

Small-arc volumetric-modulated arc therapy

A new approach that is superior to fixed-field IMRT in optimizing dosimetric and treatment-relevant parameters for patients undergoing whole-breast irradiation following breast-conserving surgery

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Abstract

Volumetric-modulated arc therapy (VMAT) is considered to deliver a better dose distribution and to shorten treatment time. There is a lack of research regarding breast irradiation after breast-conserving surgery (BCS) using VMAT with prone positioning. We developed a new small-arc VMAT methodology and compared it to conventional (fixed-field) intensity-modulated radiation therapy (IMRT) in the dosimetric and treatment relevant parameters for breast cancer patients in the prone position.

Ten early-stage breast cancer patients were included in this exploratory study. All patients underwent computed tomography (CT) simulation scan in the prone position and for each patient, IMRT and VMAT plans were generated using the Monaco planning system. Two symmetrical partial arcs were applied in the VMAT plans. The angle ranges of the 2 arcs were set to approximately 60° to 100° and 220° to 260°, with small adjustments to maximize target coverage, while minimizing lung and heart exposure. The IMRT plans used 4 fixed fields. Prescribed doses were 50 Gy in 25 fractions. The target coverage, homogeneity, conformity, dose to organs at risk (OAR), treatment time, and monitor units (MU) were evaluated.

Higher median conformal index (CI) and lower homogeneity index (HI) of the planning target volume (PTV) were respectively observed in VMAT and plans group (CI, 95% vs 91%; HI, 0.09 vs 0.12; $P < 0.001$). The volumes of ipsilateral lung receiving 30, 20, 10, and 5 Gy were lower for VMAT ($P < 0.01$), being 10%, 14.9%, 25.9%, and 44.9%, respectively, compared to 11.79%, 17.32%, 30.27%, and 50.58% for the IMRT plans. The mean lung dose was also reduced from 10.6 ± 1.8 to 9.6 ± 1.4 Gy ($P = 0.001$). The volumes of the heart receiving 30 and 40 Gy were similar for the 2 methods. In addition, the median treatment time (161 vs 412 seconds; $P < 0.001$) and the mean MU (713 vs 878; $P < 0.001$) were lower for VMAT.

Small-arc VMAT plan improved CI and HI for the target, spared the dose of lung, and reduced treatment time and MU, compared to IMRT. It is a more promising irradiation technique for post-BCS radiotherapy.

Abbreviations: CI = conformal index, D_{mean} = mean dose, HI = homogeneity index, IMRT = intensity-modulated radiation therapy, MU = monitor unit, OAR = organ at risk, PTV = planning target volume, VMAT = volumetric-modulated arc therapy.

Keywords: breast cancer, breast conservative surgery, prone position, volumetric-modulated Arc therapy

1. Introduction

Breast-conserving surgery (BCS) combined with postoperative radiotherapy to the residual whole breast has become the

standard treatment for the majority of early-stage breast-cancer patients. Whole-breast irradiation (WBI) followed by tumor-bed boost improves local control and overall survival.^[1,2] However, it has been recognized that WBI is associated with an increased incidence of long-term radiation-related toxicities, such as radiation-induced pulmonary injury and cardiovascular diseases in long term. Cosmetic outcomes can be worsened by inhomogeneous irradiation, especially for patients have small breasts, a common feature of Asians.^[3,4]

Traditionally, most post-BCS radiotherapy is delivered in the supine position. It would be advantageous to spare the lungs and cardiovascular system from radiation injury by shifting the therapeutic body position to prone, which allows the breast to elongate and hang away from the thorax.^[5,6] Volumetric-modulated arc therapy (VMAT), a novel intensity-modulated technique, can precisely and accurately deliver radiation dose by dynamic adjustment of multileaf collimators (MLCs) motion, dose rates, and gantry rotations.^[7] It has been reported that VMAT can achieve similar target coverage, reduced exposure of organs at risk (OAR) and shorter treatment times compared with conventional fixed-gantry (fixed-field) intensity-modulated radiation therapy (IMRT).^[8,9] However, VMAT has been found to significantly increase the low-dose irradiation volume of the lungs, for example, V5 or V10, and

