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## Post-mastectomy radiotherapy for left-sided breast cancer patients: comparison of advanced techniques

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### Abstract

Post-mastectomy radiotherapy (PMRT) has been shown to improve the overall survival for invasive breast cancer patients, and many advanced radiotherapy technologies were adopted for PMRT. The purpose of our study is to compare various advanced PMRT techniques including fixed-beam intensity-modulated radiotherapy (IMRT), non-coplanar volumetric modulated arc therapy (NC-VMAT), multiple arc VMAT (MA-VMAT), and Tomotherapy (TOMO). Results of standard VMAT and mixed beam therapy that were published by our group previously were also included in the plan comparisons. Treatment plans were produced for nine PMRT patients previously treated in our clinic. The plans were evaluated based on planning target volume (PTV) coverage, dose homogeneity index (DHI), conformity index (CI), dose to organs at risk (OARs), normal tissue complication probability (NTCP) of pneumonitis, lifetime attributable risk (LAR) of second cancers, and risk of coronary events (RCE). All techniques produced clinically acceptable PMRT plans. Overall, fixed-beam IMRT delivered the lowest mean dose to contralateral breast ( $1.56 \pm 0.4$  Gy) and exhibited lowest LAR ( $0.6 \pm 0.2\%$ ) of secondary contralateral breast cancer; NC-VMAT delivered the lowest mean dose to lungs ( $7.5 \pm 0.8$  Gy), exhibited lowest LAR ( $5.4 \pm 2.8\%$ ) of secondary lung cancer and lowest NTCP ( $2.1 \pm 0.4\%$ ) of pneumonitis; mixed beam therapy delivered the lowest mean dose to heart ( $7.1 \pm 1.3$  Gy) and shown lowest RCE ( $8.6 \pm 7.1\%$ ); TOMO plans provided the most optimal target coverage while delivering higher dose to OARs than other techniques. Both NC-VMAT and MA-VMAT exhibited lower values of all OARs evaluation metrics compare to standard VMAT. Fixed-beam IMRT, NC-VMAT, and mixed beam therapy could be the optimal radiation technique for certain breast cancer patients after mastectomy.

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Conflict of interest statement

The authors have no conflicts of interest.

## Keywords

Post-mastectomy radiotherapy; intensity-modulated radiotherapy; volumetric modulated arc therapy; Tomotherapy

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## Introduction

About 1 in 8 women will develop invasive breast cancer over the course of her lifetime in the US ([www.cancer.org](http://www.cancer.org)). Due to the prevalence of microscopic diseases after the mastectomy, post-mastectomy radiotherapy (PMRT) is commonly performed on these patients to sterilize the residual tumor cells, and has been shown to improve the overall survival for invasive breast cancer patients by reducing the risk of tumor recurrence and cancer mortality.<sup>1</sup>

The role of PMRT in breast cancer care is evolving rapidly with the adoption of new radiotherapy technologies: fixed beam intensity-modulated radiotherapy (IMRT) has been shown to be a preferred technique for PMRT patients and has a good balance of target coverage and normal tissue sparing;<sup>2</sup> the standard of care for PMRT at our institution has been volumetric modulated arc therapy (VMAT) or Helical Tomotherapy (TOMO).<sup>3, 4</sup> Both modalities provide good target coverage and dose homogeneity, but the stray radiation dose to organs at risk (OARs) is a concern;<sup>5</sup> bolus electron conformal therapy (BECT) mixed with IMRT and VMAT (mixed beam therapy) for PMRT has been recently evaluated for real patients' treatment planning by our group and can potentially reduce risks of normal tissue complications.<sup>6</sup> Apart from these previously reported PMRT techniques, multiple arc VMAT (MA-VMAT) which consists of 6 small partial arcs showed good feasibility and OAR sparing<sup>7</sup> for whole breast radiotherapy but has not been evaluated for PMRT; non-coplanar VMAT (NC-VMAT) has been shown to improve OAR dosimetry for intracranial tumors,<sup>8, 9</sup> early stage Hodgkin's lymphoma,<sup>10</sup> liver cancer<sup>11</sup> and prostate cancer,<sup>12</sup> but has not been investigated for PMRT either.

There have been some treatment planning studies of PMRT,<sup>2-4, 6, 13-18</sup> but most of them did not include any or only one advanced PMRT technique. The literature is largely incomplete regarding the systematic comparison of advanced technologies for post-mastectomy patients and these techniques are therefore implemented with very little evidence for safety or efficacy.

The purpose of this study was to compare predicted treatment outcomes (target coverage and risks of developing of radiogenic side effects) for a sample of PMRT patients using various advanced PMRT modalities, including fixed-beam IMRT, NC-VMAT, MA-VMAT, and TOMO. Standard VMAT and mixed beam therapy for PMRT have been reported by our group previously<sup>6</sup> for the same sample of patients, and the outcome results using these modalities will be compared with the PMRT techniques investigated in this study.

