, i.e. 110% of 50 Gy prescription dose; 53.5 Gy, i.e. 107%; 47.5 Gy i.e. 95% of 50 Gy prescription dose. (note the helping structure, a horizontal dummy along the posterior part of the body was used for blocking the entry of the beamlets).

3DCRT, three-dimensional conformal radiotherapy; conv., conventional; FIF, field in field; HI, homogeneity index; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; max., maximum; min., minimum; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); TREAT PTV, term for volume common to reference volume and PTV; V_x , target volume receiving at least X% of prescribed dose. The values in the table are expressed as mean (standard deviation).

used for treatment) and modulation factor (MF) need to be selected. Then, the dose distribution for each beamlet that passes through the target is calculated by a convolution/superposition algorithm. Once the beamlet calculation step is completed, the optimization process begins and an iterative least-squares minimization method is used to optimize the objective function. During the final dose computation, the optimized sinogram is converted to the delivery sinogram, taking into account the leaf fluence output factors and latency data. A fine calculation grid $(256 \times 256$ pixels) was used both in the optimization and calculation processes. The TPS was driven by dose-based objectives, their associated penalties and ROI-based weighting factors (for HT-IMRT and TD-IMRT). For target volumes, the minimum and maximum dose values and their respective penalties were used in addition to a dose–volume histogram (DVH)-based prescription point. OAR objectives were described by a maximum dose, a DVH-based constraint and their respective penalties.

TomoDirect planning

TomoDirect three-dimensional conformal radiotherapy for whole breast/chest wall: The TD-3DCRT mode represents a

simpler planning mode in which the DVH-based prescription was selected for target structures, which in turn influences the optimization process by only setting two parameters: the tissue compensation and the normal tissue homogeneity. All plans were performed with the normal tissue homogeneity option and setting the tissue compensation to high, in order to allow for a more meaningful comparison with other techniques. In general, two to four beams were selected for each side such that it covers the PTV adequately and avoids entry through couch whenever possible, otherwise the conflict message was ignored. An entrance beam block was placed on the heart to minimize dose to the heart.

TomoDirect intensity-modulated radiotherapy for whole breast/chest wall: Two or four tangential beams for each side with a jaw width of 2.5 cm were used. Beam angles were selected in order to minimize the dose to OARs taking into consideration the CLD and MHD. Only those MLC leaves required to treat the target were used. Three MLC leaves were kept open on the anterior edge of the beams. A "fine" calculation grid was used for both optimization and calculation. In the TD-IMRT mode,

Variables	Comparisons						
	Conv vs FIF	Conv vs HT-IMRT	Conv vs TD-3DCRT	Conv vs TD-IMRT			
Left PTV							
Mean	0.019	0.035	0.000	0.023			
V_{90}	0.023	0.000	0.089	0.002			
$V_{\rm 107}$	0.009	0.218	0.529	0.631			
V_{110}	0.481	0.529	0.001	0.001			
HI	0.971	0.631	0.043	0.035			
Right PTV							
Mean	0.001	0.280	0.000	0.001			
V_{90}	0.035	0.004	0.000	0.000			
V_{107}	0.000	0.000	0.004	0.023			
V_{110}	0.063	0.193	0.529	0.089			
HI	0.971	0.971	0.002	0.029			
Conformity index	0.353	0.005	0.000	0.015			
Volume of body receiving $>107\%$ of prescribed dose	0.001	0.015	0.063	0.863			

Table 2. Significant p-values using Mann-Whitney U test [comparing planning target volume (PTV) TREAT coverage parameters as given in Table 11

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HI, homogeneity index; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; TD, TomoDirect™; Vx, target volume receiving at least X% of prescribed dose. Significant p-values are shown in bold.

a 30-mm ring around the PTV was used to help reduce skin overdosage. Helping structures were created within the body volume outside the PTV where significant hotspots were likely to occur. A directional block was placed on the heart to minimize dose to the heart. OARs were used as avoidance structures for the optimization process. A MF of 2.0–3.0 was used in all IMRT plans.

Tumour bed boost planning: Boost to the TB was planned using HT with parameters described as below.

Sum plan TD-3DCRT and TD-IMRT plans were summated with the boost plan to simulate complete treatment plan.