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these are potential predictors of radiation pneumonitis (RP).^[10,11]

Aiming to minimize the therapeutic toxicity of VMAT, while improving its efficacy, we first established a new methodology using small arcs. In order to assess these potential improvements, we compared treatment plans for the small-arc VMAT versus those for fixed-field IMRT in terms of the target coverage, homogeneity, conformity, dose to OARs, treatment time, and monitor units (MU).

2. Materials and methods

2.1. Patients clinical data

From October 2012 to April 2013, 10 breast-cancer patients (4 left-side and 6 right-side; pT1/2; N0–1) were enrolled in the study. All patients underwent BCS plus axillary clearance or sentinel node biopsy. The median age was 48 years old (34–58) and they did not suffer from any serious systemic or autoimmune diseases. Adjuvant chemotherapy, hormonal therapy, or targeted therapy (trastuzumab) was applied according to postoperative pathology results (Table 1).

2.2. CT-simulation and target definitions

Patients were positioned prone on a breast board (Civco Medical Solutions, Orange City, IA), and the ipsilateral breast was allowed to hang downward, away from the thorax. Simulation-images were acquired via a Big Bore CT (Philips Medical, Fitchburg, MI), scanning from the upper level of the mandible to the lower level of diaphragm without contrast enhancement and with a slice thickness of 5 mm. All the CT images were exported to the Monaco planning system (version 3.30, Elektra AB, Stockholm, Sweden) for further contouring and treatment planning.

The clinical target volume (CTV) was defined according to the breast-cancer delineation atlas of the Radiation Therapy Oncology Group (RTOG). The tumor bed was determined according to tumor bed clips, surgery-related seroma, or postoperative skin scars. A margin (1.0 cm in the cranial-caudal direction, 0.5 cm scale out in the transverse level) was added to formulate the planning target volume (PTV). The OARs were defined according to the guidelines described by Feng et al.^[12]

Given that our patients were at a relatively early stage of the disease, the axilla and supraclavicular area were not assessed.

2.3. Radiotherapy planning

A fixed 4-field (60°, 80°, 210°, and 240°) IMRT plan was created for each patient. Of these, the 80° and 240° fields were applied to the whole PTV and the remaining 2 were used to improve dose homogeneity and to minimize irradiation of the OARs. The small-arc VMAT plan used 2 nearly symmetrical partial arcs. The average angle ranges for the 2 arcs were 60° to 100° and 220° to 260°; to reduce the exposure of OARs, small adjustments were made according to variations in the target volume (Fig. 1).

The 2 types of plan were generated by 6-MV photons and optimized for each individual patient, under the following conditions: $\geq 95\%$ of the PTV volume receives 50 Gy, 95% of the prescribed dose ($V_{95\%}$) covers $\geq 99\%$ of the PTV, and the hot spot was $<107\%$ of the prescribed dose. V_{20} (percentage of organ volume receiving 20 Gy) was $<20\%$ for the lung and V_{30} was $<10\%$ for the heart. The dose to the contralateral breast was minimized.

With regard to targets, we evaluated the minimum dose received by 95% of the target volume (D_{95}), maximal dose (D_{max}), mean dose (D_{mean}), conformal index (CI), and homogeneity index (HI). The CI and HI were calculated as follows: $CI = V_{ref}/V_T$; $HI = (D_2 - D_{98})/D_{prescribed}$. V_{ref} represents the volume of PTV covered by the reference isodose line (in this case the 95% isodose line), and V_T represents the PTV. Values of CI close to one indicate greater conformity and values of HI close to zero indicate greater homogeneity. We calculated V_{30} , V_{10} , and V_5 for the heart, and V_{30} , V_{20} , V_{10} , V_5 , and the D_{mean} were calculated for the ipsilateral lung. MU and treatment delivery time were also assessed.