## Methods and Materials

### Patient selection

Nine consecutively sampled left-sided post-mastectomy patients were retrospectively selected. All patients received a modified radical mastectomy and were treated at our institution. Computed tomography (CT) scans had been acquired and all patients were scanned in the supine position with the free breathing CT data sets including all anatomy from the top of the head down to the lower abdomen. All CT data sets were anonymized<sup>19</sup> and assigned a unique research identifier, CW1 to CW9. The planning target volume (PTV) and organs at risk (OARs) for each patient were previously contoured by the same radiation oncologist. PTV included the left chest wall, left supraclavicular and axillary area, and internal mammary chain area. The patients had a 1-cm thick Superflab bolus (Radiation Products Design, Inc., Albertville, MN, USA) placed on the surface of their ipsilateral chest wall for the purpose of dose buildup.<sup>4</sup> OARs included lungs, whole heart, contralateral breast, esophagus, trachea, and spinal cord.

### Treatment planning

All plans used a prescribed dose of 50 Gy in 25 fractions. The following criteria were met for each treatment plan to be considered clinically acceptable: the volume of the PTV receiving at least 95% of the prescribed dose is greater than or equal to 95%; the volume of total lungs receiving at least 20 Gy is less than 20%;<sup>20</sup> the volume of heart receiving at least 22.5 Gy is less than 20%.<sup>21</sup>

Fixed-beam IMRT plan was generated in a commercial treatment planning system (TPS) (Pinnacle<sup>3</sup> v9.8, Philips Medical Systems, Fitchburg, WI, USA) using the direct machine parameter optimization (DMPO) optimization algorithm. Four or five co-planar 6 MV IMRT beams ranging from 150° to 315° were used to give enough PTV coverage. Each beam angle was individualized arranged for every patient in order to limit dose to the surrounding organs. Both NC-VMAT and MA-VMAT plans used 6 MV photon beams and were generated in Pinnacle using the SmartArc optimization algorithm. NC-VMAT plans utilized two partial arcs (Fig. 1 (a)): the first arc was planned to be delivered counterclockwise (CCW) with starting gantry angles between 170° to 180° and stopping gantry angles between 305° to 320° (same as standard VMAT plans that were previously reported by our group<sup>6</sup>) and with 15° couch angle, the second arc was planned to be delivered clockwise (CW) to over the same range of gantry angle and with 345° couch angle. The collimator was rotated to align with the long axis of PTV in both arcs. MA-VMAT plans consisted of six partial arcs (ARC01 to ARC06), each with 60° or 70° gantry rotations (Fig. 1 (b)). ARC01 to ARC03 were delivered CW and ARC04 to ARC06 were delivered CCW. The ARC01 started between 170° to 180° and ARC03 stopped between 305° to 320°. The ARC04 started between 305° to 320° and ARC06 stopped between 170° to 180°. The starting angle of ARC01 and stopping angle of ARC03 were the same as the standard VMAT plans. The collimator was always rotated to align with the long axis of PTV in each arc. For TOMO planning, the CT images and contours in Pinnacle were imported into TomoTherapy® Hi-Art TPS (Accuray, Madison, WI) for plan optimization. Parameters for TOMO plan optimization included a pitch of 0.287, a modulation factor of 2.8 and a field width of 5.02

cm. The final TOMO dose distributions were transferred back to Pinnacle for comparison with other plans. The details of standard VMAT and mixed beam therapy treatment planning can be found in our previous publication.<sup>6</sup>

### Plan comparison metrics

Dose-volume histograms (DVHs) and dose-volume metrics were calculated for target volume, total lungs, heart and contralateral breast. Dose homogeneity index (DHI)<sup>22</sup> and conformity index (CI)<sup>23</sup> were calculated for the target coverage. Risks of developing of radiogenic side effects were calculated including lifetime attributable risk (LAR) of secondary lung and contralateral breast cancer, normal tissue complication probability (NTCP) for pneumonitis, and radiation-induced risk of coronary events (RCE).

LAR was calculated as the integration of excess absolute risk (EAR) using BEIR VII model<sup>24</sup>:

$$LAR(D, e) = \int_{a=e+L}^{a_{max}} EAR * \frac{s(a)}{s(e)} da$$

where  $e$  is age at exposure,  $a$  is attained age,  $L$  is a risk-free latent period,  $\frac{s(a)}{s(e)}$  is the probability of surviving to age conditional on survival to age  $e$ .<sup>25</sup> EAR is calculated using following equations:

$$EAR = \beta * \mu * OED$$

$$OED = \frac{1}{V_T} \sum_i (v_i * D_i)$$

where OED is organ equivalent dose,  $\beta$  is dose response initial slope ( $\beta_{Lung}=7.5$ ,  $\beta_{Breast}=9.2$ )<sup>26</sup>,  $\mu$  is age correction factor,  $V_T$  is the total organ volume, and  $v_i$  is the volume receiving dose  $D_i$ .  $\mu$  was calculated for each patient according to Schneider *et al.*<sup>26</sup> as follows:

$$\mu = \exp(\gamma_e * (age - 30) + \gamma_a * \ln(\frac{age}{70}))$$

where the age modifying factor  $\gamma_e$  and  $\gamma_a$  ( $\gamma_{e,Lung}=0.002$ ,  $\gamma_{a,Lung}=4.23$ ,  $\gamma_{e,Breast}=-0.037$ ,  $\gamma_{a,Breast}=1.7$ ) were taken from by Schneider *et al.*<sup>26</sup>

The Lyman-Kutcher-Burman (LKB) model<sup>27-29</sup> was used to calculate NTCP for pneumonitis using the following equations:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{t^2}{2}} dt$$