Helical planning

HT plan parameters consisted of a 2.5-cm FW, 0.3 pitch and 3.0 MF. The heart was directionally blocked to prevent beamlets from entering through those organs. Avoidance structures were used as needed in order to decrease high dose spill over into the non-delineated normal tissues. SIB planning was carried out in a similar manner keeping different priorities for boost PTV and TREAT PTV.

Dose prescription

For all plans, the intended dose prescription was to deliver 50 Gy in 25 fractions to TREAT PTV (in whole breast irradiation/chest wall irradiation alone) and sequential boost to the TB to a dose of 15 Gy in 6 fractions [for $\alpha/\beta = 3$, biologically effective dose (BED) = 110.83 Gy]. In HT, 61 Gy in 25 fractions were delivered to boost PTV in HT-SIB plan (for $\alpha/\beta = 3$, BED = 110.61 Gy). The boost prescription for the rest of the plans was 15 Gy in six fractions ([Figure 2\)](#page-2-0). The plans were evaluated with reference to the ICRU criteria of 95% of the target volume getting covered with 95% of the prescribed dose with minimum spillage to the surrounding normal tissue. In order to achieve this, the dose prescription was modified in most patients. Dose prescriptions in most patients were such that 95% of the PTV will receive 47.5 Gy dose, *i.e.* 95% of the prescribed dose 50 Gy. Various permutations and combinations were used to ensure adequate coverage of PTV without any hotspots and maximum OAR sparing.

Owing to paucity of data in SBBC, OAR doses achieved with the conventional bitangential plan were used as the reference and other techniques were optimized against these values.

Plan evaluation

Evaluation of plans was based on DVH analysis. For the PTV, the values of mean, minimum and maximum doses with $V_{90\%}$, $V_{95\%}$, $V_{107\%}$ and $V_{110\%}$ (the volumes receiving at least 90%, 95%, 107% or 110% of the prescribed dose) were reported.

The homogeneity of the dose distribution was measured by:

Homogeneity index (HI) =
$$
\frac{D_{2\%} - D_{98\%}}{D \text{ prescription}} \times 100
$$

Minimum dose received by 2% and 98% of the PTV $(D_{2\%})$ and $D_{98\%}$) served as the maximum and the minimum doses, respectively. Therefore, a lower HI is indicative of a more homogeneous dose distribution across the PTV.

Figure 3. Dose received by TREAT planning target volume (PTV). 3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); TREAT PTV, term for volume common to reference volume and PTV; V_x, volume receiving at least x% of prescribed dose.

A conformity index (CI) was defined as:

$$
CI = 1 + \frac{V100_N}{V100_{\text{PTV}}}
$$

 $V100_N$ and $V100_{PTV}$ signify the volume of normal tissue outside the PTV and the volume of the PTV receiving 100% of the prescribed dose, respectively.

The CI measures the degree of isodose conformity to the PTV, and it is crucial in the treatment efficiency. A plan with a lower CI value was more conformal.

For OARs, the analysis included the mean dose, the maximum dose and the minimum dose and a set of $V \times Gy$ (OAR volume receiving at least \times Gy) such as V_5 , V_{10} , V_{20} , V_{30} and V_{40} for the lung and heart along with CLD and MHD for the lung and heart, respectively.

Statistical analysis

As the data were non-parametric, the Kruskal–Wallis one-way analysis of variance was used to compare dosimetric differences among the plans. For pairwise comparisons among the five techniques, a Bonferroni correction was applied and an adjusted p-value of 0.0125 was considered to be significant to meet the overall significance level of < 0.05 . A less rigid test would be to report uncorrected *p*-values, *i.e.* considering a *p*-value of ≤ 0.05 as significant. This would account for significant p -values for few a dosimetric parameters that are of borderline significance with the correction applied. However, as multiple pairwise comparisons were made, the final results have been presented with the corrected p-values. Other techniques were compared with conventional techniques as standard technique with Mann–Whitney U tests. All statistical tests were performed using SPSS® statistics software v. 22.0.0.0 (SPSS Inc., Chicago, IL).

RESULTS

The mean volume of PTV was 486.72 cm^3 (range, 389.50–607.00 cm^3) and 562.04 cc (range, $930.1-313.2$ cm³) for the right and left PTVs, respectively. The mean volume of PTV was 596.77 cm³ (range, $453.7 - 930.1 \text{ cm}^3$) and 451.99 cm^3 (range, $313.2 - 597.3 \text{ cm}^3$) for the breast conservation side and post-mastectomy side. The mean value of PTV for TB boost was 115.31 cc (range, $77.9 - 149.9$ cm³).

