



Original paper

Dosimetric advantages afforded by a new irradiation technique, Dynamic WaveArc, used for accelerated partial breast irradiation

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ABSTRACT

Purpose: To identify dosimetric advantages of the novel Dynamic WaveArc (DWA) technique for accelerated partial breast irradiation (APBI), compared with non-coplanar three-dimensional conformal radiotherapy (nc3D-CRT) and coplanar tangential volumetric modulated arc therapy (tVMAT) with dual arcs of 45–65°.

Methods: Vero4DRT enables DWA by continuous gantry rotation and O-ring skewing with movement of the multi-leaf collimator. We compared the dose distributions of DWA, nc3D-CRT and tVMAT in 24 consecutive left-sided breast cancer patients treated with APBI (38.5 Gy in 10 fractions). The average doses and volumes to the planning target volume (PTV) and organs at risk, especially heart and left anterior descending artery (LAD) were compared among DWA, nc3D-CRT and tVMAT.

Results: The doses and volumes to the PTVs did not differ significantly among the three plans. For the DWA plans, the mean dose to the heart was 0.2 ± 0.1 Gy, less than those of the nc3D-CRT and tVMAT plans. The $D_{2\%}$ values of the planning organ at risk volume of the LAD were $9.3 \pm 10.9\%$, $28.2 \pm 31.9\%$ and $20.3 \pm 25.7\%$ for DWA, nc3D-CRT and tVMAT, respectively. The V_{20Gy} and V_{10Gy} of the ipsilateral lung for the DWA plans were also significantly lower.

Conclusions: DWA allowed to find a better compromise for OAR which overlapped with the PTV. Use of the DWA for APBI improved the dose distributions compared with those of nc3D-CRT and tVMAT.

1. Introduction

Breast-conserving therapy is well-accepted for early-stage breast cancer [1,2]. Accelerated partial breast irradiation (APBI) targets tissues surrounding the lumpectomy cavity and reduces the doses to the organs at risk (OARs); APBI is an option after breast-conserving surgery. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 performed a phase III randomized trial to evaluate the effectiveness of APBI compared with whole-breast irradiation (WBI) for early-stage breast cancer patients [3]. APBI can be delivered via several techniques, including brachytherapy [4–7], intraoperative radiotherapy [8–10] and external radiotherapy [11,12] using three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT). In addition, it was proposed to use

dedicated devices such as the Cyberknife (Accuray, Incorporated, Sunnyvale, CA) or the Vero4DRT (Mitsubishi Heavy Industries, Ltd., Japan and BrainLAB AG, Feldkirchen, Germany) [13–15].

Although the toxicities associated with breast irradiation are rather infrequent today, breast irradiation has been associated with cardiac toxicity [16–18], radiation pneumonitis [19,20] and poor cosmesis [21]. APBI planning studies have been conducted using several delivery techniques [22,23]. Among them, IMRT and VMAT spread the low-dose regions toward the heart, lungs and contralateral breast. Even low-dose irradiation can trigger secondary cancers in early-stage breast cancer patients [24,25]. To resolve this problem, Shaitelman et al. and Popescu et al. suggested a new irradiation technique: continuous arc rotation of the couch (C-ARC) or continuous couch and gantry dynamic arc therapy [26,27]. This technique maintains the benefits of standard tangent beam APBI performed using non-coplanar 3D-CRT (nc3D-CRT); the

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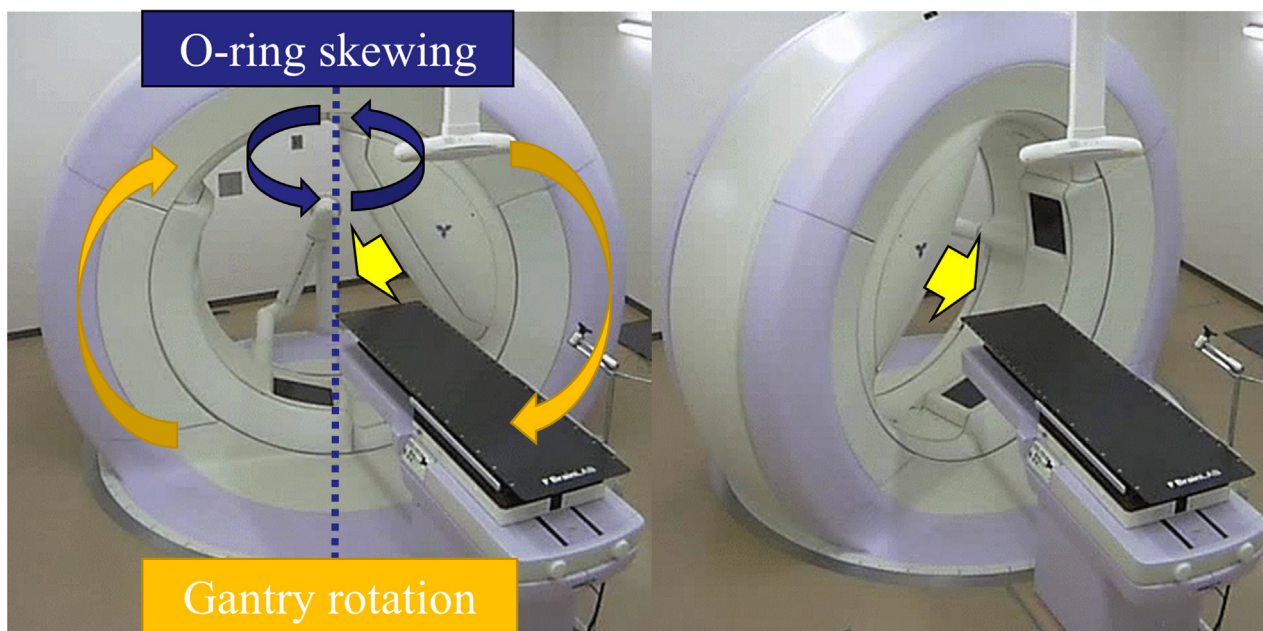


Fig. 1. The Vero4DRT has an X-ray head (arrow) that can rotate around the inner surface of the O-ring. The O-ring gantry can also skew around the vertical axis, enabling delivery of DWA therapy.

couch is rotated through one medial and one lateral arc. In addition, the technique reduces radiation doses to the OARs without compromising target coverage and is similar to VMAT. To put it simply, C-ARC exhibits the best features of both nc3D-CRT and VMAT. Although C-ARC is theoretically possible, C-ARC is seldom applied in practice, because most linear accelerator units do not possess the necessary capabilities. Moreover, C-ARC may be associated with setup errors caused by intra-fraction motion when dynamically rotating the couch.

