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Accelerated hypofractionated radiotherapy for chest wall and nodal irradiation using hybrid techniques

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Abstract

Aim: This study compares three different hybrid plans, for left-sided chest wall (CW) and nodal stations irradiation using a hypofractionated dose regimen.

Materials and methods: Planning target volumes (PTVs) of 25 breast cancer patients that included CW, supraclavicular (SCL) and internal mammary node (IMN) were planned with 3 different hybrid techniques: 3DCRT+IMRT, 3DCRT+VMAT and IMRT+VMAT. All hybrid plans were generated with a hypofractionated dose prescription of 40·5 Gy in 15 fractions. Seventy per cent of the dose was planned with the base-dose component and remaining 30% of the dose was planned with the hybrid component. All plans were evaluated based on the PTVs and organs at risk (OARs) dosimetric parameters.

Results: The results for PTVs parameters have shown that the 3DCRT+IMRT and 3DCRT+ VMAT plans were superior in uniformity index to the IMRT+VMAT plan. The OARs dose parameters were comparable between hybrid plans. The IMRT+VMAT plan provided a larger low dose volume spread to the heart and ipsilateral lung ($p < 0.001$). The 3DCRT+VMAT plan required less monitor units and treatment time ($p = 0.005$) than other plans.

Conclusion: The 3DCRT+VMAT hybrid plan showed superior results with efficient treatment delivery and provide clinical benefit by reducing both low and high dose levels.

Introduction

Breast cancer is the most commonly occurring tumour in women worldwide.^{[1](#page-5-0)} In developing nations like India, although the overall incidence is lower compared to that of developed nations, the burden of locally advanced breast cancer (LABC) is relatively high around 30 to 60%.^{[2](#page-5-0)} Radiation therapy (RT) is an integral part of the multimodal management of LABC patients after surgery and systemic therapies. The rationale of RT is to improve the therapeutic ratio between tumour control probability and normal tissue (NT) complication probability. Since many of these women are young of ages 30 to 40 years^{[2](#page-5-0)} and are long-term survivors, the aim is to reduce the long-term RT-related morbidity.

Hypofractionation has established itself in clinical trials as one of the factors to improve the therapeutic ratio. Clinical trials on the accelerated hypofractionated chest wall (CW) and regional nodal RT have shown promising results.^{3–[7](#page-6-0)} Dosimetric comparison studies that utilise hypofractionated dose regimens for CW and nodal regions are sparse.

Post-mastectomy CW and nodal stations RT planning is always a difficult task due to the thin and concave shape of the CW with irregular body surface.⁸ In addition, the reduction of RT-related toxicities like lung and heart complications and secondary cancer risk in contralateral breast (CB) are highly anticipated. Three-dimensional conformal radiotherapy (3DCRT) or field-in-field (FinF) technique for the CW and supraclavicular (SCL) RT provides a reduced dose to organs at risk (OARs). However, the inclusion of internal mammary node (IMN) irradiates more volumes of heart and ipsilateral lung (IL) by the wide tangent fields of the 3DCRT plan.^{[9](#page-6-0)} Intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) techniques provide conformal and homogeneous doses to the planning target volumes (PTVs). These techniques reduce the high dose irradiation to NT while delivering increased low dose bath than the 3DCRT. In addition, these techniques required more monitor units (MU), thereby increases unwanted leakage and scattered radiation to out-of-field areas which might increase the risk of secondary cancer incidence to the $CB^{10,11}$ In this context, the contributions of modulated beams along with the 3DCRT fields are desirable to acquire balanced results between the PTV and OARs dosimetric parameters.

A novel hybrid approach has been explored in the literature to compensate for disagreements of the conventional and advanced techniques.^{[12](#page-6-0)-[16](#page-6-0)} The hybrid technique is a blend of 3DCRT and IMRT/VMAT with different dose ratios that simultaneously deliver in each treatment fraction. Improvement in the dosimetric parameter results of hybrid plans for the WB and CW with SCL nodal RT has been described in many articles.^{[12](#page-6-0)-[16](#page-6-0)} While, there is a paucity of hybrid planning studies that include the CW, SCL and IMN.