The mean volume of the total lung, right lung, left lung and heart were 1808.44 cm³ (range, 1388.0–2456.3 cm³), 1006.53 cm³ $(\text{range}, 813.7-1349.2 \text{ cm}^3), 807.43 \text{ cm}^3 (\text{range}, 569.3-1115.3 \text{ cm}^3)$ and 468.02 cm^3 (range, 317.9–693.1 cm³), respectively.

Analysis of treatment parameters for whole breast/ chest wall radiation compared with conventional technique

Planning target volume coverage

PTV coverage on both sides with 95% isodose was slightly better with tomotherapy techniques though with marginal decrease in coverage with 90% isodose. FIF technique reduced hot spot (volume receiving $>107\%$ of prescribed dose) in the PTV on

Variable	Technique						
	Conv	FIF	HT-IMRT	TD-3DCRT	TD-IMRT		
Heart							
Max. (Gy)	49.99 (1.57)	47.09(6.01)	42.88(6.61)	50.19(12.13)	48.11 (13.50)		
Min. (Gy)	2.51(2.60)	0.61(0.21)	1.57(0.32)	0.78(0.12)	0.70(0.11)		
Mean (Gy)	5.33(1.67)	3.67(2.59)	4.68(0.96)	3.65(1.96)	3.38(2.04)		
V_{40}	2.39(2.95)	2.99(4.62)	0.20(0.32)	2.49(2.89)	2.31(3.18)		
V_{30}	3.25(3.37)	3.84(5.25)	1.04(1.10)	3.27(3.36)	3.08(3.71)		
V_{20}	4.15(3.75)	4.65(5.74)	2.77(1.90)	4.10(3.86)	3.93(4.26)		
V_{10}	5.79(4.36)	5.89(6.35)	7.44(3.57)	5.41(4.68)	5.16(5.07)		
V_5	19.04(8.51)	8.17(7.21)	19.33 (7.24)	7.25(5.90)	6.81(6.04)		
Total lung							
Max. (Gy)	51.24(1.23)	49.68(1.5)	50.16(2.07)	53.35 (1.49)	52.72 (1.26)		
Min. (Gy)	0.391(0.30)	0.17(0.13)	0.93(0.348)	0.38(0.89)	0.35(0.07)		
Mean (Gy)	6.75(1.21)	5.86(1.81)	5.99 (0.981)	5.30(0.76)	4.76(1.06)		
V_{40}	5.51(1.87)	5.73(2.97)	0.97(0.72)	5.18(1.19)	4.17(1.75)		
V_{30}	7.36(2.02)	7.98(3.35)	3.67(1.18)	6.93(1.33)	5.91(1.91)		
V_{20}	9.03(2.23)	9.63(3.66)	7.25(1.65)	8.57(1.42)	7.56(2.02)		
V_{10}	13.52(3.28)	12.64(4.36)	14.13 (2.44)	11.33(1.69)	10.28(2.38)		
V_5	26.55(6.93)	19.09(6.11)	26.37 (7.70)	15.80(2.20)	14.34 (2.94)		

Table 3. Dosimetric parameters for organ at risk sparing (without boost)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; max., maximum; min., minimum; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); V_x, volume of OAR receiving at least x Gy. The values in the table are expressed as mean (standard deviation).

both sides while tomotherapy reduced the same for right-sided PTV only. When the entire body is concerned, volume of hot spot was markedly reduced with FIF technique (1.58 vs

47.43 cm³; $p < 0.01$) as expected and reduced marginally with HT-IMRT technique (37.54 vs 47.43 cm³; $p =$ non-significant). However, the TD-3DCRT plans not only resulted in higher

Table 4. Significant p-values using Mann-Whitney U test (comparing parameters for organ at risk sparing as given in Table 3)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); V_x, volume of OAR receiving at least x Gy. Significant p-values are shown in bold.

Figure 4. Dose received by lungs and heart (comparing plans without boost). 3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA).

volume of hotspot within the body but also lower homogeneity index (10.51 for left PTV and 9.37 for right PTV). CI for HT-IMRT (1.27) was better than for all other techniques ([Tables 1](#page-3-0) and [2,](#page-4-0) [Figures 2](#page-2-0) and [3](#page-5-0)).