Dynamic WaveArc (DWA) therapy is a new irradiation technique implemented in Vero4DRT [28]. The Vero4DRT has a unique feature of the O-ring gantry (Fig. 1). The gantry head can be rotated $\pm 180^\circ$ around the inner circumference. The O-ring can be rotated 360° around the isocenter and can be skewed $\pm 60^\circ$ around its vertical axis [29]. DWA therapy is a novel irradiation approach that represents the continuous and simultaneous rotation of both the gantry head and O-ring. The O-ring skewing replaces couch rotation; non-coplanar irradiation is performed effectively and safely. Our group developed a commissioning and quality assurance procedure for DWA [30,31]. The clinical application of DWA has been realized using RayStation for Vero4DRT [32]. We hypothesized that we could use Vero4DRT to create ideal irradiation for APBI.

In the present study, we adapted the novel DWA technique for APBI and generated two arcs of DWA trajectory to avoid direct beam entry into OARs, especially the heart. To explore dosimetric advantages afforded by DWA treatment, we compared the dose distributions of DWA, nc3D-CRT and coplanar tangential VMAT (tVMAT) with dual arcs of $45\text{--}65^\circ$. Furthermore, to verify that DWA could be delivered, we employed a three-dimensional diode array and measured the delivery time. To the best of our knowledge, this is the first attempt to perform APBI using DWA.

2. Materials and Methods

2.1. Patient population

From November 2011 to April 2016, 48 breast cancer patients were treated with APBI using nc3D-CRT in a single-institution clinical trial approved by our institutional review board. The eligible patients were women > 40 years with early-stage breast cancer (maximum diameter

3-cm) eligible for breast-conserving surgery; clipping of the surgical margin was required. In the present study, we examined the data from 24 consecutive left-sided breast cancer patients in terms of the irradiated volumes in the heart and coronary artery. The distances from the surface of the heart to the cavity were measured three dimensionally, and the closest distance was defined as the distance from the heart to the cavity. Table 1 lists the tumor locations and heart-to-cavity distances.

2.2. Contouring of target volumes and OARs

CT images (2.5-mm thick) were obtained from the mandible to the upper abdomen and transferred to the treatment planning system. The lumpectomy cavity was outlined, and the clinical target volume (CTV) was expanded by adding 1-cm margins. The planning target volume (PTV) was defined by adding 1-cm margins to the CTV. To evaluate dose coverage, PTV evaluation (PTV_EVAL) was performed, excluding 2-mm beneath the body surface.

The heart was contoured from the level at which the pulmonary trunk branched into the left and right pulmonary arteries [3]. The left anterior descending artery (LAD) was contoured using the University of

Table 1
Location of the tumors and distance from the heart to the cavity.

Patient	Quadrant of the breast	Distance from the heart (cm)	Patient	Quadrant of the breast	Distance from the heart (cm)
1	A	3.7	13	B	1.1
2	C	7	14	B	1.2
3	D	1.5	15	CD	2
4	A	4.6	16	B	1.5
5	A	4.5	17	A	4
6	A	6	18	A	5.1
7	C	4.3	19	BD	1.2
8	CD	1.2	20	AB	3.5
9	C	4	21	AC	4.8
10	CD	3	22	AC	5.5
11	C	5.6	23	C	6.4
12	CD	4.7	24	B	1

A: upper inner; B: lower inner; C: upper outer; D: lower outer.

