

# RapidArc radiotherapy for whole pelvic lymph node in cervical cancer with 6 and 15 MV: a treatment planning comparison with fixed field IMRT

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Dosimetric differences were investigated among single and dual arc RapidArc and fixed-field intensity-modulated radiotherapy (f-IMRT) treatment plans for whole pelvic irradiation of lymph nodes. A total of 12 patients who had undergone radical surgery for cervical cancer and who had demonstrated multiple pelvic lymph node metastases were treated with radiotherapy. For all 12 cases, 7-field IMRT, single-arc RapidArc and dual-arc RapidArc were applied with 6 MV and 15 MV X-ray energies. The radiation dosimetric parameters for the different plans were compared with one another. All the plans met the clinical requirements. The homogeneity, conformity and external volume indices of f-IMRT and dual-arc RapidArc were better than for single-arc RapidArc ( $P < 0.05$ ), while the differences between f-IMRT and dual-arc RapidArc were not significant. There were no significant differences in the radiation dose to organs at risk, except for the small bowel receiving  $>40$  Gy (f-IMRT and dual-arc  $<$  single-arc,  $P < 0.05$ ). The differences in dose distributions between the two applied X-ray energies for each of the modality plans were not significant. RapidArc plans resulted in fewer monitor units than the corresponding f-IMRT plans. Also, there were no differences between the two photon energies, except for a reduction in the number of MUs for 15 MV ( $P > 0.05$ ). Compared to f-IMRT, no significant dosimetric benefits were found using RapidArc for whole pelvic lymph node irradiation. However, RapidArc has been associated with shorter treatment time and fewer monitor units, supporting the case for its safety and efficacy for pelvic irradiation.

**Keywords:** RapidArc; intensity-modulated radiotherapy; dosimetry; cervical cancer; lymph node metastases

## INTRODUCTION

Cervical cancer is the most common gynecological malignancy and the second leading cause of cancer mortality in Chinese women [1, 2]. In patients who undergo radical surgery as their primary treatment, pelvic lymph node or para-aortic lymph node metastases are the most important prognostic factor for recurrence [3]. Thus, whole pelvic lymph node irradiation is commonly used in the treatment of early-stage cervical cancer after radical hysterectomy, due to its survival advantage [4, 5].

Pelvic lymph node regions lie adjacent to the major pelvic organs such as the small bowel, bladder and rectum. Due to the cup-shaped volume formed by the pelvic floor and iliac lymph nodes, most of the pelvis

contents are exposed to the prescribed radiation dose [6]. This leads to increased acute and late toxicities. Grade III radiation cystitis and proctitis are in the range of 3–15% after radiation alone and, in combination with chemotherapy, toxicity can be expected to be still higher [7, 8].

In the treatment of gynecologic malignancies, multiple studies have shown that intensity-modulated radiotherapy (IMRT) is dosimetrically superior in limiting the radiation delivered to normal tissue [9–11], and is associated with favorable clinical outcomes such as lower rates of gastrointestinal, genitourinary and hematologic toxicity after whole pelvic irradiation [12–14]. Optimizing IMRT plans may make further dose escalation possible without increasing normal tissue toxicities [15, 16].

Recently, intensity-modulated arc therapy technologies have been developed. These include helical TomoTherapy (Accuray, Sunnyvale, CA), volumetric-modulated arc therapy (VMAT; Elekta, Sweden, CA), and RapidArc (RA; Varian Medical Systems, Palo Alto, CA) radiotherapy. These new techniques have triggered interest in performing comparative planning studies for their application in the treatment of cervical cancer.

RA is a type of VMAT, and falls into the more general category of intensity-modulated arc therapy [17, 18]. It uses progressive variations of the instantaneous dose rate, multi-leaf collimator (MLC) positions, and gantry rotation speed to optimize dose distribution. It has potential dosimetric benefits and reduces the treatment delivery time while maintaining equivalent plan quality for prostate cases [19, 20].