Organ at risk sparing (total lung and heart)

On comparing doses to OARs, not only were higher dose volumes significantly less with HT-IMRT but HT-IMRT also had comparable low dose volumes. The V_{40} and V_{30} for the total lung was reduced from 5.51% to 0.97% $(p < 0.01)$ and from 7.36% to 3.67% ($p < 0.01$), respectively. Similarly, for the heart, V_{40} was reduced from 2.39% to 0.20% $(p < 0.01)$ [\(Tables 3](#page-6-0) and [4,](#page-6-0) Figure 4).

Low dose volume (V_5) was significantly reduced using TD-3DCRT and TD-IMRT, both for the total lung as well as the heart ($p < 0.01$) for both total lung and heart). A similar finding is reflected in the mean doses of the total lung and heart with TD-IMRT ($p < 0.01$) but only for the total lung with TD-3DCRT ($p < 0.01$). However, FIF technique reduced the mean dose to the heart only, by lowering the V_5 volume ($p < 0.01$ for both V_5 and mean heart dose). Overall, TD-IMRT seemed to be both pulmonary and cardiac sparing for bilateral irradiation of the breast/chest wall alone, whereas FIF-IMRT seemed to be only cardiac sparing.

Analysis of treatment parameters for adjuvant whole breast with boost compared with

conventional technique

Planning target volume coverage

All the three techniques (sequential electron boost with bitangential or FIF technique, sequential HT boost with TD and SIB using HT) of delivering boost to the TB were comparable with each other in terms of PTV coverage [\(Tables 5](#page-8-0) and [6](#page-9-0), [Figure 5](#page-9-0)).

Organ at risk sparing (total lung and heart)

On comparing OAR sparing, results similar to that seen with the whole breast and/or chest wall irradiation alone were noted. HT with SIB was significantly better for high dose volume with comparable low dose volume, especially for the total lung. On the other hand, TD-3DCRT and TD-IMRT with HT boost were significantly better for low dose volumes [\(Tables 7](#page-10-0) and [8,](#page-10-0) [Figure 6\)](#page-11-0).

For HT-SIB, on comparison with conventional techniques, the percentage decrease in heart dose was 1915.38%, 379.45%, 135.26%, 24.36% and 50.07% for V_{40} , V_{30} , V_{20} , V_{10} and V_5 , respectively. Similarly, the decrease in lung dose was 386.16%, 118.07%, 47.49%, 36.51% and 22.63%, respectively, for V_{40} , V_{30} , V_{20} , V_{10} and V_5 . Similar changes were also seen with other techniques but not as marked as that seen in HT-SIB. Overall, HT-SIB seemed to be the best cardiac- and pulmonary-sparing technique in the setting of SBBC.

DISCUSSION

Although breast cancer is one of the common malignancies, synchronous presentation is rare and accounts for only 0.4–2.8% of all newly diagnosed breast cancer cases. Unlike treatment of unilateral breast cancer, RT planning and treatment of SBBC is challenging. The goal of this pilot study was to assess the dosimetric feasibility and the pros and cons of various RT techniques for SBBC, including FIF-IMRT, HT and TD (both 3DCRT mode

Variable	Technique					
	$Conv + E$	$FIF + E$	HT-SIB	TD-3DCRT with HT Boost	TD-IMRT with HT Boost	
Left PTV						
Max. (Gy)	69.16(2.15)	68.79 (2.17)	64.73 (0.49)	68.45 (2.87)	68.89 (2.25)	
Min. (Gy)	48.41 (16.93)	47.50 (18.33)	54.23 (2.73)	49.76 (20.85)	45.21 (19.88)	
Mean (Gy)	64.33(0.83)	63.61(1.17)	62.45(0.76)	63.53(0.36)	64.48(0.51)	
V_{90} (%)	98.72 (1.32)	98.00(2.13)	99.79 (0.30)	99.52 (0.95)	99.52 (0.95)	
V_{95} (%)	89.59 (3.13)	91.10 (4.54)	98.93 (0.92)	98.33 (1.75)	99.34 (1.03)	
V_{107} (%)	0.01(0.02)	0.15(0.30)	0.00(0.00)	0.52(1.05)	0.27(0.54)	
V_{110} (%)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.10(0.20)	0.02(0.03)	
Right PTV						
Max. (Gy)	69.62(0.89)	69.00 (1.39)	64.66 (0.98)	67.94 (2.99)	68.02 (1.67)	
Min. (Gy)	52.19 (16.27)	51.19 (15.68)	52.39 (5.28)	56.18 (4.77)	56.28 (5.36)	
Mean (Gy)	65.13(1.12)	64.65 (0.74)	62.41(0.63)	63.60 (0.26)	64.46 (0.42)	
V_{90} (%)	99.59 (0.64)	99.27 (0.97)	99.78 (0.23)	99.13(0.16)	99.79 (0.28)	
V_{95} (%)	96.47 (3.70)	93.86 (4.70)	98.16 (1.78)	98.87 (0.24)	99.20 (0.55)	
V_{107} (%)	0.02(0.04)	0.002(0.004)	0.12(0.28)	0.24(0.48)	0.16(0.41)	
V_{110} (%)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.08(0.20)	0.00(0.00)	