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)}$$

$$TD_{50}(v) = \frac{TD_{50}}{v^n}$$

where  $TD_{50}$  is the uniform dose given to the entire lung that results in 50% complication risk ( $TD_{50} = 30.8$  Gy),  $m$  is a measure of the slope of the dose-response curve ( $m = 0.37$ ),  $n$  is the volume effect parameter ( $n = 0.99$ ), and  $v$  is the fractional volume irradiation to the uniform dose  $D$ .<sup>29</sup>

RCE was estimated using the dose-response model reported by Darby *et al.*<sup>30</sup>:

$$RCE = 1.074 * D * R_{baseline}$$

where  $D$  (Gy) is the mean heart dose,  $R_{baseline}$  is the baseline risk of coronary events and was calculated using Reynolds risk model<sup>31</sup> assuming medium risk type.

### Statistical analysis

The *post hoc* Tukey test was used to determine the statistical significance of the differences between two PMRT techniques. All statistical analyses were conducted with R software (version 3.2.3) and the differences were considered significant when  $p < 0.05$ .

### Results

The dose distributions and DVHs for a representative patient are shown in Figs. 2 and 3, respectively. Table 1 lists the total average number of monitor units (MU), PTV and OARs evaluation metrics for various advanced PMRT techniques. The results of *post hoc* Tukey tests and  $p$  values are shown in Table 2.

The four PMRT techniques evaluated in this study as well as two techniques studied previously all meet clinical requirement of PTV coverage. Overall, TOMO plans exhibit the most optimal PTV coverage by showing the lowest  $D_{max}$  in PTV, but deliver relatively higher dose to OARs than other plans: significantly higher  $D_{mean}$ ,  $V_5$ ,  $V_{10}$  and NTCP for lung, significantly higher  $V_{10}$  for heart, the highest LAR for lung, the highest  $D_{mean}$ ,  $V_5$  for heart. Fixed-beam IMRT plans induce the lowest  $D_{mean}$ ,  $V_5$  and LAR for contralateral breast, but induce the highest  $V_{30}$  for heart and the highest  $D_{max}$  for lung, and yield the significantly higher  $D_{max}$  for heart and contralateral breast than other techniques. Compared with standard VMAT, both NC-VMAT and MA-VMAT significantly reduce  $D_{mean}$  for lungs, heart and contralateral breast, and also significantly reduce  $V_5$  and RCE for heart. NC-VMAT plans exhibit the minimum  $D_{mean}$ ,  $V_5$ ,  $V_{10}$ ,  $V_{20}$ , NTCP and LAR values for lungs and the minimum  $V_{10}$  for the heart compared with other plans. Mixed-beam therapy plans show significantly higher  $D_{max}$ , DHI and  $V_{107\%}$  for PTV than other techniques, and the highest  $V_{20}$  for lungs, but provide the lowest  $D_{mean}$ ,  $V_5$ ,  $V_{22.5}$ ,  $V_{30}$  and RCE for heart, the

lowest  $V_5$  and the second lowest  $D_{\text{mean}}$  and LAR for contralateral breast compared with other techniques.

## Discussion

This study evaluated four advanced radiotherapy techniques for treating post-mastectomy breast cancer patients, and these techniques were compared with another two PMRT techniques in the literature. Dosimetric and radiobiological endpoints were used to assess the dose to the target and normal tissues. All six techniques provide acceptable dose coverage to target region. Fixed-beam IMRT exhibits the best sparing of contralateral breast, but increases dose to lungs and heart. NC-VMAT provides the best sparing of lungs. Mixed beam therapy provides the best sparing of heart and good sparing of contralateral breast at the cost of inducing less homogenous dose to PTV.

Wang *et al.*<sup>2</sup> drew a conclusion that four fields IMRT has the best balance of target coverage and normal tissue sparing compared with conventional tangential beams, tangential IMRT and single arc VMAT. In our study, we used four to five IMRT beams in fixed-beam IMRT plans because the separation between PTV and OARs is small in some patients and four beams will introduce significantly high dose to OARs. Fixed-beam IMRT plans provide the lowest doses to contralateral breast, which is mainly because this technique is characterized by the limited gantry angles and low dose spread to the organs. On the other hand, also due to the limited gantry angles that are used to cover the entire PTV, the edge of some IMRT beams need to transmit through lungs, heart and contralateral breast in some plans. As a result, the fixed beam IMRT plans yield the highest maximum dose to OARs, which is contradictory to what has been reported in Wang *et al.*<sup>2</sup> These results show that fixed-beam IMRT is not the optimal technique for all PMRT patients and its application should be judged based on the complexity of the target and patient geometry.

Both NC-VMAT and MA-VMAT provide superior OAR sparing than standard VMAT and NC-VMAT offers the best sparing of lungs, which indicates OARs can be spared more for PMRT patients by adjusting the couch angle or splitting a single arc into multiple partial ones since these will provide more degrees of freedom for plan optimizations. Instead of using 50° gantry rotation for each arc in MA-VMAT as reported by Tsai *et al.*<sup>7</sup> for whole breast, we chose larger rotation angle (60° or 70°) in this study in order to achieve enough PTV coverage and optimal OAR sparing. For NC-VMAT, non-coplanar geometries are fixed (couch angle and collimator angle are fixed) in this study, while studies have shown that dynamic couch/gantry rotation and dynamic collimator rotation during VMAT delivery can further improve target coverage or normal tissue sparing<sup>9, 32, 33</sup> and should be investigated for PMRT in the future.