With the increasing use of RA and other intensity-modulated radiation delivery techniques, comparisons among the various modalities have attracted the attention of the radiation oncology community. Ost *et al.* [20] reported that VMAT allowed dose escalation to intraprostatic lesions with better sparing of the rectum than fixed-field IMRT (f-IMRT). Cozzi *et al.* [21] concluded that, compared with f-IMRT, a RapidArc plan for cancer of the cervix uteri improved the sparing of organs at risk (OARs), such as the intestine and bladder, with uncompromised target coverage.

RA is considered an important technological advance. In this study, we conducted a dosimetric comparison of f-IMRT and novel RA techniques, because f-IMRT is now the treatment of choice for eligible patients treated at our Institution. The purpose of this study was to establish whether there is a dosimetric advantage in the RA plan over that of the f-IMRT plan, and to determine which is optimal for whole pelvic lymph node irradiation. Additionally, the benefits of 6 MV and 15 MV photon beams in these treatment plans were compared with one another.

## MATERIALS AND METHODS

### Patient selection and simulation

Twelve patients who had undergone radical hysterectomy for cervical cancer between February 2011 and November 2011 were enrolled in the study. Tumor stages were IA2–IIB, based on the guidelines of the International Federation of Gynecology and Obstetrics (FIGO 2009). All the enrolled patients had multiple pelvic node metastases, proved by computed tomography (CT) or magnetic resonance imaging, and were treated with whole pelvic lymph node irradiation. Patients who had CT-confirmed para-aortic node metastasis were excluded from the study.

The patients were scanned in the supine position using a Brilliance 16 CT simulator (Philips Medical Systems, Nederland B.V.) with a slice thickness of 3 mm. The

superior margin of the scan was located at the top of the fifth lumbar vertebra, and the inferior border of the obturator foramen was the inferior margin. The images were transferred to an Eclipse radiotherapy treatment planning system (Version 8.6, Varian Medical System, Palo Alto, CA) for contouring and planning.

The Institutional Review Board approved this study, and each patient gave informed consent.

### Contour of targets and OARs

All contouring was carried out by the same experienced gynecological radiation oncologist. The clinical target volume (CTV) was delineated according to the consensus guidelines of Taylor *et al.* [22]. The pelvic lymphatic vessels and lymph nodes were contoured on CT simulation images using the corresponding pelvic blood vessels as surrogate targets. The CTV consisted of internal, external and common iliac nodes. For patients with cervical stromal invasion, the presacral lymph node region was also contoured to the inferior border of the S2 vertebra. A margin of 0.7 cm was added to the vessel contours in all dimensions and modified by anatomic boundaries (as clinically indicated for individual patients) to create the nodal CTV, from which the pelvic bones, femoral heads, and vertebral bodies were excluded. The planning target volume (PTV) was the CTV plus a one-centimeter margin in all directions, based on the guidelines of the Radiation Therapy Oncology Group [23].

The OARs included the bladder, rectum, small bowel and pelvic bones. The superior and inferior extent of the OARs were outlined on all CT slices in which portions of the PTV existed, as well as an additional 2 cm superior and inferior to the limits of the PTV. The rectum was contoured from the rectosigmoid flexure to the anus. The small bowel was defined as all individual bowel loops, contoured together as one structure. The external contour of all pelvic bones was delineated to define the bone marrow. The pelvic bones consisted of the ilium, lower pelvis and lumbosacral spine. No expansion of the OARs was made to account for organ motion or set-up error.

### Treatment planning

The planning optimization objectives used as input for the inverse treatment planning process were: PTV minimal and maximal doses, 53.2 and 61.1 Gy, respectively; 95% of PTV 56 Gy; 35% of bowel 35 Gy; 40% of bladder 40 Gy; 60% of rectum 40 Gy; and 20% of bone marrow 20 Gy. In all cases, planning objectives were transposed into numerical dose–volume constraints used in the optimization phase and tailored to the specific patient characteristics. Priorities were adjusted during optimization to achieve the best results for each case.

For each patient, treatment plans were created using f-IMRT, one-arc RA and two-arc RA for delivery on a

Varian Trilogy accelerator. The f-IMRT plan was used in the actual treatment. For each delivery technique, plans were optimized separately for 6 MV and 15 MV photon beams. All plans were generated using a Varian Eclipse v8.6 treatment planning system. Dose calculation followed an anisotropic analytical algorithm (AAA). Dose distribution was performed with clinically acceptable accuracy (i.e. a resolution of 2.5 mm). The external radiation prescription dose delivered to the PTV was 56 Gy (2 Gy/fraction, 28 fractions). The 100% dose level was normalized to the mean PTV dose.