Most of the hybrid studies compared hybrid plans with pure VMAT or IMRT plans.^{[14](#page-6-0)-[16](#page-6-0)} Publications that compared different combinations of hybrid plans together are scarce. The aim of this study is a dosimetric assessment of three different hybrid planning techniques: 3DCRT (base-dose plan) combined with IMRT (3DCRT+IMRT), 3DCRT (base-dose plan) combined with VMAT (3DCRT+VMAT) and IMRT (base-dose plan) combined with VMAT (IMRT+VMAT) for the left-sided CW with SCL and IMN nodal RT using the accelerated hypofractionated dose regimen.

Materials and Methods

Patient selection

Locally advanced post-mastectomy breast cancer patients who received adjuvant RT between 1 January 2018 and 31 December 2020 were reviewed for this study. Twenty-five patients were randomly selected as fulfilling the following inclusion criteria: (1) patients with left-sided CW, (2) patients with SCL and IMN nodal stations and (3) patients simulated in a deep inspiration breath-hold (DIBH) setting. Exclusion criteria were (1) patients with bilateral mastectomy and (2) patients with axillary nodes. The median age of these patients was 49 years. The institutional scientific and ethics board has approved this study and informed consent was obtained from each patient.

Simulation and contouring

For simulation, patients were placed in a supine position using a customised vacuum bag. A planning computed tomography (CT) scans had been generated with 2.5-mm slice thickness by Discovery IQ CT scanner (GE Healthcare, Chicago, IL, USA). Clinical target volumes (CTVs) of CW, SCL and IMN nodal regions were delineated. The CW PTV (PTV_{CW}), SCL PTV (PTV_{SCL}) and IMN PTV (PTV_{IMN}) were created by giving margin to the CTVs around 5 mm. The $\mathrm{PTV}_{\mathrm{SCL}}$ was brought in 5 mm from the skin surface, while the PTV_{CW} included the skin region. A wax bolus material of 5 mm thickness was placed on the body surface beside the PTV_{CW} to achieve adequate dose coverage in the near skin region. The OARs delineated were the heart, left anterior descending coronary artery (LAD), right coronary artery (RCA), IL, contralateral lung, CB, spinal cord, oesophagus, trachea, coeliac plexus and gastroesophageal junction (GEJCP), and NT, defined as the body volume minus PTVs were delineated.

Treatment planning

For each patient, 3DCRT+IMRT, 3DCRT+VMAT and IMRT+ VMAT hybrid treatment plans were created in the Eclipse treatment planning system using 6, 10, 15 MV photon beams of Truebeam linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). A hypofractionated dose prescription of 40·5 Gy (2·7 Gy per fraction) in 15 fractions was used for all PTVs. The dose weightings utilised were 70% of the prescription dose for the basedose component and 30% of the prescription dose for the hybrid component.[12](#page-6-0) Table 1 presents the clinical dose constraints of OARs to be considered in planning. Both the IMRT and VMAT plan optimisations were performed by the photon optimiser (PO) algorithm. Volume dose was computed by analytical anisotropic algorithm (AAA) using a dose grid of 2·5 mm. All individual

Table 1. Clinical dose constraints for organs at risk

Organs at risk	Dose limits
IL	$V_{5GV} \le 60$ %; $V_{20GV} \le 30$ % $V_{35Gv} \le 10\%$; D _{Mean} $\le 12\}$ Gy
CL	$V_{5GV} \leq 5\%$; D _{Mean} ≤ 2 Gy
CB	$V_{5GV} \leq 5\%$; $D_{Mean} \leq 2$ Gy
Heart	V5Gy \leq 40 %; V25Gy \leq 10 % V35Gy \leq 5 %; D _{Mean} \leq 5 Gy
LAD	$V_{30GV} \leq 30\%$; D _{Mean} $\leq 20\}$ Gy
RCA	$D_{Mean} \leq 4$ Gy
Oesophagus, Trachea	$D_{Mean} \leq 10$ Gy
GEJCP	$D_{Mean} \leq 3$ Gy
SC	$D_{\text{Max}} \leq 10$ Gy
NT	$V_{5GV} \leq 20\%$; $D_{Mean} \leq 5$ Gy