The mean lung and heart doses from TOMO are the highest among all the PMRT techniques and can be explained by the fact that radiation to these organs is not limited enough due to the characteristic of TOMO (the beam is delivered from 360 degrees around the body). The other group in our institution independently evaluated TOMO and VMAT for PMRT previously<sup>4</sup>. Our study shows lower lung and heart doses than theirs, which can be explained by the fact different planning goals (they were trying to achieve 90% volume of the PTV

receiving the prescribed dose) were used in these two studies and only one optimization objective could be specified for a given OAR in their TOMO TPS, i.e., it was not feasible for them to include more dose objectives to further optimize their plans then. In contrast, the latest TOMO planning system used in our study is capable of including multiple objectives for one OAR.

The CT data representation, contouring and dose calculation algorithm may introduce uncertainties to the dosimetric values. Previous studies<sup>34, 35</sup> reported that using thick CT slice thickness may underdose target volume. Slice thickness of 2.5mm is an optimal and standard choice and was used in our study, and effect of CT data uncertainty on dose values should be minimal. Inter-observer variability in contouring is a major contributor to uncertainty in radiation treatment planning<sup>36, 37</sup>. Kirli *et al.*<sup>38</sup> reported variability in intra-observer contouring was similar to inter-observer variability and can be reduced by following certain contouring atlas. In our study, all the contours were generated by the same physician following the RTOG atlas and were used for the comparison between different techniques. Thus the uncertainty of inter-observer contouring does not exist and the uncertainty of intra-observer contouring should be minimal. For dose calculation algorithm, we did a test and calculated dose distributions for several patients using adaptive algorithm and fast convolution algorithm besides the standard collapsed-cone convolution superposition algorithm in Pinnacle treatment planning system. The dose differences among three different algorithms for PTV and OARs were very small (within 4%). The we do not expect dramatic changes of relative values, i.e. the rank of alternative RT techniques.

Deep inspiration breath hold has been shown to significantly reduce cardiac exposure in patients receiving PMRT,<sup>39</sup> which translates to the reduction of risk of heart disease. However, free breathing is the standard of care for PMRT patients in our clinic and breath hold was not adopted for the patients used in this study, neither in most of the previous PMRT studies. Acquiring patients' CT images with breath hold and comparing various advanced radiotherapy techniques for breath hold patients will be further investigated in the near future.

We only compared various photon and electron radiotherapy techniques while did not include proton therapy. Actually proton PMRT was also evaluated by our group previously,<sup>18</sup> and the superior dose distribution makes proton PMRT dominant among all PMRT techniques. However, due to the limited availability and much higher cost, proton PMRT is not as popular as photon or electron PMRT. Robust proton treatment planning is more challenging compared with photon treatment due to uncertainties related to imaging, setup, proton range, dose calculation algorithm, biological effectiveness etc.<sup>40</sup>, although Hernandez *et al*<sup>18</sup> reported that relative plan comparisons between standard VMAT and proton plans were robust to patient setup errors (up to 1 cm), proton range uncertainty (up to 10%) and uncertainty in dose-risk models. Evidence on the effectiveness and safety of proton therapy from clinical trials is lacking and will not be available until years or decades later, and it is controversial if the additional cost of proton therapy is justified by the potential advantages.

## Conclusions

Four advanced PMRT techniques were evaluated in this study and were compared with another two PMRT techniques in the literature. Our analysis shows it is feasible to use NC-VMAT and MA-VMAT for PMRT patients. Among all techniques, fixed-beam IMRT might reduce contralateral breast dose, NC-VMAT could reduce lungs dose, and mixed beam therapy might lower the heart and contralateral breast doses. Based on evaluated target coverage and estimated risks for OARs, fixed-beam IMRT, NC-VMAT, mixed-beam therapy might be the appropriate PMRT techniques for certain patients who are prone to develop radiogenic side effects.