The f-IMRT gantry angles were 0°, 51°, 102°, 153°, 204°, 255° and 306°, with 20 intensity levels and a dose rate of 400 monitor units (MU)/min. Doses were delivered using the step-and-shoot method. Two RapidArc plans were generated for each patient. RA1 was one coplanar full arc of 358° (counter-clockwise from 179° to 181°) with a collimator angle of 45° during delivery. RA2 consisted of two coplanar full arcs set counter-clockwise 179° to 181° with a collimator angle of 30°, and clockwise 181° to 179° with a collimator angle of 330°. The highest dose rate was 600 MU/min, and the maximum gantry rotation velocity was 4.8°/s.

### Dosimetric comparison

The cumulative dose-volume histograms were generated by the Eclipse software for evaluation and comparison. The analysed dosimetric parameters included the homogeneity index (HI), conformity index (CI) and external volume index (EVI). The HI was defined as the ratio of the minimum dose in 5% of the PTV that received the highest dose (D5%), to the minimum dose in 95% of the PTV that received the highest dose (D95%), that is, D5%/D95%.

The CI is a measure of how well the prescribed dose conforms to the target volume. Since not all parts of the PTV are covered by the prescribed dose, the CI is calculated as a multiple of the cover factor (CF) and the spill factor (SF), or  $CI = CF \times SF$ , where the CF is the percentage of the PTV volume receiving  $\geq$  prescribed dose, and the SF is the volume of the PTV receiving  $\geq$  prescription dose relative to the total volume receiving the prescription dose. The closer the CI value is to one, the better the dose conformity.

The EVI is the ratio of the volume of normal tissue receiving  $\geq$  prescription dose, to the volume of the PTV. The closer the EVI value is to zero, the smaller the normal tissue volume receiving the prescription dose.

To quantify the dose distribution of the OARs, the percentage of the volume of the OARs receiving doses of >5, 10, 20, 30, or 40 Gy ( $V_5$ ,  $V_{10}$ ,  $V_{20}$ ,  $V_{30}$ , and  $V_{40}$ , respectively) were evaluated. Technical parameters of delivery of the three techniques, including total MUs, MLC apertures and treatment times (computed from the start of the first

field to the end of the last field), were compared with one another.

### Statistical analyses

To compare the results of the treatment plans, two-sided analysis of variance with a *post-hoc* test (Bonferroni's test) was used. A direct comparison of the dosimetric parameters between 6 MV and 15 MV was also performed using a two-tailed paired-sample *t*-test. *P*-values <0.05 were considered statistically significant. The analysis was performed using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, USA).

## RESULTS

Tables 1 and 2 are overview summaries of the PTV coverage and OAR dosimetric parameters with application of 6 MV or 15 MV photon beams, with the data given as the mean  $\pm$  standard deviation. No association was observed between the technique used and the photon energy ( $P > 0.05$ ). The f-IMRT showed a slightly improved target coverage compared to RA1 in terms of CI, HI and EVI ( $P < 0.05$ ), but was not better than RA2 ( $P > 0.05$ ). A pairwise comparison of the techniques indicated that f-IMRT and RA2 had significantly better target coverage than RA1 ( $P < 0.05$ ).

Typical dose distributions obtained with f-IMRT and RA are shown in Fig. 1. Doses to the OARs (rectum, bladder and bone marrow) with f-IMRT did not significantly differ from that with RA. However, f-IMRT slightly decreased the pelvic bone volume receiving <10 Gy compared with RA, although the decrease was not statistically significant. Additional efforts were made in the optimization process of RA1 to reduce the dose delivered to the small bowel. However,  $V_{40}$  in the small bowel was significantly lower when using the f-IMRT and RA2 plans ( $P < 0.05$ ). With RA1, the time to deliver a single arc was 75 s, i.e. significantly shorter than f-IMRT (Tables 1 and 2).