Table 5. Dosimetric parameters for planning target volume (PTV) boost coverage (with boost)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; E, electron boost to tumour bed; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; max., maximum; min., minimum; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnnyvale, CA); V_x , target volume receiving at least $X\%$ of prescription dose. The values in the table are expressed as mean (standard deviation).

and IMRT mode) in comparison with the conventional bitangential technique.

Although the Radiation Therapy Oncology group³⁴ and the Danish group³⁵ have published guidelines for delineating the whole breast or chest wall as well as the TB, these guidelines are not used universally. Clinical marking to define borders of RT portals is the most commonly used method. $36,37$ In the present study, we also used a similar method for defining target volume, which was subsequently modified using isodose volume (95% isodose volume of conventional treatment plan) as described earlier. This method has also been explored by others to maintain similarity in target volume when comparing modern techniques with conventional methods.^{38,[39](#page-14-0)} Similar problems were also encountered while delineating $TB₁⁴⁰$ $TB₁⁴⁰$ $TB₁⁴⁰$ The margins given to grow the CTV for TB is not standardized, which can be one of the reasons for the large boost volume seen in the present study, apart from the large volume of TB itself.^{[37](#page-13-0)} In one study,³⁷ only a 5-mm margin was given to create CTV TB. In another study, 41 the average boost volume was 36 cm^3 , which is less than one-third of that in the present study. Hence, the heterogeneity of target volume delineation has to be kept in mind while comparing the dosimetric results of different techniques across all studies.

FIF-IMRT is routinely used to reduce the volume of hotspots (volume receiving $>107\%$ of the prescription dose). This was

also confirmed in the present study as the mean value of the body receiving $>$ 107% of the prescribed dose was only 1.58 cm³ with FIF compared with 47.44 cm^3 with conventional technique with equivalent coverage of TREAT PTV. Moreover, 107% isodose volume with FIF was also much lower than with the other techniques (HT-IMRT, 37.54 cm³; TD-3DCRT, 80.38 cm³; TD-IMRT, 48.59 cm³). Considering OAR sparing, mean doses to the lungs and heart were less than those achieved with conventional techniques, although not statistically significant for the total lung (5.86 vs 6.75 Gy; p-value not significant, and 3.67 vs 5.33 Gy; $p < 0.01$). Thus, FIF-IMRT was cardiac sparing but not lung sparing. These results were similar to some other reports in the literature for unilateral breast cancer. In one study of 30 females treated for adjuvant whole breast irradiation, the PTV coverage with FIF was 96.7% (vs 93.2% of the present study), but the mean lung and heart doses were 8.42% and 3.07% (vs 5.73% and 3.67% of the present study).^{[36](#page-13-0)} Similarly, Pili et al⁴² have shown improved OAR sparing with the use of FIF in unilateral breast cancer treatment, and a similar trend was also seen in the present study.

HT is advantageous in terms of better coverage of PTV and OAR sparing across most of the sites. 43 This potential of HT was explored for SBBC and consistent results were seen. The mean dose to PTV and V_{95} coverage was comparable with the conventional plan with significantly better CI (1.27 vs 1.36). Major

Table 6. Significant p-values using Mann-Whitney U test [comparing planning target volume (PTV) boost coverage parameters as given in [Table 5\]](#page-8-0)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; E, electron boost to tumour bed; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnnyvale, CA); V95, target volume receiving at least 95% prescription dose.