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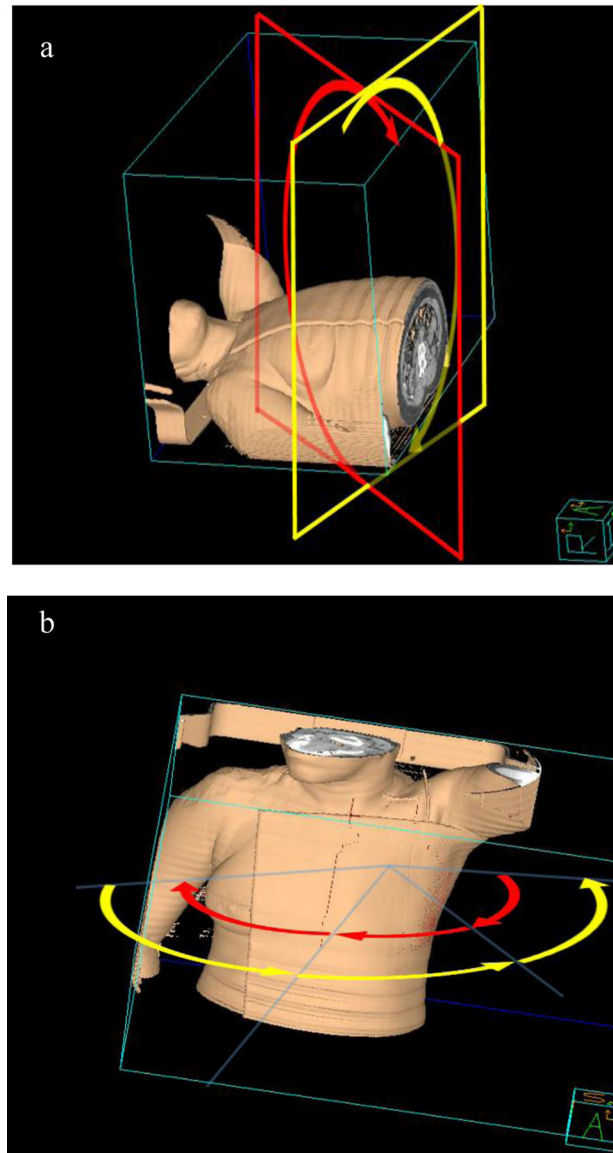
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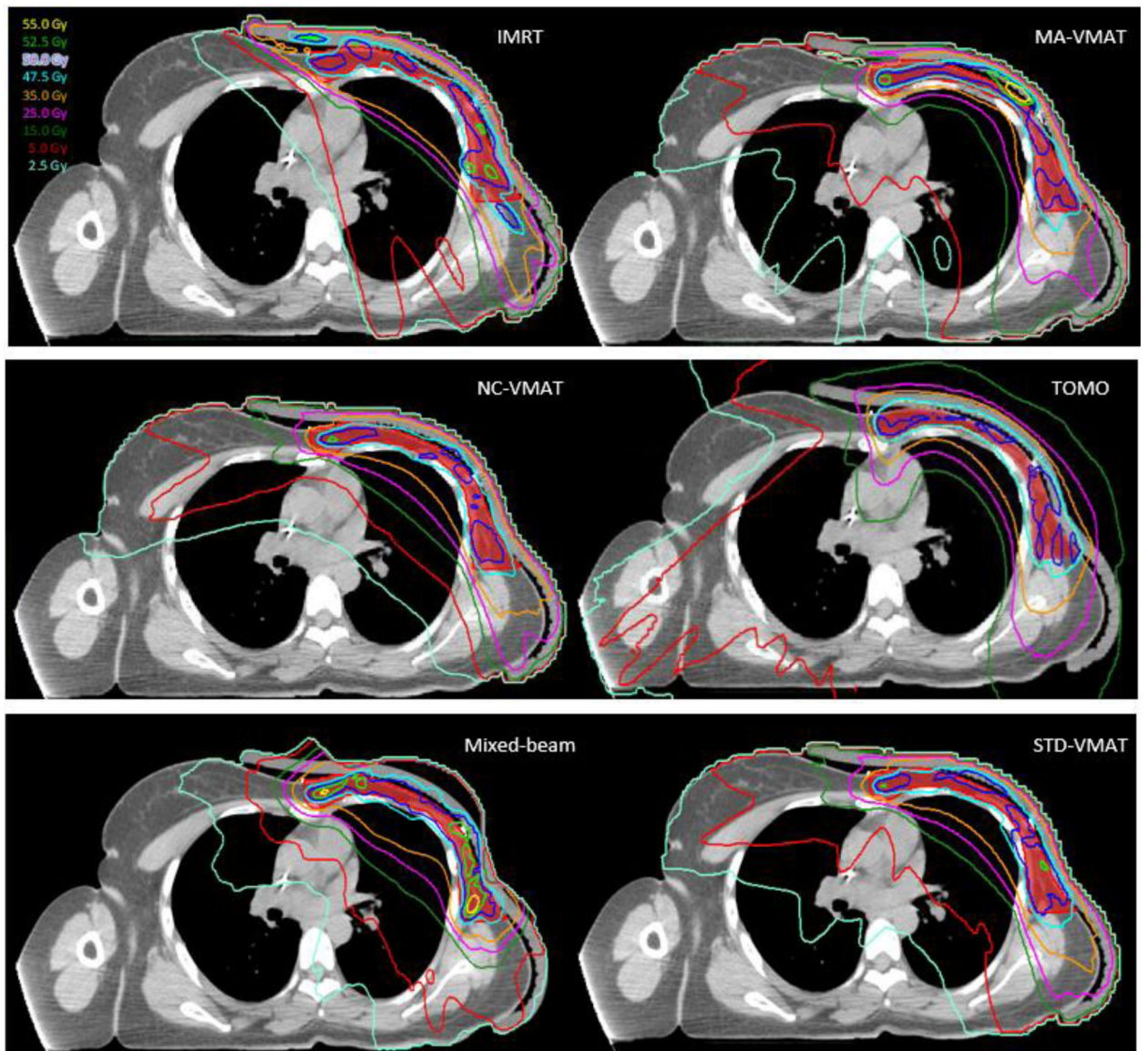