There were no statistically significant differences in dosimetric parameters between the 6 or 15 MV photon beam applications in any of the treatment plans, while there was a trend toward reduced MUs for 15 MV ( $P > 0.05$ ). The mean MUs were reduced by 10% with the 15 MV beam (Table 3). Compared with f-IMRT, RA needed fewer MUs ( $P < 0.05$ ).

## DISCUSSION

This study provides a dosimetric evaluation of f-IMRT and RA to assess optimal treatment planning for pelvic lymph node irradiation. Our results indicate that f-IMRT had better conformal PTV coverage and sparing of OARs than did RA. Dosimetric parameters in the RA2 plans were similar to the f-IMRT, whereas RA1 plans were slightly

**Table 1:** Comparison of treatment techniques for target structures and OARs when applying 6-MV X-rays

Variable	f-IMRT	RA1	RA2	P
PTV				
CI	0.92 ± 0.03	0.90 ± 0.03	0.93 ± 0.02	a,c
HI	1.07 ± 0.01	1.08 ± 0.01	1.07 ± 0.01	a,c
EVI	0.07 ± 0.04	0.08 ± 0.04	0.06 ± 0.03	a,c
Small bowel				
V <sub>10</sub>	85.0 ± 3.3	85.1 ± 4.3	84.7 ± 4.7	>0.05
V <sub>20</sub>	69.4 ± 5.6	68.9 ± 5.0	68.9 ± 7.3	>0.05
V <sub>30</sub>	41.5 ± 8.0	42.4 ± 3.2	45.6 ± 5.1	>0.05
V <sub>40</sub>	15.2 ± 3.9	21.0 ± 3.0	16.5 ± 2.3	a,c
Rectum				
V <sub>10</sub>	92.0 ± 16.0	91.7 ± 16.4	92.0 ± 16.2	>0.05
V <sub>20</sub>	87.3 ± 20.0	84.6 ± 20.7	84.5 ± 20.7	>0.05
V <sub>30</sub>	79.1 ± 24.6	75.9 ± 27.9	74.1 ± 29.6	>0.05
V <sub>40</sub>	47.9 ± 35.7	55.0 ± 33.2	46.1 ± 36.8	>0.05
Bladder				
V <sub>20</sub>	73.3 ± 45.2	72.6 ± 46.2	72.4 ± 45.7	>0.05
V <sub>30</sub>	59.3 ± 38.6	64.9 ± 43.9	66.1 ± 44.7	>0.05
V <sub>40</sub>	31.5 ± 23.0	46.2 ± 31.0	46.4 ± 32.8	>0.05
Pelvic bones				
V <sub>5</sub>	91.3 ± 7.7	93.6 ± 6.4	93.6 ± 6.4	>0.05
V <sub>10</sub>	87.0 ± 9.0	88.6 ± 9.3	89.1 ± 9.0	>0.05
V <sub>20</sub>	77.1 ± 9.2	76.9 ± 12.6	77.4 ± 11.1	>0.05
V <sub>30</sub>	55.6 ± 8.6	57.9 ± 10.5	57.9 ± 11.3	>0.05
V <sub>40</sub>	32.6 ± 6.2	35.2 ± 10.2	33.8 ± 10.2	>0.05
MUs				
6 MV	1658 ± 53	553 ± 40	578 ± 21	a,b
MLC apertures	726 ± 34	177 ± 0	354 ± 0	a,b,c
Treatment time (s)	625 ± 16	75 ± 0	170 ± 0	a,b,c

Statistically significant differences ( $P < 0.05$ ) determined via Bonferroni's test for three plans, <sup>a</sup>IMRT compared to RA1, <sup>b</sup>IMRT compared to RA2, <sup>c</sup>RA1 compared to RA2.

inferior. Similar results were observed by Yoo *et al.* [19]. However, this observation is not consistent with observations of Palma *et al.* [24] and Cozzi *et al.* [21], in which RA proved superior to f-IMRT with better dosimetric results. The major difference between the present study and others was the volume and shape of the PTV, and this may be the cause of the discrepancies. Because of the complexity of the target volume and its closeness to normal pelvic organs, the single arc (i.e. RA1) was not as good as expected.