2.4. Statistics

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL). The normal distribution of our data was verified via a Kolmogorov–Smirnov test. Two-sided paired *t* tests and Mann–Whitney *U* tests were used to analyze differences between the 2 techniques. A *P* value less than 0.05 was considered statistically significant.

3. Results

There was no direct intervention in patients' treatment or care in this observational study. Hence, ethical approval and patient consent are not required.

3.1. Treatment toxicities and outcome

The median follow-up time for all patients was 39 months (36–43 months). According to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTC 3.0), 3 patients had grade 2 radiation pneumonitis and 3 patients had grade 1. No radiation-

Table 1

Patient characteristics.

	n	%
Age, year		
Median age 48		
Range (34–58)		
Lesion location		
Left	4	40%
Right	6	60%
Molecular subtype		
Luminal A	7	70%
Luminal B	1	10%
Her-2+	1	10%
Basal like subtype	1	10%
Normal tissue type	0	0%
Ki67		
Median 20%		
Adjuvant chemotherapy		
Yes	3	30%
No	7	70%
Trastuzumab		
Yes	1	10%
No	9	90%
Hormone treatment		
Yes	8	80%
No	2	20%

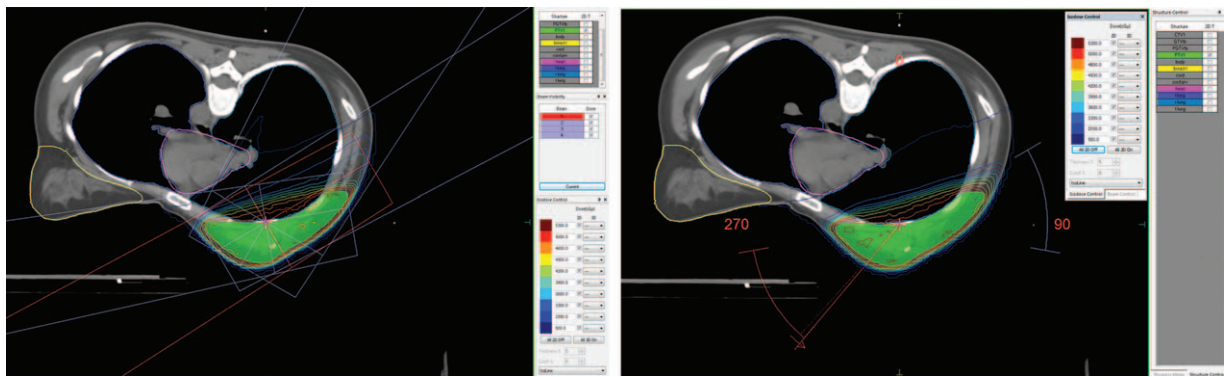


Figure 1. Axial CT slices from the 2 treatment plans for a representative case. They show the anatomy and the dose distribution at the PTV, ipsilateral lung, and heart. The IMRT plan is on the left and the VMAT plan is on the right. CI=conformal index, IMRT=intensity-modulated radiation therapy, PTV=planned target volume, VMAT=volumetric-modulated arc therapy.

related cardiovascular toxicities were observed in this group of patients.

Of the 10 patients, 1 basal like subtype one developed a liver metastasis in 22 months after surgery. Subsequently, she underwent the stereotactic radiotherapy for the liver lesion. The rest 9 patients were alive without any sign of relapse and metastasis.

3.2. PTV dose evaluation

The median of the PTV was 362.85 cm³ (range, 381.3–1046.7 cm³). Figure 2 shows a dose-volume histogram (DVH) for a typical patient. The differences in D_{mean}, D_{max}, and D₉₅ between the 2 techniques were not statistically significant (see Table 2).

Our small-arc VMAT plan showed improved HI and CI (*P* < 0.01) when compared to the fixed-field IMRT plan (Fig. 3, Table 2).