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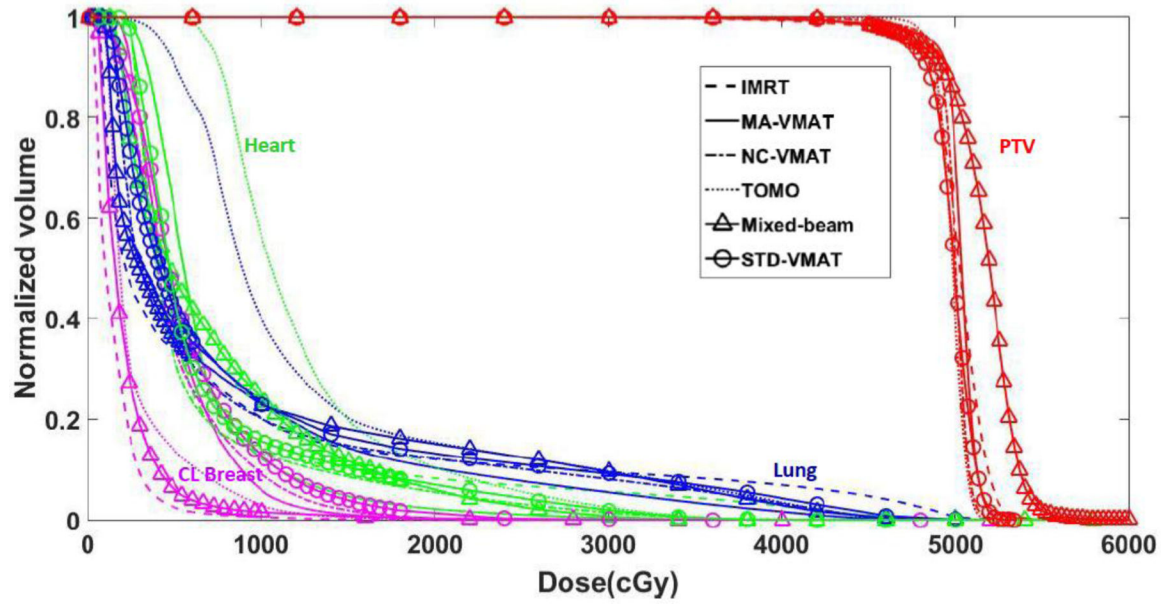
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**Fig. 1.** Three-dimensional display of (a) two non-coplanar partial arcs for NC-VMAT. Red plane represents gantry plane at 15° couch angle and the yellow plane represents gantry plane at 345° couch angle; (b) six partial arcs for MA-VMAT. The CW arcs display in yellow curvature and CCW arcs in red curvature.



**Fig. 2.** Axial view of isodose distribution for fixed-beam IMRT, MA-VMAT, NC-VMAT, TOMO, mixed-beam therapy and standard VMAT plans for a typical PMRT patient. The red color wash represents the PTV.



**Fig. 3.** DVHs for fixed-beam IMRT, MA-VMAT, NC-VMAT, TOMO, mixed-beam therapy and standard VMAT plans for a typical PMRT patient.

**Table 1**

MU, PTV and OAR evaluation metrics (mean  $\pm$  standard deviation) for nine PMRT patients. NC-VMAT: non-coplanar VMAT; MA-VMAT: multiple-arc VMAT; TOMO: Tomotherapy; Mixed: mixed beam therapy; MU: monitor unit; PTV: planning target volume; CL breast: contralateral breast. LAR: lifetime attributable risk; RCE: risk of coronary events.