We compared the number of MLC apertures (which represent the degree of modulation) to explain why f-IMRT

provides a higher-quality plan than the RA1. In this study, the f-IMRT plans consisted of 694 to 772 MLC apertures, while a full rotation arc consisted of 177 apertures, and two arcs had 354 apertures (i.e. one aperture per 2°). Consequently, using more MLC apertures will shape dose distributions to the tumor target volume better; f-IMRT and RA2 had better dosimetric results than RA1 for this complex PTV. Thus, increasing MLC aperture number is associated with better dose conformity and sparing of OARs. This may explain why f-IMRT provides a higher-quality plan than RA1 for whole pelvic irradiation of lymph nodes.

**Table 2:** Comparison of treatment techniques for target structures and OARs applying 15-MV X-rays

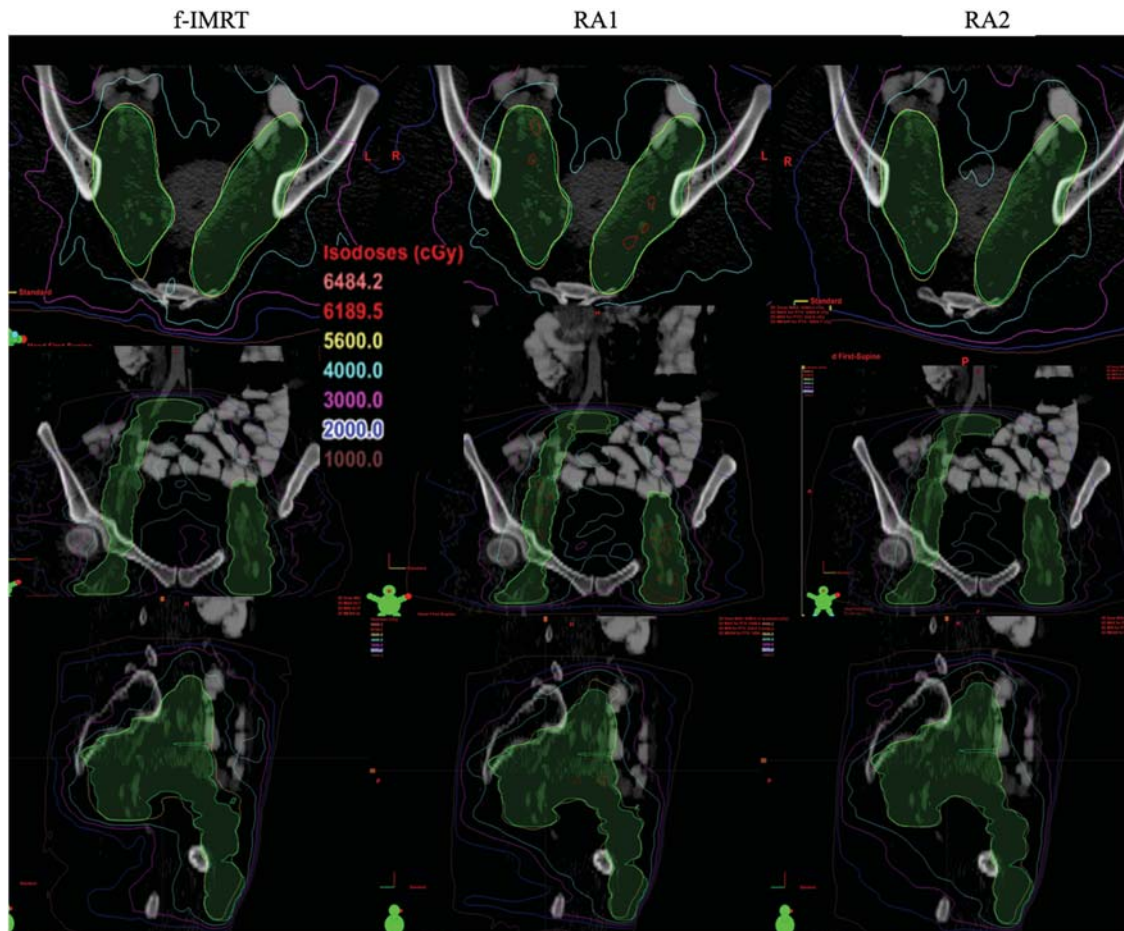
Variable	f-IMRT	RA1	RA2	P
PTV				
CI	0.93 ± 0.03	0.89 ± 0.04	0.93 ± 0.03	a,c
HI	1.05 ± 0.04	1.08 ± 0.02	1.07 ± 0.01	a,c
EVI	0.06 ± 0.37	0.09 ± 0.05	0.05 ± 0.03	a,c
Small bowel				