3.3. OAR dose evaluation

The VMAT plan achieved significantly lower dose of irradiation exposing for both the ipsilateral lung and heart (Fig. 4; Table 3).

V₁₀, V₅, and D_{mean} of heart were remarkably reduced in VMAT plan (*P* < 0.05). For the ipsilateral lung V₂₀, V₁₀, V₅, and mean lung dose were also significantly reduced (*P* = 0.001).

3.4. Evaluation of monitor units and treatment delivery time

The VMAT plan reduced the MU from 878 ± 50 to 713 ± 112 (*P* < 0.001) and treatment time from 421 ± 24 to 164 ± 9 seconds (*P* < 0.001).

4. Discussion

In this study, we developed a novel VMAT methodology and assessed it at the treatment-planning stage. The method was based on the use of 2 small arcs and was aimed at improving the efficacy and safety of prone-positioned WBI after BCS. The new VMAT method significantly improved the CI and HI of the PTV and reduced the V₃₀, V₂₀, V₁₀, V₅, and D_{mean} of the ipsilateral lung. Also reduced were the heart V₁₀ and V₅ along with the median treatment time and MU required.

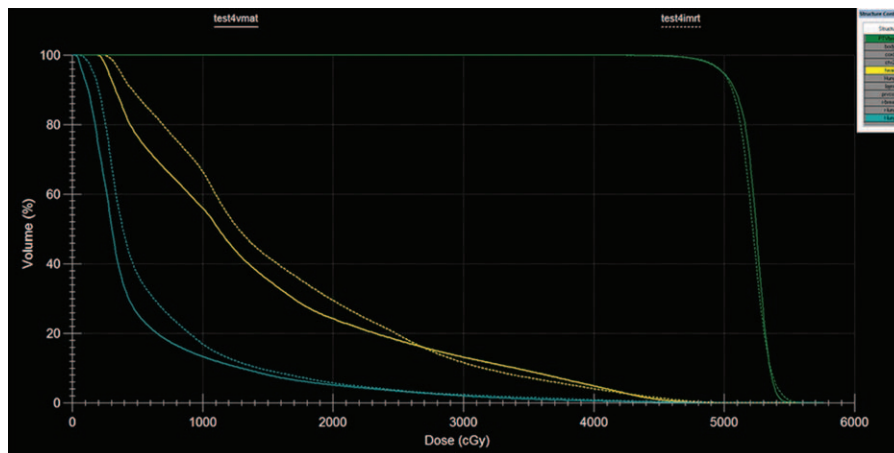


Figure 2. Comparison of VMAT and IMRT using a dose-volume histogram for the PTV, heart, and ipsilateral lung from 1 representative case. The VMAT plan is represented by the solid line, while the IMRT plan is shown as a dashed line. IMRT=intensity-modulated radiation therapy, PTV=planned target volume, VMAT=volumetric-modulated arc therapy.

Table 2
Coverage (mean ± SD) of the PTV.

PTV	IMRT	VMAT	P
D _{mean} Gy	51.75 ± 0.19	51.75 ± 0.19	0.636
D _{max} Gy	55.69 ± 0.87	55.42 ± 0.42	0.791
D ₉₅ Gy	49.48 ± 0.88	50.04 ± 0.20	0.226
HI	0.12 ± 0.027	0.09 ± 0.015	0.003
CI	91 ± 4%	95 ± 0.5%	0.004

CI=conformal index, D₉₅=the minimum dose received by 95% of the target volume, D_{max}=maximum dose of PTV, D_{mean}=mean dose of PTV, HI=homogeneity index, IMRT=intensity-modulated radiation therapy, PTV=planning target volume, SD=standard deviation, VMAT=volumetric-modulated arc therapy.