	NC-VMAT	MA-VMAT	Fixed-beam IMRT	TOMO	Standard VMAT <sup>a</sup>	Mixed <sup>a</sup>
Average total MU	13000.0 $\pm$ 1725	14108.3 $\pm$ 1839	18130.6 $\pm$ 2155	97347.2 $\pm$ 8824	11833.3 $\pm$ 792	16916.7 $\pm$ 3949
<b>PTV</b>						
D <sub>mean</sub> (Gy)	49.7 $\pm$ 0.2	49.8 $\pm$ 0.3	50.0 $\pm$ 0.3	49.8 $\pm$ 0.4	49.7 $\pm$ 0.3	51.6 $\pm$ 0.4
D <sub>max</sub> (Gy)	54.1 $\pm$ 1.1	54.9 $\pm$ 2.3	55.9 $\pm$ 2.7	52.4 $\pm$ 0.6	53.5 $\pm$ 0.7	59.9 $\pm$ 3.6
V <sub>107%</sub> (%)	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.1	15.0 $\pm$ 8.6
CI	0.7 $\pm$ 0.0	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1	0.6 $\pm$ 0.1	0.7 $\pm$ 0.0	0.5 $\pm$ 0.1
DHI	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.2 $\pm$ 0.0
<b>Lungs</b>						
D <sub>mean</sub> (Gy)	7.5 $\pm$ 0.8	7.7 $\pm$ 0.9	7.9 $\pm$ 0.6	10.6 $\pm$ 1.5	8.7 $\pm$ 0.6	8.4 $\pm$ 0.9
D <sub>max</sub> (Gy)	47.7 $\pm$ 1.9	48.5 $\pm$ 2.6	52.8 $\pm$ 1.7	47.0 $\pm$ 1.7	51.1 $\pm$ 1.6	52.0 $\pm$ 2.2
V <sub>5</sub>	33.3 $\pm$ 4.9	35.7 $\pm$ 4.9	34.4 $\pm$ 3.1	69.5 $\pm$ 20.3	43.5 $\pm$ 5.8	33.5 $\pm$ 2.6
V <sub>10</sub>	20.0 $\pm$ 2.2	21.3 $\pm$ 3.6	24.9 $\pm$ 4.0	31.2 $\pm$ 7.9	24.3 $\pm$ 2.4	23.4 $\pm$ 2.9
V <sub>20</sub>	12.3 $\pm$ 1.0	12.3 $\pm$ 1.8	15.2 $\pm$ 5.1	12.9 $\pm$ 2.1	13.0 $\pm$ 1.0	15.5 $\pm$ 2.6
NTCP (%)	2.1 $\pm$ 0.4	2.2 $\pm$ 0.5	2.3 $\pm$ 0.3	3.8 $\pm$ 1.3	2.7 $\pm$ 0.3	2.7 $\pm$ 0.5
LAR (%)	5.4 $\pm$ 2.8	5.5 $\pm$ 2.8	5.7 $\pm$ 2.8	7.2 $\pm$ 3.8	6.3 $\pm$ 3.1	6.3 $\pm$ 3.3
<b>Heart</b>						
D <sub>mean</sub> (Gy)	7.4 $\pm$ 1.2	7.7 $\pm$ 1.1	8.53 $\pm$ 1.33	10.3 $\pm$ 2.2	9.3 $\pm$ 1.1	7.1 $\pm$ 1.3
D <sub>max</sub> (Gy)	41.4 $\pm$ 4.7	40.1 $\pm$ 2.7	48.8 $\pm$ 5.4	38.7 $\pm$ 4.3	42.8 $\pm$ 3.6	38.9 $\pm$ 4.6
V <sub>5</sub>	44.6 $\pm$ 13.6	48.6 $\pm$ 12.3	54.4 $\pm$ 14.4	84.3 $\pm$ 18.9	66.9 $\pm$ 13.0	44.3 $\pm$ 7.6
V <sub>10</sub>	20.7 $\pm$ 5.0	21.2 $\pm$ 6.1	23.3 $\pm$ 5.0	39.1 $\pm$ 18.3	25.3 $\pm$ 4.1	21.0 $\pm$ 5.7
V <sub>22.5</sub>	6.5 $\pm$ 2.3	7.2 $\pm$ 3.7	8.8 $\pm$ 2.0	6.3 $\pm$ 3.0	9.8 $\pm$ 1.9	4.5 $\pm$ 3.4
V <sub>30</sub>	2.6 $\pm$ 2.2	2.9 $\pm$ 2.7	5.3 $\pm$ 2.5	2.0 $\pm$ 1.7	5.0 $\pm$ 2.6	1.3 $\pm$ 1.8
RCE (%)	8.9 $\pm$ 7.3	8.9 $\pm$ 7.3	9.5 $\pm$ 8.0	9.8 $\pm$ 7.7	9.7 $\pm$ 8.0	8.6 $\pm$ 7.1
<b>CL breast</b>						
D <sub>mean</sub> (Gy)	3.3 $\pm$ 1.0	3.4 $\pm$ 0.9	1.56 $\pm$ 0.4	3.9 $\pm$ 1.7	4.0 $\pm$ 1.1	1.8 $\pm$ 0.6
D <sub>max</sub> (Gy)	19.6 $\pm$ 9.1	22.1 $\pm$ 5.9	28.3 $\pm$ 7.6	18.5 $\pm$ 10.5	27.1 $\pm$ 8.4	26.6 $\pm$ 7.7
V <sub>5</sub>	16.8 $\pm$ 12.5	21.8 $\pm$ 12.9	5.1 $\pm$ 2.4	24.4 $\pm$ 21.8	24.2 $\pm$ 12.1	4.6 $\pm$ 3.2
LAR (%)	1.2 $\pm$ 0.8	1.4 $\pm$ 0.7	0.6 $\pm$ 0.2	1.6 $\pm$ 0.8	1.7 $\pm$ 0.8	1.1 $\pm$ 0.6

<sup>a</sup>Data taken from our previous work.<sup>6</sup>

Table 2

p values for statistic comparison of six advanced PMRT techniques using *post hoc* Tukey test. NC-VMAT: non-coplanar VMAT; MA-VMAT: multiple-arc VMAT; TOMO: Tomotherapy; Mixed: mixed beam therapy; STD VMAT: standard VMAT; PTV: planning target volume; CL breast: contralateral breast.