LAD, left anterior descending coronary artery; RCA, right coronary artery; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast; GEJCP, coeliac plexus and gastroesophageal junction; SC, spinal cord; NT, normal tissue; Gy, Gray; V_{XGy}, volume receiving X Gy dose; D_{Mean} , mean dose; D_{Max} , maximum dose.

plans were normalised in such a way that the plans deliver the PTVs mean dose equal to the prescribed dose.

For the 3DCRT, IMRT and VMAT plans, an isocentre was positioned at the PTV_{CW} and PTV_{SCL} junction and axially on ribs to minimise beam divergence into the IL and heart (Figure [1](#page-2-0)). Two tangential half-beam blocked fields for the PTV_{CW} , PTV_{IMN} and one anterior oblique, one posterior oblique, half-beam blocked fields for the PTV_{SCL} were used for the 3DCRT plan as shown in Figure [1](#page-2-0). Varied X-ray photon energies were utilised for 3DCRT fields depending on the skin to PTV surface distance along the beam direction, according to Balaji et al.¹² The 3DCRT plans were dose-computed for 1·9 Gy (approximately 70% of prescription dose). Similarly, the IMRT base-dose plans were created with the same beam arrangements as the 3DCRT plans. In the IMRT, each half-beam blocked field was allowed to over travel 1 cm beyond the isocentre for better modulation in field junction. Fixed jaw setting was enabled during optimisation.

For the hybrid component, IMRT and VMAT plans were generated with the remaining prescription dose of 0·8 Gy (approximately 30% of the PTVs prescription dose). The IMRT plans consisted of five fields with equally separated gantry angles 300°, 355°, 50°, 105° and 160° as shown in Fig. [2](#page-2-0). The collimator angles were set at \pm 5°. The VMAT plans utilised two coplanar partial arcs and two tangential arcs as shown in Figure [2.](#page-2-0) Arc1 rotated clockwise from 300° to 50° with 10° collimator angle, and arc2 rotated clockwise from 50° to 160° with 350° collimator angle. The tangential arc3 rotated counterclockwise from 160° to 110° with 345° collimator angle and arc4 rotated counterclockwise from 350° to 300° with 15° collimator angle. Both the IMRT and VMAT plans employed 6 MV photon beams. While doing optimisation, the corresponding basedose 3DCRT and IMRT plans were enabled. After dose computation and normalisation, plan sum of the $3DCRT+IMRT$, $3DCRT+$ VMAT and IMRT+VMAT hybrid plans were created. The entire planning and dosimetric evaluation process were executed by an experienced medical physicist to avoid any planner variability.

Dosimetric evaluation

For the PTVs quality comparison, dosimetric indices like coverage index (COI) and uniformity index (UI) were calculated for

Figure 1. (a) Location of isocentre and (b) field arrangements in base-dose 3DCRT and IMRT plans (four fields).

Figure 2. Field arrangements in (a) IMRT plan (five fields) and (b) VMAT plan (two partial and two tangential arcs).

 PTV_{CW} , PTV_{SCL} and PTV_{IMN} . Conformity index (CI) and gradient index (GI) were appraised for the combined volume of all PTVs. The COI was defined as:

$$
COI = \frac{D_p}{D_{95\%}},
$$

where D_p is the prescription dose and $D_{95%}$ is the dose received by 95% of the PTV. A COI value nearer to 1 indicates superior dose coverage to PTV. The UI was calculated as:

$$
UI = \frac{D_{2\%}}{D_{98\%}},
$$

where $D_{2\%}$ and $D_{98\%}$ are the doses received by 2% and 98% of the PTV, respectively. A UI value close to 1 specifies a more homogeneous dose distribution to PTV. The CI was defined as:

$$
CI = \frac{V_{PTV}}{V_{PTVref}} \times \frac{V_{ref}}{V_{PTVref}}
$$

;

where V_{PTV} is the volume of PTV, V_{PTVref} is the reference isodose (95%) volume within the PTV and V_{ref} is the volume of reference isodose (95%). A CI value close to 1 designates a superior conformal dose plan.^{[17](#page-6-0)} The GI was calculated as:

$$
GI = \frac{V_{50\%}}{V_{PTV}},
$$

where $\mathrm{V}_{50\%}$ is 50% isodose volume and $\mathrm{V}_{\mathrm{PTV}}$ is the volume of PTV. A GI value close to 1 specifies a better dose fall-off plan.^{[18](#page-6-0)} The dosevolume parameters evaluated for the OARs comparison were listed in Table [1.](#page-1-0)^{[19](#page-6-0)-[23](#page-6-0)} In addition, total MU and treatment time (TT) were noted to assess the delivery efficiency. A simple scoring method was utilised to calculate an overall score that incorporates all dosimetric parameters evaluated. The overall score was calculated as:

Overall Score =
$$
\frac{\sum_{i=1}^{n} \left(\frac{A_i}{M_i}\right)}{n},
$$

where A_i is the achieved value of an ith dosimetric parameter of a particular plan and M_i is the mean value of the ith dosimetric parameter of all three plans and n is the number of dosimetric parameters evaluated. The overall score close to 0 designates a superior plan.

Table 2. Dosimetric comparison results for PTVs

SD, standard deviation; PTV_{CW}, chest wall planning target volume; PTV_{SCL}, supraclavicular node planning target volume; PTV_{IMN}, internal mammary node planning target volume; COI, coverage index; UI, uniformity index; CI, conformity index; GI, gradient index; MU, monitor units; TT, treatment time; min, minute; bold, statistically significant result.

Figure 3. Dose distributions in (a) 3DCRT + IMRT plan, (b) 3DCRT + VMAT plan and (c) IMRT + VMAT plan. Cyan line indicates 38.5 Gy dose ranges, yellow line indicates 20 Gy dose ranges, dark blue line indicates 5 Gy dose ranges and light green line indicates 1 Gy dose ranges.

Statistical analysis

For statistical analyses, a non-parametric Wilcoxon signed-rank test was executed for a paired group of plan comparisons. All statistical tests were two-tailed, and a threshold value of $p < 0.05$ indicated statistically significant results.

Results

The volume of PTV_{CW} , PTV_{SCL} and PTV_{IMN} were 544 \cdot 5 \pm 103 \cdot 1, 129.1 ± 38.8 and 10.3 ± 2.8 cc respectively. The PTVs and treatment delivery parameter results for all hybrid plans are summarised in Table 2. Figure 3 displays the dose distributions comparison of all hybrid plans for a patient. All hybrid plans achieved expected coverage (COI \leq 1·05) for the PTV_{CW} and PTV_{SCL}, while PTV_{IMN} showed less coverage in the IMRT+VMAT plan. The UI of the PTV_{CW} was comparable among all hybrid plans, while the UI of the PTV_{SCL} and PTV $_{\text{IMN}}$ were slightly better in the 3DCRT+ IMRT and 3DCRT+VMAT than the IMRT+VMAT plan $(p < 0.01)$. The CI of the combined PTV had comparable results among all hybrid plans. The GI of the combined PTV was better in the IMRT+VMAT plan, related to 3DCRT+IMRT and 3DCRT+VMAT plans ($p = 0.002$). The MU and TT were less in the 3DCRT+VMAT plan ($p = 0.005$).