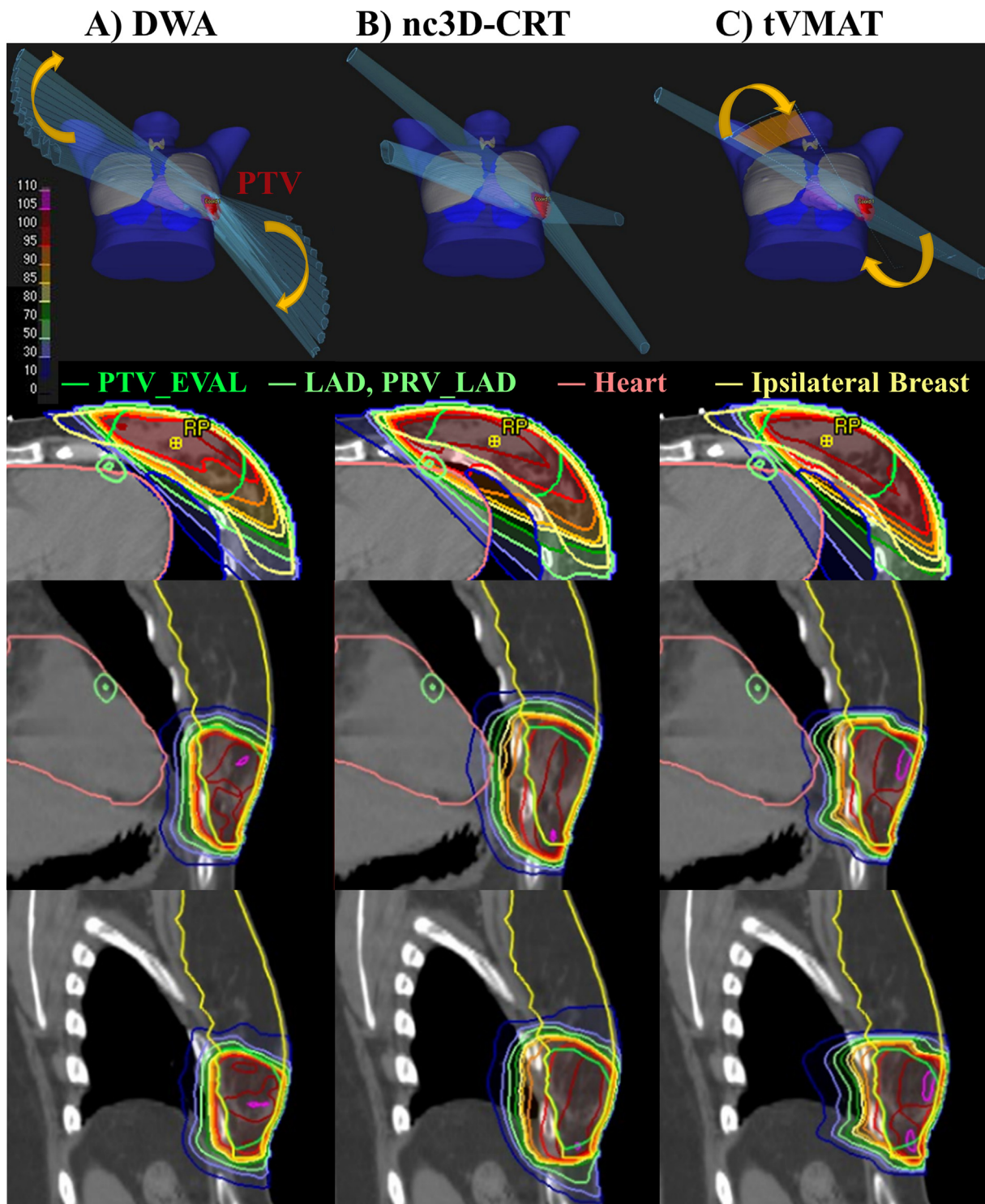


Fig. 2. Representative beam arrangements and an example of a dose distribution for the DWA, nc3D-CRT and tVMAT plans using a 3D patient model.

Michigan cardiac atlas, beginning from where the left coronary artery ran into the interventricular groove between the left and right ventricles [33]. The planning OAR volume of the LAD (PRV_LAD) included 5-mm margins. The other OARs, including the bilateral breasts, lungs, thyroid and skin were also contoured. The skin contour was created as a 2-mm layer within the body surface on the ipsilateral breast.

2.3. Treatment planning

The DWA, nc3D-CRT and tVMAT treatment plans were created by

RayStation version 4.7 (RaySearch Medical Laboratories AB, Stockholm, Sweden) running a collapsed-cone dose-calculation algorithm. Fig. 2 shows an example of the beam arrangements created. All plans used 6-MV photon beams from the Vero4DRT system. The prescribed dose was 38.5 Gy/10 fractions. In all plans, the lowest dose received by at least 50% of the PTV_EVAL volume ($D_{50\%}$) was set to 38.5 Gy. In the DWA and tVMAT plans, the $D_{90\%}$ and $D_{10\%}$ of the PTV_EVAL were restricted to within 2% of those of the 3D-CRT plans. The PTV definition resulted in an overlap of heart and PTV in several cases, however, the overlap volumes were very small. Optimization was

Table 2
Normal tissue dose constraints for APBI.

Structure	Index	Dose constraint
Ipsilateral Breast	D_{max}	< 120%
	$V_{50\%}$	< 60%
	$V_{100\%}$	< 35%
Contralateral Breast	D_{max}	< 3%
Ipsilateral Lung	$V_{30\%}$	< 15%
Contralateral Lung	$V_{5\%}$	< 15%
Heart (left breast cancer)	$V_{5\%}$	< 40%
Thyroid	D_{max}	< 3%

Abbreviations: D_{max} = maximal dose; $V^*_{\%}$ = percentage of the volume receiving *% or more.

performed for the PTV_EVAL to ensure that the OAR dose constraints were the same as those of the NSABP B-39/RTOG 0413 protocol (Table 2) [3]. A skin flash was not used during VMAT or DWA in the present study.

2.4. Non-coplanar 3D-CRT planning

The clinically applied nc3D-CRT plans comprised 4–6 non-coplanar beams using Vero4DRT. Basically, four beam angles were selected to avoid irradiating directly through the OARs. For all cases, the gantry angle was set within 110–155° and 290–355°, while the O-ring was set within 320–35°. Fields 5 and 6 were added using a field-in-field technique when it was necessary to reduce the high-dose area.

2.5. Coplanar tangential VMAT planning

The tVMAT treatment plans featured two arcs with Vero4DRT. The start and end beam angles were referred from those of the nc3D-CRT planning orientations. Thus, the beam angles were set within 110–155° and 290–355° for all cases. To deliver a coplanar beam, the O-ring was held static at 0°. The Vero4DRT multi-leaf collimator (MLC) and gantry speeds were optimized using RayStation for the Vero4DRT. The control point spacing was set as 4°.

2.6. DWA planning

DWA treatment plans were created by synchronizing the gantry ring rotation with that of the MLC [31]. The speeds of the gantry and O-ring can be controlled accurately; the gear transmission system is rigid,

maintaining system performance even during complex gantry ring movements. By effectively controlling gantry, O-ring and MLC motions, it is possible to create an intensity-modulated beam.

However, in the current version of RayStation, the available DWA trajectories are limited, because the treatment planning system supports only established templates that irradiate around the target. In the case of breast cancer, the beam irradiates the OARs directly. Consequently, the doses to adjacent OARs are rather high. To avoid direct beam entry into the OARs, we generated two arc trajectories by interpolating four nc3D-CRT beams.

Again, the current version of RayStation does not support optimization of flexible DWA trajectories. We thus simulated DWA plans based on static multi-fields; the actual deliveries were chosen via optimal interpolation of the original plans. First, we created two sets of 11 control points (at angles 315–35° to the ring angle and 110–155° and 290–355° to the gantry angle) for two non-coplanar DWA trajectories. Optimization was performed using the 22 control points as 22 multiple-field IMRT plans; that is, each IMRT beam had a single segment including the single monitor unit (MU) and MLC aperture information. The 22 multiple IMRT beams were optimized with a control spacing of 0–2° for the gantry angle and 3–8° for the ring angle. The beam weights of all fields were manually adjusted (without any significant effects on the dose distributions) to accommodate the mechanical limitations of the Vero4DRT system. Dose distribution of the 22 multiple IMRT beams was simulated in RayStation with a collapsed cone, and we assumed that the simulated dose distribution was comparable with that of DWA. Second, the DICOM-RT data of the original plans were converted to beam-delivery files using in-house software written in MATLAB (MathWorks Inc., Natick, MA, USA). MLC motions between control points were linearly interpolated using the VMAT algorithm [34]. MLC movements were limited by the machine constraints: gantry speed (0.1–6°/s), ring speed (0.1–2.5°/s), dose rate (150–400 MU/m) and MLC leaf speed (0.1–4 cm/s) [31]. It is possible to modify the dose rate with a general VMAT delivery; on the Vero4DRT, gantry speed and dose rate were constant per manipulation points where the direction of the ring rotation could change. All plans, thus created as beam-delivery files, were delivered using the maintenance mode of Vero4DRT.