The significant p-value is shown in bold.

advantage was noted in decrease in high dose volumes (V_{40}) and V_{30}) in OARs without increase in low dose volumes to OARs with HT-IMRT (for both plans with and without SIB). However, the major dosimetric advantage that was reflected in a significant reduction in MLD (and non-significant reduction in mean heart dose) was observed for plans with SIB. This finding defines a sound position of HT for adjuvant breast radiation for SBBC. Moreover, considering the concern of second cancers owing to low dose spill, it was also

reassuring to observe that the dosimetric advantages of HT were achieved without increase in low dose spill. In the literature, the role of HT in SBBC is sparse. Few case reports suggested a possible role of HT in BBC owing to complex target volume but with contrasting results. In one case report, lung doses (V_{20} > 5% and V_5 > 20%) were much less than those in the present study (V_{20} , 7.25% and V_5 , 26.37%)^{[44](#page-14-0)}, but another report suggested V_5 as high as 87% where SIB plan was used for treatment.^{[45](#page-14-0)}

Figure 5. Dose received by planning target volume (PTV) boost. 3DCRT, three-dimensional conformal radiotherapy; conv, conventional; E, electron boost to tumour bed; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA).

Table 7. Dosimetric parameters for organs at risk sparing (with boost)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; E, electron boost to tumour bed; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; max., maximum; min., minimum; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); V_x , volume of OAR receiving at least x Gy.

The values in the table are expressed as mean (standard deviation).

The role of HT is explored much more in unilateral breast cancer. Although indirect data are available from the dosimetric studies carried out for unilateral breast cancer, the results from this study are slightly different from a few of the studies reported earlier.^{[46](#page-14-0),[47](#page-14-0)} Schubert et al⁴⁷ in a similar dosimetric comparison

for left-sided whole breast irradiation (without boost) not only reported higher low dose spillage for the ipsilateral lung and heart but also higher mean doses to the contralateral lung and breast. In the present study, dosimetric advantages of HT have been achieved without an increase in the low dose spill both for

Table 8. Significant p-values using Mann-Whitney U test (comparing parameters for organs at risk sparing as given in Table 7)

3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA); V_x, volume of OAR receiving at least x Gy. Significant p-values are shown in bold.

Figure 6. Dose received by lungs and heart (comparing plans with boost). 3DCRT, three-dimensional conformal radiotherapy; conv, conventional; FIF, field in field; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; SIB, simultaneous integrated boost; TD, TomoDirect™ (Accuray Inc., Sunnyvale, CA).

whole breast irradiation alone as well as for plans with SIB. As both sides are being treated, the only OARs in case of SBBC are the total lung and heart. Hence, tomotherapy planning for SBBC becomes somewhat simpler compared with unilateral cases where the contralateral lung and breast also have to be optimized. Moreover, the low dose spill is of particularly concern in left-sided disease, as achieving heart constraints receives more priority. The present data are consistent with the large volume of studies examining the role of HT in unilateral breast cancer.

In the present study, TD has been evaluated probably for the first time for treatment of SBBC. With multiple limitations encountered in planning of TD, it cannot be concluded that TD can be safely used in treatment of SBBC. One such limitation is the limited number (i.e. 12) of fields that can be used for planning, especially when the supraclavicular fossa is also included in the treatment volume. This also limits the number of fields that can be used for delivering SIB while using TD-IMRT. In the present study, TD-3DCRT and TD-IMRT were comparable to conventional techniques in PTV coverage but a high volume of hotspots in PTV or outside PTV was seen, mainly with TD-3DCRT [\(Figure 7](#page-12-0)). This was one reason for significantly worse CI with TD-3DCRT technique. Compared with HT-IMRT, the plans were more homogeneous than the TD one. This is likely owing to the availability of a greater number of possible irradiation angles in the helical plans. The use of fixed gantry angles allows less shaping of the prescription dose to the target volume.