Table [3](#page-4-0) summarises the OARs dose comparison results of all hybrid plans. The mean dose of the IL was similar for all plans, while the V_{5Gy} was less in the 3DCRT+IMRT and 3DCRT+ VMAT plan ($p < 0.001$). The V_{20Gy} was less in the IMRT+ VMAT plan ($p < 0.03$), whereas the V_{35Gy} result was less in the 3DCRT+IMRT plan ($p = 0.005$). The mean dose and V_{5Gy} of the CB were less in the IMRT+VMAT plan ($p < 0.03$). The mean dose to the heart was less in the 3DCRT+IMRT plan ($p < 0.04$), while the V_{5Gy} was less in the 3DCRT+IMRT and 3DCRT+ VMAT plan $(p < 0.001)$. The mean doses to the oesophagus, trachea and GEJCP showed comparable results. The overall score that incorporated all dosimetric parameters (PTVs, OARs and treatment delivery) were 1.02 , 0.98 and 0.99 for 3DCRT+IMRT, 3DCRT+VMAT and IMRT+VMAT plans, respectively.

Table 3. Dosimetric comparison results for organs at risk

	Mean $±$ SD			p-Value		
Parameter	$3DCRT + IMRT (A)$	$3DCRT + VMAT$ (B)	$IMRT + VMAT (C)$	A versus B	A versus C	B versus C
IL						
D_{Mean} (Gy)	12.6 ± 0.8	12.8 ± 1.0	12.7 ± 0.9	0.103	0.139	0.162
V_{5Gy} (%)	56.5 ± 2.4	57.3 ± 2.9	60.4 ± 3.4	0.278	$<$ 0 \cdot 001	$<$ 0.001
V_{20Gy} (%)	26.4 ± 4.0	27.1 ± 4.1	25.2 ± 3.6	0.005	0.029	0.005
V_{35Gy} (%)	8.7 ± 1.3	10.7 ± 1.4	10.3 ± 1.4	0.005	0.005	0.114
CL						
D_{Mean} (Gy)	1.5 ± 0.2	1.4 ± 0.2	1.6 ± 0.3	0.384	0.757	0.204
V_{5Gy} (%)	1.6 ± 1.1	0.6 ± 0.5	0.6 ± 0.4	0.005	0.005	0.921
CB						
D_{Mean} (Gy)	1.9 ± 0.4	1.7 ± 0.4	1.5 ± 0.3	0.153	0.025	0.067
V_{5Gy} (%)	6.0 ± 1.9	4.4 ± 1.7	3.5 ± 1.4	0.005	0.005	0.005
Heart						
D_{Mean} (Gy)	6.2 ± 1.2	6.5 ± 1.4	6.8 ± 1.2	0.204	0.037	0.126
V_{5Gy} (%)	30.4 ± 5.6	30.6 ± 7.7	41.5 ± 7.9	0.936	$<$ 0.001	$<$ 0.001
V_{25Gy} (%)	7.2 ± 3.4	7.5 ± 3.9	5.7 ± 2.9	0.005	$<$ 0.001	$<$ 0.001
V_{35Gy} (%)	1.0 ± 0.8	2.3 ± 1.7	2.7 ± 1.7	$<$ 0.001	$<$ 0 \cdot 001	0.058
LAD						
D_{Mean} (Gy)	23.6 ± 4.5	25.2 ± 5.6	24.1 ± 5.5	0.059	0.447	0.072
V_{30Gy} (%)	34.1 ± 19.5	46.1 ± 22.9	39.2 ± 21.2	$<$ 001 $<$	$<$ 0.001	$<$ 0.001
RCA						
D_{Mean} (Gy)	3.5 ± 0.6	3.0 ± 0.5	3.2 ± 0.5	0.028	0.126	0.204
Oesophagus						
D_{Mean} (Gy)	8.3 ± 0.9	8.4 ± 1.6	8.2 ± 1.2	0.646	0.984	0.741
Trachea						
D_{Mean} (Gy)	7.3 ± 1.9	7.2 ± 2.4	7.0 ± 2.2	0.841	0.478	0.358
GEJCP						
D_{Mean} (Gy)	1.6 ± 0.4	1.5 ± 0.5	1.9 ± 0.7	0.509	0.447	0.114
SC						
D_{Max} (Gy)	8.5 ± 2.5	8.0 ± 1.6	8.0 ± 1.2	0.022	0.029	0.412
NT						
D_{Mean} (Gy)	4.3 ± 0.4	4.1 ± 0.4	4.0 ± 0.4	0.052	0.008	0.285
$\mathsf{V}_{\mathsf{5Gy}}$ (%)	16.6 ± 1.6	15.7 ± 1.7	16.5 ± 1.9	0.005	0.253	0.005