By using our collision map software for Vero4DRT, we confirmed that no DWA or tVMAT plan had a collision risk (Fig. 3). When the positions of the isocenter and control points are entered, the corresponding collision map and control points are displayed on the map. If some control points were within the red or yellow zones, we confirmed that the nc3D-CRT plans were clinically irradiated without collision.

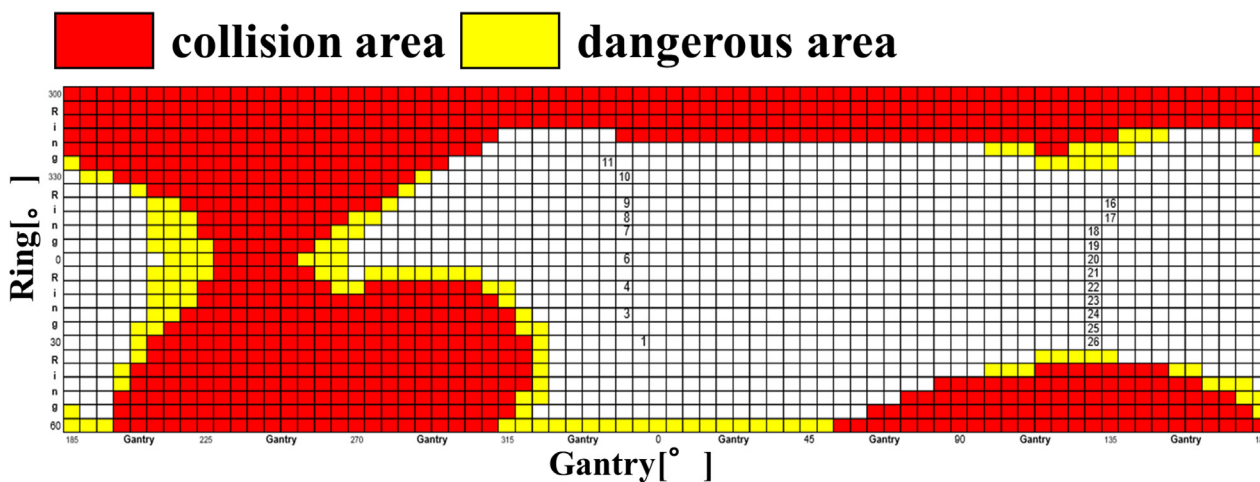


Fig. 3. A sample collision map for the Vero4DRT. When the position of the isocenter and those of the control points are entered, the collision map and the number of control points are displayed. The red zone is the collision area and the yellow zone the dangerous area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.7. Patient-specific dosimetric quality assurance

The dosimetric characteristics of VMAT and DWA were evaluated using the ArcCheck dosimeter (Sun Nuclear Corp., Melbourne, FL, USA), a cylindrical diode array with 1386 detectors spaced 10-mm apart. Gamma analysis was performed using SNC Patient software (Sun Nuclear Corp.); we compared the measured and calculated dose distributions of the DWA plans. The gamma analysis criterion of 3%/3-mm was used to assess patient-specific dosimetric quality assurance. The passing rates in regions inside the 5% isodose level were calculated using a global difference approach of the absolute dose.

2.8. Plan comparisons and statistical analysis

The average doses to specified volumes (e.g. $D_{90\%}$, $D_{10\%}$ and $D_{2\%}$) and volumes receiving a given dose (e.g. V_{20Gy} , V_{10Gy} and V_{5Gy}) of the PTV, bilateral breasts, lungs, heart, PRV_LAD, thyroid and skin were evaluated by DWA, nc3D-CRT and tVMAT. In accordance with ICRU Report 83, the maximum doses were replaced by the near-maximum ($D_{2\%}$) values [35].

Furthermore, the total MUs and delivery times were evaluated by DWA, nc3D-CRT and tVMAT. The machine treatment times were measured from the beginning to the end of irradiation, including the operator time. Differences in the dose distributions, MUs and delivery times between DWA and nc3D-CRT and between DWA and tVMAT were evaluated using the two-sided paired *t*-test. A *p* value < 0.05 was considered to reflect a significant difference.

3. Results

3.1. Target volume coverage and OAR doses

Fig. 4 shows the average dose-volume histograms (DVHs) for all 24 patients in terms of their PTVs and OARs. Table 3 summarizes the average dose volume indices for the targets and OARs and the MUs and treatment times for each technique. The three plans did not differ significantly in any PTV_EVAL parameter. The average mean doses (\pm standard deviation [SD]) to the heart were 0.2 ± 0.1 Gy, 0.5 ± 0.5 Gy and 0.5 ± 0.7 Gy for DWA, nc3D-CRT and tVMAT. The average $D_{2\%}$ values to the PRV_LAD were $9.3 \pm 10.9\%$, $28.2 \pm 31.9\%$ and $20.3 \pm 25.7\%$, respectively, thus significantly lower in the DWA plans. Table 1 shows that the tumor cavity of patient No. 24 was the closest to the heart. In that case, the mean doses to the heart were 0.4 Gy, 2.1 Gy and 1.2 Gy for DWA, nc3D-CRT and tVMAT, respectively. The $D_{2\%}$ values to the PRV_LAD were 20.7%, 97.6% and 47.2%, respectively. For the DWA, nc3D-CRT and tVMAT plans, the average $V_{50\%}$ values of the ipsilateral breast were $47.4 \pm 8.6\%$, $54.1 \pm 6.4\%$ and $50.9 \pm 7.8\%$, respectively. In comparison with the nc3D-CRT plans, the $V_{50\%}$ values of the DWA plans were significantly lower, but the $V_{100\%}$ values did not differ among the techniques. The average V_{20Gy} values of the ipsilateral lung were $0.7 \pm 1.2\%$, $3.5 \pm 2.0\%$ and $1.9 \pm 2.4\%$, and the V_{10Gy} values were $2.3 \pm 2.9\%$, $7.2 \pm 4.0\%$ and $5.9 \pm 5.0\%$ for DWA, nc3D-CRT and tVMAT, respectively. The average $D_{2\%}$ to the ipsilateral breast was significantly lower during DWA than during nc3D-CRT. The $D_{2\%}$ and mean dose of the contralateral breast and lung did not differ statistically among the three plans, except for the $D_{2\%}$ of the contralateral breast. The $D_{2\%}$ values of the contralateral breast were slightly lower for the DWA plans than the nc3D-CRT plans.