Several studies have demonstrated that BCS with postoperative WBI can achieve similar overall survival and reasonable cosmetic outcomes for early-stage breast cancer, when compared to radical mastectomy.^[13–15] Studies also showed that patients who received radiotherapy for breast cancer had an increased risk of developing nonbreast complications in the long term.^[16–18] In order to reduce late toxicities, some institutions developed WBI methodologies for prone positioning. Fernández-Lizarbe et al^[19] demonstrated that V₂₀ of the ipsilateral lung significantly decreased for prone versus supine positioning. Mulliez et al^[20] reported that when using tangent IMRT with prone positioning, V₂₀ of the ipsilateral lung could be reduced to less than 1%. However, few previous studies have focused on low-dose exposure of the lung (e.g., V₅ or V₁₀); such exposure has been recently determined as a significant predictor of radiation-induced pulmonary injury.^[21–24]

VMAT, a relatively new development in IMRT, has shown optimized dose distribution and efficacy for many kinds of cancers, such as head-and-neck, prostate, and rectal cancers.^[25–27] However, dosimetric studies have shown that VMAT failed to achieve favorable low-dose distributions in normal tissues (especially the lung) in WBI patients.^[28,29] In our study, we applied 2 symmetrical small arcs in the VMAT planning protocol, and combined it with a prone treatment

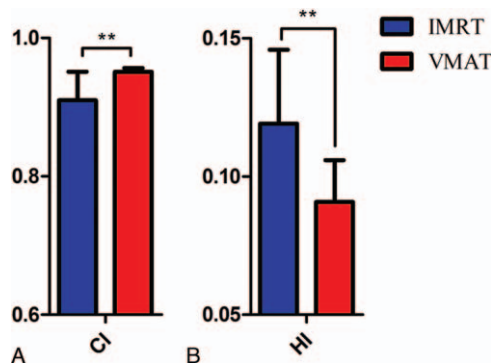


Figure 3. Comparison of VMAT and IMRT on CI and HI. (A) CI for VMAT was superior to that for IMRT: 95% ± 0.5% versus 91% ± 4% (P=0.004); (B) HI for VMAT was more favorable (lower) than that for IMRT: 0.09 ± 0.015 versus 0.12 ± 0.027 (P=0.003). Statistical analysis was performed using paired t tests. ** < 0.01; *** < 0.001. CI=conformal index, HI=homogeneity index, IMRT=intensity-modulated radiation therapy, PTV=planning target volume, VMAT=volumetric-modulated arc therapy.

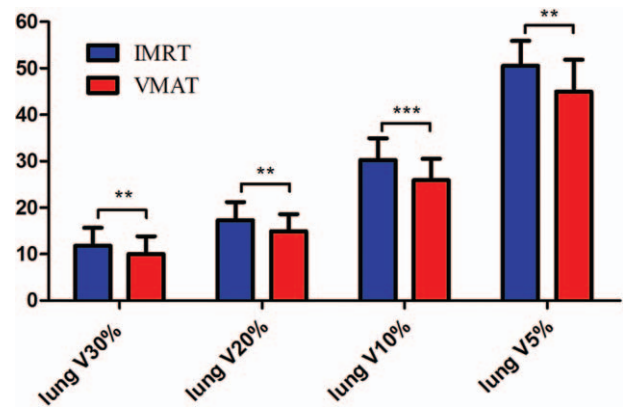


Figure 4. Comparison of VMAT and IMRT on ipsilateral-lung dose-volume parameters. The VMAT plan reduced V₃₀, V₂₀, V₁₀, and V₅ from 11.79% to 10.01% (P=0.007), 17.32% to 14.93% (P=0.001), 30.27% to 25.90% (P<0.001), and 50.58% to 44.96% (P=0.001), respectively. ** < 0.01; *** < 0.001. IMRT=intensity-modulated radiation therapy, VMAT=volumetric-modulated arc therapy.

position to improve target coverage while minimizing the amount of radiation passing through the thorax. We observed that our new VMAT method reduced not only V₂₀ for the ipsilateral lung, but also V₅ (50.58% vs 44.96%) and V₁₀ (30.27% vs 25.90%).