SD, standard deviation; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast; LAD, left anterior descending coronary artery; RCA, right coronary artery; SC, spinal cord; GEJCP, coeliac plexus and gastroesophageal junction; NT, normal tissue; Gy, gray; D_{Mean}, mean dose; D_{Max}, maximum dose; V_{XGy}, volume receiving X dose; bold, statistically significant result.

Discussion

In this dosimetric comparison study, three different hybrid plan combinations, 3DCRT+IMRT, 3DCRT+VMAT and IMRT+ VMAT, were evaluated with a hypofractionated dose regimen for left-sided CW along with SCL and IMN targets. Few studies used a mixture of the IMRT and VMAT in their hybrid study.^{[14](#page-6-0),[15](#page-6-0)} However, the present study showed that the 3DCRT plan is optimal for the base-dose plans as it utilised less planning time, demanding fewer MUs compared to the IMRT plan. In spite of the use of optimisation bolus and PTV extension, the impacts of set-up and breathing movements in the IMRT are higher than in the 3DCRT. 24 24 24 The 3DCRT beams are capable to limit these uncertainties with extended fields, along the body surface region. 12

Between IMRT and VMAT, the suggested technique for the CW and nodal RT is varied in published studies.^{[8](#page-6-0)} However, with 30% of dose weightings, the influence of IMRT and VMAT techniques as a hybrid component is minimal. Because of this, the hybrid plans in the present study showed almost similar results to the PTVs and OARs dosimetric parameters. Table [4](#page-5-0) displays the dosimetric parameter appraisal of favoured technique from other published studies $9,25-27$ $9,25-27$ $9,25-27$ $9,25-27$ $9,25-27$ and the present study.

DIBH, deep inspiration breath hold; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast; NT, normal tissue; Gy, gray; D_{Mean}, mean dose; D_{Max}, maximum dose; V_{XGy}, volume receiving X dose; NA, data not available.

The DIBH method is capable to reduce the dose to the heart, LAD and RCA.^{[28,29](#page-6-0)} Nevertheless, this practice might not be achievable for all patients. Holding the breath for a few minutes is a difficult task for certain patients. The $3DCRT+VMAT$ plan with fewer MUs delivers the hypofractionated dose more rapidly that helps the DIBH patients regarding breath-hold constancy, less intrafraction variation and comfort. Nevertheless, the trade-off between the DIBH and free breath needs to be evaluated in a clinical setting for each patient.^{[30](#page-6-0)}

The exclusion of axillary node was the limitation of this study. Irradiation of axillary node does not improve the overall and cancer-specific survival. 31 As a result, the axillary lymph node was not included in this study. However, further investigation including axillary node is required, which could be desirable in some clinical setting. Another limitation was the non-usage of electron beams in this hybrid setting, which might be useful for thin CW patients. Further, a prospective study on thin CW patients is warranted to find the trade-off between photon and electron beams for these patients.

Conclusion

The 3DCRT-based hybrid VMAT technique shows superior results with less MU and delivery time, thereby increasing patient comfort. It is worth mentioning that the decrease in heart dose parameters subsequently increases the IL doses and vice versa. Therefore, dose balance between the heart and IL by considering its tolerance doses is desirable. Further, considering the individuality of each patient, the choice of an optimal hybrid plan between $3\mathrm{DCRT}+\mathrm{VMAT}$ and $3\mathrm{DCRT}+\mathrm{IMRT}$ needs to be considered with regard to planning complexity and time taken for plan generation in a clinical setting.

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