3.2. Total MUs and delivery times

The average (\pm SD) prescribed MUs were 486.2 ± 40.4 , 442.7 ± 22.0 and 467.6 ± 35.7 MU for the DWA, nc3D-CRT and tVMAT plans, respectively. The total MUs of the DWA plans were 9.8% higher than those of the nc3D-CRT plans, but the DWA and tVMAT plans did not differ significantly.

The mean (\pm SD) machine treatment times were 131.5 ± 10.5 s, 218.0 ± 23.7 s and 123.1 ± 8.6 s for the DWA, nc3D-CRT and tVMAT plans, respectively. The DWA treatment time was slightly longer than that of tVMAT but 40% less than that of nc3D-CRT.

3.3. Dose verification during DWA quality assurance

Using the gamma analysis criterion of 3%/3-mm, with a 5% threshold, the means \pm SD of the average passing rates were $94.8 \pm 3.0\%$ (range, 87.6–99.0%) and $94.8 \pm 3.0\%$ (range, 88.8–100%) for DWA and tVMAT, respectively.

4. Discussion

This novel DWA irradiation technique was proven to be effective and safe [30,31]. Our group has reported several planning studies and demonstrated dosimetric advantages afforded by DWA for pancreatic cancer, pituitary adenomas and craniopharyngiomas [29,36]. In the present study, we evaluated the dose distributions and treatment times of DWA for APBI and compared them with those of nc3D-CRT and tVMAT.

Qiu et al. reported an APBI planning study conducted using the currently available irradiation techniques IMRT and VMAT [23]. The VMAT plans reduce the doses to the OARs but increase the low-dose areas in the ipsilateral lung. We showed that the DWA plans for the Ver04DRT system significantly reduced the doses to the OARs without compromising target coverage and reduced the treatment time.

One of the advantages of APBI compared with WBI is the reduced dose to the heart, which is important for long-term breast cancer survivors [25,37]. Darby et al. reported that the rates of major coronary events increased linearly with the mean dose to the heart, by 7.4% per Gy [17]. Abdel-Qadir et al. suggested that the risks of death from breast cancer and cardiovascular causes in women ≥ 66 years of age at 10 years after treatment were 11.9% and 7.6%, respectively [16]. In those who survived for > 5 years after breast cancer diagnosis, cardiovascular disease supplanted breast cancer as the leading cause of death at 10 years after diagnosis. Moreover, among patients with prior cardiovascular disease, the risks of death from breast cancer and cardiovascular death were the same during the first 5 years after treatment, after which the risk of death from cardiovascular causes became more significant. Notably, DWA reduced the mean dose to the heart by 5%. Major et al. reported that the mean heart dose using multi-catheter interstitial brachytherapy was higher than that using IMRT (4.5% vs. 2.0%) [13,22]. Xu et al. reported that the $V_{5\%}$ of the heart volume using Cyberknife was higher than that using IMRT, as reported by Leonard et al. (range: 0–27.9% vs. 0–22%) [13,38]. In the present study, we observed that DWA, compared with IMRT and 3D-CRT, reduced the mean dose and $V_{5\%}$ to the heart, because the trajectory of DWA can avoid direct beam entry into the heart, thus reducing the risk of cardiac toxicity.

We also focused on the LAD. Feng et al. proposed that use of a cardiac atlas significantly improved contour accuracy [33]. Nilsson et al. reported that, in patients with irradiated left- versus right-sided breast cancer, the odds ratios for grades ≥ 3 stenosis in the LAD and distal diagonal branch were 4.38 and 7.22, respectively [18]. The LAD is a serial organ, and confining a high radiation dose to a small volume increases the risk of coronary stenosis. DWA afforded marked reductions in the $D_{2\%}$ and mean dose to the PRV_LAD compared with nc3D-CRT and tVMAT. Even if the mean doses to the heart differ only trivially, a lower dose to the LAD would be clinically meaningful, preventing cardiovascular disease in long-term breast cancer survivors.

Here, it should be noted that the positions of the heart and LAD relative to the PTV were an important factor for the treatment planning outcome. A large distance between the heart and PTV would result in a very low dose regardless of the technique. On the other hand, when the heart is close to the PTV, DWA can exert its potential because of the