V <sub>10</sub>	85.7 ± 3.6	85.5 ± 3.5	84.4 ± 4.7	>0.05
V <sub>20</sub>	68.3 ± 5.5	68.6 ± 5.3	67.1 ± 7.3	>0.05
V <sub>30</sub>	40.8 ± 5.4	42.4 ± 3.9	44.4 ± 5.0	>0.05
V <sub>40</sub>	13.3 ± 1.3	18.7 ± 3.7	17.3 ± 3.0	>0.05
Rectum				
V <sub>10</sub>	91.8 ± 16.4	92.3 ± 15.5	92.3 ± 15.4	>0.05
V <sub>20</sub>	87.2 ± 20.2	84.5 ± 20.1	86.2 ± 20.0	>0.05
V <sub>30</sub>	79.0 ± 24.8	74.0 ± 30.1	75.3 ± 22.7	>0.05
V <sub>40</sub>	48.8 ± 32.6	57.3 ± 34.5	48.2 ± 32.6	>0.05
Bladder				
V <sub>20</sub>	73.4 ± 46.1	73.2 ± 46.2	72.8 ± 45.7	>0.05
V <sub>30</sub>	60.7 ± 39.8	66.7 ± 44.4	67.1 ± 44.6	>0.05
V <sub>40</sub>	28.6 ± 20.5	47.3 ± 31.9	49.5 ± 34.3	>0.05
Pelvic bones				
V <sub>5</sub>	90.7 ± 8.2	92.2 ± 7.3	92.1 ± 7.1	>0.05
V <sub>10</sub>	87.0 ± 9.2	88.3 ± 9.2	88.6 ± 9.4	>0.05
V <sub>20</sub>	75.9 ± 9.7	76.9 ± 11.2	76.0 ± 11.4	>0.05
V <sub>30</sub>	54.1 ± 9.6	55.9 ± 11.5	56.9 ± 11.7	>0.05
V <sub>40</sub>	31.0 ± 6.0	34.9 ± 10.9	34.3 ± 9.5	>0.05
MUs				
15 MV	1560 ± 57	455 ± 45	490 ± 20	a,b
MLC apertures	771 ± 60	177 ± 0	354 ± 0	a,b,c
Treatment time (s)	612 ± 14	75 ± 0	170 ± 0	a,b,c