After lung injury, cardiovascular toxicities appear to be the most significant long-term adverse events of WBI, which could even offset the overall survival benefit of the postoperative irradiation, especially for left sided breast cancers.^[30,16] Exposure of the heart or left anterior descending coronary artery (LAD) was found to be strongly associated with the occurrence of cardiovascular disease; the incidence of major coronary events increased by 7% per Gy of heart of irradiation.^[31] As is the case for the lungs, protection of the heart and LAD can be improved by the use of prone positioning.^[32,33] It was recently reported that the prone position combined with the deep-inspiration breath-hold technique significantly reduced the mean heart and LAD dose to 1.3 ± 0.3 and 3.3 ± 1.8 Gy, respectively.^[34] Similarly, our results indicated a significant benefit in terms of heart protection, with D_{mean} being reduced from 10.01 ± 6.48 to 6.57 ± 3.35 Gy, V₁₀ from 36.32% ± 22.98% to 22.13% ± 15.64%, and V₅ from 57.73% ± 24.45% to 35.22% ± 20.18%.

Table 3
OAR dose evaluation (mean ± SD).

OAR	Parameter	IMRT	VMAT	P
ipsilateral lung	V ₃₀	11.79 ± 3.90%	10.01 ± 3.84%	0.007
	V ₂₀	17.32 ± 3.90%	14.93 ± 3.65%	0.001
	V ₁₀	30.27 ± 4.67%	25.90 ± 4.60%	<0.001
	V ₅	50.58 ± 5.31%	44.96 ± 6.91%	0.001
MLD	Gy	10.56 ± 1.82	9.61 ± 1.48	0.001
	Gy	10.01 ± 6.48	6.57 ± 3.35	0.046
Heart	V ₄₀	3.01 ± 2.56%	2.09 ± 2.05%	0.436
	V ₃₀	7.33 ± 5.53%	5.19 ± 4.57%	0.280
	V ₁₀	36.32 ± 22.98%	22.13 ± 15.64%	0.013
	V ₅	57.73 ± 24.45%	35.22 ± 20.18%	0.010
	Gy	10.01 ± 6.48	6.57 ± 3.35	0.046

IMRT=intensity-modulated radiation therapy, MHD=mean dose of heart, MLD=mean dose of ipsilateral lung, OAR=organ-at-risk, SD=standard deviation, V₃₀=percentage of the organ receiving 30 Gy, VMAT=volumetric-modulated arc therapy.

Previous studies found that patients with large or pendulous breasts were more likely to experience the clinical and cosmetic benefits of prone positioning than those with a low BMI or small breasts.^[19,35] Despite the fact that our study sample consisted of small-breasted Asian patients, we still achieved homogeneous target coverage and reduced OAR irradiation; however, our V_{20} , V_{10} , V_5 , mean lung dose, and mean heart dose did not decrease by as much as was reported by others.^[20–22] A possible explanation is that the mean breast volumes in our study were smaller than those of the European people in previous studies, and therefore the PTV did not drop away from the lung and heart to the same degree.

Owing to the widespread use of fixed-field IMRT, more MU were probably delivered to the normal tissue. Our results indicated that the MU were lower for our VMAT plan than for the IMRT plan, and that it provided the additional benefit of shorter treatment times. These improvements would likely decrease the risk of radiation-induced secondary cancers.^[36,37]

Considering the small sample size and the fact that not all were left sided breast cancers, we did not analyze the dose exposing to LAD to avoid evaluation bias. Another potential shortcoming was that we did not analyze late toxicities and long-term cosmetic outcomes, which would probably benefit from the optimized dosimetry. Thus, radiation-associated late toxicity and effects on the quality of life will need to be included in larger future studies.

In conclusion, our new small-arc VMAT methodology yielded superior target-volume coverage, dose conformity, and protection of normal tissue, when compared to fixed-field IMRT. Furthermore, it reduced treatment time and the number of MU required. It appears to be a more promising approach for WBI after BCS, and worth promoting for treatment for of early-stage breast cancer patients.

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