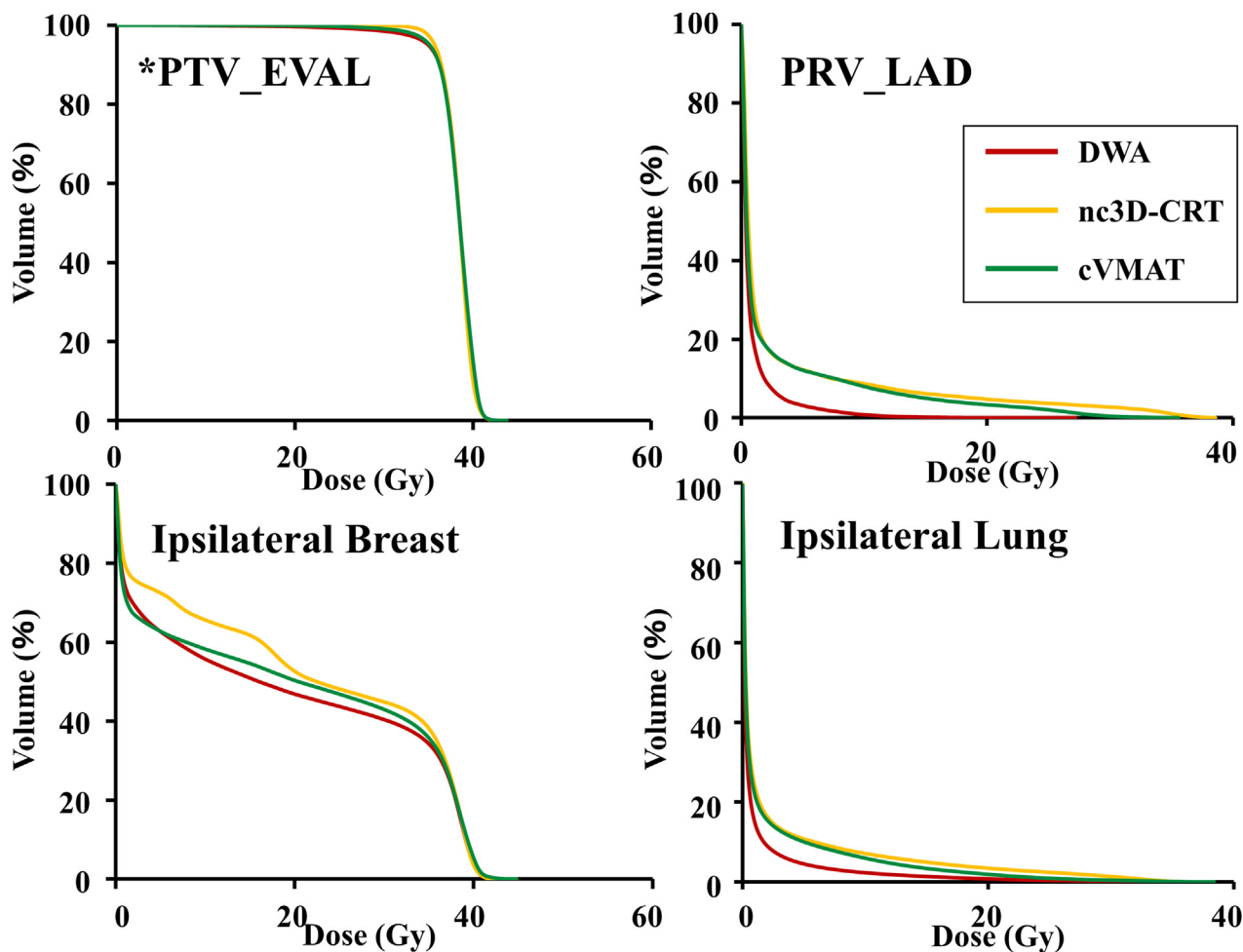


Fig. 4. Averaged dose-volume histograms for 24 patients treated using each technique for PTV_EVAL, ipsilateral breast, ipsilateral lung and PRV_LAD.

trajectories to avoid direct beam entry into OARs.

During DWA optimization, a reduction in the cardiac dose also reduced the dose to the ipsilateral lung. Recht et al. recommended that the ipsilateral lung $V_{20\text{Gy}}$ should be $< 3\%$, the $V_{10\text{Gy}} < 10\%$ and the $V_{5\text{Gy}} < 20\%$, when pure coplanar techniques are used for APBI [19]. Similarly, Shikama et al. reported that an ipsilateral lung $V_{10\text{Gy}}$ of $> 10\%$ might be associated with symptomatic radiation pneumonitis [20]. In our study, we found that DWA reduced the $V_{20\text{Gy}}$ and $V_{10\text{Gy}}$ of the ipsilateral lung by 2.8% and 4.9%, respectively, compared with nc3D-CRT. Thus, DWA may reduce the risk of radiation pneumonitis.

Jagsi et al. reported that the $V_{50\%}$ of the ipsilateral breast was lower in patients with acceptable cosmesis than in those with unacceptable cosmesis (34.6% vs. 46.1%); the $V_{100\%}$ was also lower in the former patients (15.5% vs. 23%) [21]. In our present study, the PTV_EVAL $D_{90\%}$ and $D_{10\%}$ were restricted much more severely than were the clinical doses. As a result, no plan met the dose limitation goals for acceptable cosmesis. If it were possible to limit the PTV_EVAL coverage to a clinically acceptable level, this would reduce the doses to the OARs including the ipsilateral breast.

Importantly, a skin flash was not used to account for movement of the breast during VMAT and DWA in this planning study. Considering the potential movement of the breast during treatment, an artificial bolus should be added to the skin surface clinically. Nicolini et al. implemented this skin flash method and achieved target coverage without under-dosing during treatment [27,39].

The Vero4DRT system has the potential to reduce the PTV margins because of improved registration accuracy using implanted surgical clips [14]. In addition, our group assessed the intrafractional internal

target motions in APBI [15]. From these findings, we were able to define appropriate margins to the target and reduce complications in normal tissue. Moreover, the dynamic tumor-tracking technique, which is a feature of the Vero4DRT or Cyberknife, may result in a smaller PTV margin [13]. DWA reduced the treatment time, which could offer the possibility to track the tumor without increasing the treatment time much higher than for conventional treatments.

We acknowledge that several limitations are apparent when applying the technique clinically. First, the current version of RayStation does not allow trajectories to be generated freely; only template trajectories can be used for DWA plans [32]. The existing DWA trajectory template for breast cancer cannot eliminate direct beam entry into the lungs and heart. We had to create new trajectories to reduce the dose to the OARs effectively. Second, the control point resolution of the ring angle was not integrated in the optimization process but was dependent on the ring rotation and control points of the gantry angle. Burghilea et al. also mentioned control point variation in the ring angle for DWA [31]. However, we confirmed that the delivered dose distribution showed good agreement with the simulated dose distribution for DWA. Thus, the dose approximation method for DWA in this study was sufficient to compare VMAT and 3D-CRT planning. Finally, our DWA plans were optimized as multi-field IMRT without reference to any limitation in MLC movement. If the RayStation could generate trajectories freely, the MLC movements would differ from those of our current plans, further optimizing the results. Once the software is modified to solve these problems, DWA plans may be made more easily and flexibly.