Statistically significant differences ( $P < 0.05$ ) determined via Bonferroni's test for three plans, <sup>a</sup>IMRT compared to RA1, <sup>b</sup>IMRT compared to RA2, <sup>c</sup>RA1 compared to RA2.

A promising trend observed in previous studies has been a lower incidence rate of acute hematologic toxicity with whole pelvic IMRT, particularly in gynecologic patients treated with chemotherapy. Various dosimetric [9, 10, 25] studies have documented the benefit of bone marrow-sparing IMRT in pelvic irradiation, but very few outcome studies have used RapidArc. Most of the total body bone marrow reserve is located within the lower lumbar spine and pelvic bones, and whole pelvic IMRT has been reported to reduce the volume of pelvic bone marrow irradiated [26]. Brixey *et al.* [12] reported lower acute Grade 2

(or higher) hematologic toxicity in patients treated with IMRT compared with conventional RT techniques (31% compared with 60%). However, limiting the volume of marrow receiving 10 Gy to ≤90% could reduce the risk of myelotoxicity [25]. Our observations are that RA has no potential to lower the dose to the irradiated marrow volume to below that of IMRT.

The current challenges in pelvic IMRT for cervical cancer are set-up errors and organ motion, which are random and usually not evaluated prior to treatment delivery [27, 28]. However, surrounding organ status, motion of



**Figure 1:** Dose distributions on axial (top row), coronal (middle), and sagittal (bottom) views for one representative case. From left to right, plans using f-IMRT, RA1, and RA2. The green volume is PTV, and the thin lines are the isodose curves of marked levels.

the bladder and small bowel and rectal filling also affect the overall size of the PTV or margins. IMRT especially requires accurate target volume definition and margins because its greater conformity depends on quantifying organ motion and translating it into adequate margins [29]. Image-guided radiotherapy (IGRT) permits smaller margins and lower radiation exposure to nearby critical organs because of improved setup accuracy and reproducibility. In our department, we use cone-beam CT to verify the locale of the target before each treatment. All things considered, IMRT in conjunction with IGRT is likely to allow tighter PTV margins [30]. As for RA, the use of a 600 MU/min dose rate and the smallest fraction of gantry speed modulation results in the shortest treatment times; in the present study the mean time to deliver a single arc was 75 s. A short dose delivery time significantly benefits individual motion management in terms of improved comfort, reduced body and organ motion, and saves more treatment time for IGRT.

In this study, we compared 6- and 15-MV photon beams for each of the treatment techniques. No statistically significant differences were found between the two energy levels in regard to dose distribution, except for a reduction in the number of MUs for 15 MV. In addition, RA allowed a strong reduction of MUs compared to f-IMRT. This may explain why IMRT carries the risk of increased low-dose irradiation of normal tissue, which potentially increases the risk of second malignancies [23]. Our results are consistent with the data of Ost *et al.* [20] who found that high-energy photons had no advantage over low-energy photons in the treatment of prostate cancer. Moreover, high-energy photons could also lead to an increased risk of secondary malignancies owing to the presence of neutrons generated in the accelerator head at treatment energies  $>8$  MV [31, 32]. Therefore, 6-MV photons may be the prudent choice for pelvic radiotherapy.

In our study, no significant dosimetric benefits were found using RapidArc for whole pelvic lymph node

**Table 3:** Comparison of 6- and 15-MV photons for target structures and OARs

Target (Gy)	6 MV	15 MV	P
PTV			
CI	0.91 ± 0.03	0.91 ± 0.04	>0.05
HI	1.07 ± 0.01	1.07 ± 0.03	>0.05
EVI	0.07 ± 0.04	0.06 ± 0.04	>0.05
Small bowel			
V <sub>10</sub>	84.9 ± 3.7	85.2 ± 3.6	>0.05
V <sub>20</sub>	69.0 ± 5.5	68.0 ± 5.6	>0.05
V <sub>30</sub>	43.1 ± 5.6	42.5 ± 4.6	>0.05
V <sub>40</sub>	17.6 ± 3.8	16.4 ± 3.5	>0.05
Rectum			
V <sub>10</sub>	91.9 ± 14.7	92.1 ± 14.2	>0.05
V <sub>20</sub>	85.5 ± 18.6	86.0 ± 18.2	>0.05
V <sub>30</sub>	76.3 ± 24.9	76.1 ± 23.7	>0.05
V <sub>40</sub>	49.7 ± 32.1	51.4 ± 30.4	>0.05
Bladder			
V <sub>20</sub>	72.8 ± 41.3	73.1 ± 41.6	>0.05
V <sub>30</sub>	63.4 ± 38.6	64.8 ± 39.01	>0.05
V <sub>40</sub>	41.4 ± 27.4	41.8 ± 28.5	>0.05
Pelvic bones			
V <sub>5</sub>	92.9 ± 6.3	91.7 ± 6.9	>0.05
V <sub>10</sub>	88.2 ± 8.3	88.0 ± 8.4	>0.05
V <sub>20</sub>	77.1 ± 10.0	76.2 ± 9.8	>0.05
V <sub>30</sub>	57.1 ± 9.3	55.6 ± 10.0	>0.05
V <sub>40</sub>	33.8 ± 8.2	33.4 ± 8.4	>0.05
MUs	929.2 ± 539.2	835.3 ± 537.0	>0.05

irradiation compared to f-IMRT, however, our findings suggest that using RapidArc will have a favorable impact on treatment time and monitor units.

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