Variable	NC-VMAT vs NC-VMAT	NC-VMAT vs Fixed beam IMRT	NC-VMAT vs TOMO	NC-VMAT vs Mixed	NC-VMAT vs STD VMAT	MA-VMAT vs Fixed beam IMRT	MA-VMAT vs TOMO	MA-VMAT vs STD VMAT	MA-VMAT vs Mixed	Fixed-beam MRI vs STD VMAT	Fixed-beam MRI vs Mixed	Fixed-beam IMRT vs Mixed	TOMO vs STD VMAT	TOMO vs Mixed	STD VMAT vs Mixed
<b>PTV</b>															
D <sub>mean</sub>	0.999	0.526	1.000	<0.001*	0.997	0.776	1.000	0.953	<0.001*	0.595	0.243	<0.001*	0.992	<0.001*	<0.001*
D <sub>max</sub>	0.971	0.057	0.487	<0.001*	0.982	0.328	0.111	0.676	<0.001*	<0.001*	0.006*	0.028*	0.895	<0.001*	<0.001*
V <sub>107</sub> %	1.000	1.000	1.000	<0.001*	1.000	1.000	1.000	1.000	<0.001*	1.000	1.000	<0.001*	1.000	<0.001*	<0.001*
CI	0.0943	<0.001*	<0.001*	<0.001*	1.000	<0.001*	<0.001*	0.124	<0.001*	0.516	<0.001*	1.000	<0.001*	0.734	<0.001*
DHI	1.000	0.158	0.253	<0.001*	0.525	0.202	0.202	0.601	<0.001*	<0.001*	0.984	<0.001*	0.001*	<0.001*	<0.001*
<b>Lung</b>															
D <sub>mean</sub>	0.990	0.845	<0.001*	0.004*	0.004*	0.993	<0.001*	0.034*	0.286	<0.001*	0.152	0.643	<0.001*	<0.001*	0.952
D <sub>max</sub>	0.955	<0.001*	0.956	<0.001*	0.636	<0.001*	0.515	0.984	<0.001*	<0.001*	<0.001*	0.938	0.155	<0.001*	0.004*
V <sub>5</sub>	0.988	0.999	<0.001*	0.063	0.063	0.999	<0.001*	0.268	0.993	<0.001*	0.127	0.999	<0.001*	<0.001*	0.073
V <sub>10</sub>	0.981	0.058	<0.001*	0.136	0.136	0.291	<0.001*	0.495	0.814	0.004*	0.999	0.959	<0.001*	<0.001*	0.996
V <sub>20</sub>	1.000	0.159	0.996	0.989	0.989	0.164	0.996	0.990	0.091	0.411	0.487	0.999	1.000	0.271	0.333
NTCP	0.999	0.942	<0.001*	0.078	0.187	0.995	<0.001*	0.193	0.382	<0.001*	0.486	0.727	<0.001*	<0.001*	0.999
LAR (%)	0.999	0.966	<0.001*	0.096	0.143	0.999	<0.001*	0.235	0.321	<0.001*	0.469	0.580	0.116	0.076	1.000
<b>Heart</b>															
D <sub>mean</sub>	0.994	0.360	<0.001*	0.008*	0.008*	0.711	<0.001*	0.044*	0.876	0.019*	0.686	0.113	0.533	<0.001*	<0.001*
D <sub>max</sub>	1.000	<0.001*	0.591	0.958	0.682	<0.001*	0.756	0.878	0.831	<0.001*	0.006*	<0.001*	0.137	1.000	0.186
V <sub>5</sub>	0.989	0.643	<0.001*	0.006*	0.006*	0.947	<0.001*	0.047*	0.984	<0.001*	0.361	0.613	0.068	<0.001*	0.005*
V <sub>10</sub>	0.999	0.986	<0.001*	0.864	1.000	0.995	<0.001*	0.914	1.000	0.001*	0.997	0.992	0.007*	<0.001*	0.896
V <sub>22.5</sub>	0.986	0.262	0.999	0.032*	0.425	0.670	0.941	0.177	0.118	0.152	0.957	<0.001*	0.014*	0.598	<0.001*
V <sub>30</sub>	0.999	0.021*	0.979	0.056	0.639	0.049*	0.917	0.116	0.454	0.002*	0.999	<0.001*	0.006*	0.965	<0.001*

Variable	NC-VMAT vs MA-VMAT	NC-VMAT vs Fixed beam IMRT	NC-VMAT vs TOMO	NC-VMAT vs STD VMAT	NC-VMAT vs Mixed VMAT	MA-VMAT vs TOMO	MA-VMAT vs STD VMAT	MA-VMAT vs Mixed VMAT	Fixed-beam MRI vs TOMO	Fixed-beam MRI vs STD VMAT	Fixed-beam IMRT vs Mixed VMAT	TOMO vs STD VMAT	TOMO vs Mixed VMAT	STD VMAT vs Mixed VMAT
<b>RCE (%)</b>	1.000	0.252	0.009*	0.025*	0.931	0.337	0.015*	0.040*	0.874	0.823	0.943	1.000	<0.001*	<0.001*
<b>CL breast</b>														
<b>D<sub>mean</sub></b>	0.998	0.001*	0.644	0.596	0.007*	<0.001*	0.878	0.846	0.001*	<0.001*	0.997	1.000	<0.001*	<0.001*
<b>D<sub>max</sub></b>	0.905	0.006*	0.005*	0.029*	<0.001*	0.135	0.113	0.342	0.027*	1.000	0.997	0.995	0.995	0.898
<b>V<sub>5</sub></b>	0.930	0.215	0.688	0.712	0.181	0.017*	0.996	0.997	0.127	0.003*	1.000	1.000	0.002*	0.002*
<b>LAR (%)</b>	0.965	0.259	0.760	0.528	0.997	0.035*	0.995	0.949	0.788	0.006*	0.548	0.999	0.450	0.245

\* indicates statistical significant.