The major advantage of TD was seen with sparing of the heart and lung tissue. It reduced low dose volume significantly. For the total lung, mean dose was significantly reduced from 6.75 Gy for conventional technique to 5.30 Gy for TD-3DCRT and 4.76 Gy for TD-IMRT (without SIB plans). A similar decline was seen for all volumetric parameters, but more marked for V_5 and V_{10} . The mean dose to the heart was also significantly reduced from 5.33 Gy for conventional technique to 3.65 Gy for TD-3DCRT and 3.38 Gy for TD-IMRT technique (without SIB plans). As seen in the lung, a statistically significant difference was also seen for heart volume receiving low doses such as V_5 and V_{10} . However, for plans with SIB, non-significant reduction in OAR doses was observed with both the techniques. Trends similar to those in the present study were seen by Schubert et al⁴⁷ while comparing 3DCRT technique with forward planning IMRT, inverse planning IMRT, HT-IMRT and TD-IMRT.

Here, three different methods of delivering boost to TB were evaluated in combination with whole breast irradiation. It can be safely concluded that the most effective method of delivering TB boost was using SIB with HT. HT-SIB had better OAR sparing than did the other methods (sequential boost with electron or HT) compared here. A part of it is because of lower dose in HT-SIB (61 Gy in HT-SIB plan vs 65 Gy in other plans). It should be noted that plans using TD-IMRT with dynamic jaw, *i.e.*
TomoEDGE™ (TomoTherapy Inc.), were not considered in this study. Low physical dose (61 Gy with HT-SIB vs 65 Gy for other methods) may also contribute to the decrease in dosimetric Figure 7. Hot spot with TomoDirect™ (Accuray Inc., Sunnyvale, CA) three-dimensional conformal radiotherapy (strip of high dose volume seen at lateral end outside planning target volume). Dose volumes are given with reference to prescription dose. 55 Gy, *i.e.* 110% of 50 Gy prescription dose; 53.5 Gy, i.e. 107%; 47.5 Gy, i.e. 95% of 50 Gy prescription dose.

parameters for OAR but still cannot completely explain the approximately 90% reduction in V_{40} doses of the heart and lung when compared with conventional techniques with electron boost. Similar trends were obtained by Hijal et $al⁴⁸$ comparing HT-SIB with conventional 3DCRT. Another study by Franco et al 49 with TD-3DCRT combined with HT boost confirms similar results. It is less pronounced with conventional plans and sequential electron boost compared with sequential HT boost after TD-3DCRT or TD-IMRT. Here, the decrease in low dose volume to the OAR is more evident than the high dose volume, owing to similar results seen with whole breast RT with TD-3DCRT or TD-IMRT.

Limitations of study

This is a feasibility study carried out on data sets of a heterogeneous patient population of 10 females with SBBC (4 with breast conserved on both side, 4 with post mastectomy on both sides,

and 2 with breast conserved on one side and mastectomy on another side); results of this study should be validated by a study with larger sample size and a more homogenous population (only chest wall or SIB alone). In the present study, in order to keep target volumes simpler, irradiation of supraclavicular fossa with conventional plans or tomotherapy was not considered. This is a dosimetric study with no clinical outcome data so the result of this study need to be validated with clinical outcomes. In these patients, the average interfield separation of 22.3 and 22.4 cm for the left side and right side, respectively. This may not be ideal for treatment using 6-MV photons and would contribute to the high volume hotspots as noted in this. One must also acknowledge nuances of inverse planning IMRT for treatment of breast cancer. It leads to an increase in low dose spill over to non-target tissue. Increase in treatment time for delivery may also introduce uncertainty owing to intrafraction movement. Electron boost to TB was planned on the same CT data set taken for whole breast RT in the supine position, which may lead to the use of erroneously high electron energy for target coverage leading to high doses to OARs (although precaution was taken to angulate the gantry perpendicular to the skin surface). Moreover, not all methods of delivering TB boost were explored in this study.

CONCLUSION

RT to bilateral breast or bilateral chest wall is a challenging task in view of large and complex target volume and significant doses that are received by the heart and lungs. The findings of this study suggest that while it is possible to produce acceptable coverage of PTV with 95% isodose using conventional techniques, the radiation doses to the heart and lung is still significant.

This dosimetric study of different techniques demonstrates the ability of these modern techniques to reduce radiation doses, especially volume of the lung and heart receiving high dose of radiation without compromising PTV coverage (specifically HT delivering SIB) in the setting of SBBC.

This study requires further confirmation of dosimetric results in larger number of patients as well as clinical validation to assess clinical feasibility of delivering treatment, and associated acute and late toxicity.

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