Table 3
Comparison of dosimetric parameters among DWA, nc3D-CRT and tVMAT.

	DWA	nc3D-CRT	tVMAT		
	mean ± SD	mean ± SD	p value (vs. DWA)	mean ± SD	p value (vs. DWA)
<i>*PTV_EVAL</i>					
D _{90%} [%]	94.2 ± 1.3	94.6 ± 0.9	0.2	94.0 ± 1.1	0.5
D _{10%} [%]	104.2 ± 0.9	104.0 ± 1.1	0.3	104.6 ± 0.7	0.08
D _{2%} [%]	106.1 ± 1.4	105.7 ± 1.6	0.3	106.4 ± 1.2	0.2
<i>Heart</i>					
V _{20Gy} [%]	0.01 ± 0.02	0.39 ± 0.97	0.08	0.30 ± 0.96	0.2
V _{10Gy} [%]	0.07 ± 0.16	0.91 ± 1.62	< 0.05	1.11 ± 2.75	< 0.05
V _{5Gy} [%]	0.2 ± 0.5	1.3 ± 2.1	< 0.05	2.2 ± 4.5	< 0.05
Mean dose [Gy]	0.2 ± 0.1	0.5 ± 0.5	< 0.05	0.5 ± 0.7	< 0.05
<i>PRV_LAD</i>					
D _{2%} [%]	9.3 ± 10.9	28.2 ± 31.9	< 0.05	20.3 ± 25.7	< 0.05
Mean dose [Gy]	0.9 ± 0.8	3.0 ± 4.1	< 0.05	2.4 ± 3.5	< 0.05
<i>Ipsilateral Breast</i>					
V _{100%} [%]	15.4 ± 3.4	16.5 ± 3.6	0.5	16.2 ± 3.4	0.2
V _{50%} [%]	47.4 ± 8.6	54.1 ± 6.4	< 0.05	50.9 ± 7.8	0.06
Mean dose [Gy]	18.9 ± 3.2	21.6 ± 2.5	< 0.05	19.7 ± 2.9	0.2
<i>Contralateral Breast</i>					
D _{2%} [%]	0.5 ± 0.3	0.6 ± 0.3	< 0.05	0.7 ± 0.4	0.1
Mean dose [Gy]	0.05 ± 0.03	0.06 ± 0.03	0.2	0.06 ± 0.03	0.2
<i>Ipsilateral Lung</i>					
V _{20Gy} [%]	0.7 ± 1.2	3.5 ± 2.0	< 0.05	1.9 ± 2.4	< 0.05
V _{10Gy} [%]	2.3 ± 2.9	7.2 ± 4.0	< 0.05	5.9 ± 5.0	< 0.05
V _{5Gy} [%]	4.5 ± 4.4	10.9 ± 5.6	< 0.05	10.0 ± 7.2	< 0.05
Mean dose [Gy]	1.0 ± 0.7	2.2 ± 1.0	< 0.05	1.8 ± 1.2	< 0.05
<i>Contralateral Lung</i>					
V _{5Gy} [%]	0.00 ± 0.01	0.00 ± 0.02	0.3	0.00 ± 0.01	0.3
Mean dose [Gy]	0.02 ± 0.01	0.03 ± 0.02	0.05	0.03 ± 0.02	0.3
<i>Thyroid</i>					
Mean dose [Gy]	0.02 ± 0.03	0.03 ± 0.04	0.3	0.02 ± 0.03	0.1
<i>Skin</i>					
D _{2%} [%]	0.96 ± 0.05	0.97 ± 0.03	0.3	0.95 ± 0.03	0.2
Mean dose [Gy]	15.0 ± 2.8	16.8 ± 2.4	< 0.05	15.2 ± 2.2	0.2
Monitor Unit	486.2 ± 40.4	442.7 ± 22.0	< 0.05	467.6 ± 35.7	0.07
Treatment Time [s]	131.5 ± 10.5	218.0 ± 23.7	< 0.05	123.1 ± 8.6	< 0.05

*PTV_EVAL = modified planning target volume.

Abbreviations: DWA = Dynamic WaveArc; 3D-CRT = three-dimensional conformal radiotherapy; VMAT = volumetric modulated arc therapy; SD = standard deviation; PRV = planning organ at risk volume; LAD = left anterior descending artery; D_{2%} = lowest dose received by at least 2% of the volume; V_{2%} = percentage of the volume receiving at least 2% of the volume; V_{5Gy} = percentage of the volume receiving 5Gy or more.

5. Conclusions

The use of DWA for APBI reduced irradiation to the OARs, especially the heart and LAD, without compromising target coverage, compared with nc3D-CRT and tVMAT.

Conflict of interest

Kyoto University Hospital has a collaborative research agreement with Brainlab AG. T. Mizowaki received research funding from

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Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, and our Institutional Ethical Review Board approved the work (approval number R0470-1). Written informed consent was obtained from all patients.

References

- [1] Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–41.
- [2] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.
- [3] National Surgical Adjuvant Breast Bowel Project (NSABP)/Radiation Therapy Oncology Group (RTOG) NSABP protocol B-39/RTOG protocol 0413: A randomized Phase III study of conventional whole breast irradiation (WBI) versus partial breast irradiation (PBI) for women with Stage 0, I, or II Breast Cancer. Available at: <http://atc.wustl.edu/protocols/nsabp/b-39/0413.pdf> (accessed March 29, 2017).
- [4] Polgár C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:259–68.
- [5] Zourari K, Major T, Herein A, Peppas V, Polgar C, Papagiannis P. A retrospective dosimetric comparison of TG43 and a commercially available MBDCA for an APBI brachytherapy patient cohort. *Phys Med* 2015;31:669–76.
- [6] Cifter G, Chin J, Cifter F, Altundal Y, Sinha N, Sajo E, et al. Targeted radiotherapy enhancement during electronic brachytherapy of accelerated partial breast irradiation (APBI) using controlled release of gold nanoparticles. *Phys Med* 2015;31:1070–4.
- [7] Ouyang Z, Mainali MK, Sinha N, Strack G, Altundal Y, Hao Y, et al. Potential of using cerium oxide nanoparticles for protecting healthy tissue during accelerated partial breast irradiation (APBI). *Phys Med* 2016;32:631–5.
- [8] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013;14:1269–77.
- [9] Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383:603–13.
- [10] Petoukhova A, Russel I, Nijst-Brouwers J, van Wingerden K, van Egmond J, Jacobs D, et al. In vivo dosimetry with MOSFETs and GAFCHROMIC films during electron IORT for accelerated partial breast irradiation. *Phys Med* 2017;44:26–33.
- [11] Rodriguez N, Sanz X, Dengra J, Foro P, Membrive I, Reig A, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys* 2013;87:1051–7.
- [12] Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015;51:451–63.
- [13] Xu Q, Chen Y, Grimm J. Dosimetric investigation of accelerated partial breast irradiation (APBI) using CyberKnife. *Med Phys* 2012;39:6621–8.
- [14] Inoue M, Yoshimura M, Sato S, Nakamura M, Yamada M, Hirata K, et al. Improvement of registration accuracy in accelerated partial breast irradiation using the point-based rigid-body registration algorithm for patients with implanted fiducial markers. *Med Phys* 2015;42:1904–10.
- [15] Hirata K, Yoshimura M, Mukumoto N, Nakamura M, Inoue M, Sasaki M, et al. Three-dimensional intrafractional internal target motions in accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. *Radiother Oncol* 2017;122:118–23.
- [16] Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol* 2016;2:88–93.
- [17] Darby S, Ewertz M, McGale P, Bennet A, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98.

- [18] Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjogren I, Lagerqvist B, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012;30:380–6.
- [19] Recht A, Ancukiewicz M, Alm El-Din MA, Lu XQ, Martin C, Berman SM, et al. Lung dose-volume parameters and the risk of pneumonitis for patients treated with accelerated partial-breast irradiation using three-dimensional conformal radiotherapy. *J Clin Oncol* 2009;27:3887–93.
- [20] Shikama N, Kumazaki YU, Miyazawa K, Miyaura K, Kato S, Nakamura N, et al. Symptomatic radiation pneumonitis after accelerated partial breast irradiation using three-dimensional conformal radiotherapy. *Anticancer Res* 2016;36:2475–9.
- [21] Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, Hayman JA, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys* 2010;76:71–8.
- [22] Major T, Stelczer G, Pesznyak C, Meszaros N, Polgar C. Multicatheter interstitial brachytherapy versus intensity modulated external beam therapy for accelerated partial breast irradiation: a comparative treatment planning study with respect to dosimetry of organs at risk. *Radiother Oncol* 2017;122:17–23.
- [23] Qiu JJ, Chang Z, Horton JK, Wu QR, Yoo S, Yin FF. Dosimetric comparison of 3D conformal, IMRT, and V-MAT techniques for accelerated partial-breast irradiation (APBI). *Med Dosim* 2014;39:152–8.
- [24] Grantzau T, Mellekjaer L, Overgaard J. Second primary cancers after adjuvant radiotherapy in early breast cancer patients: a national population based study under the Danish Breast Cancer Cooperative Group (DBCG). *Radiother Oncol* 2013;106:42–9.
- [25] Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: a systematic review and meta-analysis of population-based studies including 522,739 patients. *Radiother Oncol* 2016;121:402–13.
- [26] Shaitelman SF, Kim LH, Yan D, Martinez AA, Vicini FA, Grills IS. Continuous arc rotation of the couch therapy for the delivery of accelerated partial breast irradiation: a treatment planning analysis. *Int J Radiat Oncol Biol Phys* 2011;80:771–8.
- [27] Popescu C, Beckham W, Patenaude V, Olivetto AI, Vlachaki M. Simultaneous couch and gantry dynamic arc rotation (CG-Darc) in the treatment of breast cancer with accelerated partial breast irradiation (APBI): a feasibility study. *J Appl Clin Med Phys* 2013;14:161–75.
- [28] Mizowaki T, Takayama K, Nagano K, Miyabe Y, Matsuo Y, Kaneko S, et al. Feasibility evaluation of a new irradiation technique: three-dimensional unicursal irradiation with the Vero4DRT (MHI-TM2000). *J Radiat Res* 2013;54:330–6.
- [29] Kamino Y, Takayama K, Kokubo M, Narita Y, Hirai E, Kawawda N, et al. Development of a four-dimensional image-guided radiotherapy system with a gimbaled X-ray head. *Int J Radiat Oncol Biol Phys* 2006;66:271–8.
- [30] Sato S, Miyabe Y, Takahashi K, Yamada M, Nakamura M, Ishihara Y, et al. Commissioning and quality assurance of Dynamic WaveArc irradiation. *J Appl Clin Med Phys* 2015;16:73–86.
- [31] Burghelma M, Verellen D, Poels K, Hung C, Nakamura M, Dhont J, et al. Initial characterization, dosimetric benchmark and performance validation of Dynamic Wave Arc. *Radiat Oncol* 2016;11:63.
- [32] Burghelma M, Verellen D, Dhont J, Hung C, Gevaert T, Van den Begin R, et al. Treating patients with Dynamic Wave Arc: first clinical experience. *Radiother Oncol* 2017;122:347–51.
- [33] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 2011;79:10–8.
- [34] Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. *Med Phys* 2008;35:310–7.
- [35] ICRU. International Commission on Radiation Units and Measurements. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU Report 83. *J ICRU* 2010;10:1–106.
- [36] Uto M, Mizowaki T, Ogura K, Miyabe Y, Nakamura M, Mukumoto N, et al. Volumetric modulated Dynamic WaveArc therapy reduces the dose to the hippocampus in patients with pituitary adenomas and craniopharyngiomas. *Pract Radiat Oncol* 2017;7:382–7.
- [37] Marcu LG, Santos A, Bezak E. Risk of second primary cancer after breast cancer treatment. *Eur J Cancer Care* 2014;23:51–64.
- [38] Leonard C, Carter D, Kercher J, Howell K, Henkenberns P, Tallhamer M, et al. Prospective trial of accelerated partial breast intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;67:1291–8.
- [39] Nicolini G, Fogliata A, Clivio A, Vanetti E, Cozzi L. Planning strategies in volumetric modulated arc therapy for breast. *Med Phys* 2011;38:4025–31.