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ORIGINAL ARTICLE

Dosimetric Comparison of Static Field Intensity-Modulated Radiotherapy and Volumetric Modulated Arc Therapy for Adjuvant Treatment of Patients with Endometrial Cancer

Olgun ELİCİN,[1,2] Gülyüz ATKOVAR,[2] Şefika Arzu ERGEN,[2] Servet İPEK,[2] Songül KARACAM,[2] İsmet ŞAHİNLER[2]

[1]Department of Radiation Oncology, University of Bern, Bern University Hospital, Bern-*İsviçre*
[2]Department of Radiation Oncology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul-*Türkiye*

OBJECTIVE

The extent of previously published studies comparing static intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) in the adjuvant setting of endometrial cancer is limited and reports do not cover the whole landscape of today's clinical practice. The aim of this study was to compare these treatment techniques.

METHODS

Using 12 image sets, VMAT with double arcs and IMRT with 7 fields were planned. The femoral heads, rectum, bladder, iliac bone marrow, and bowels were contoured as organs at risk (OARs). Planned treatment volume (PTV) was prescribed to be 45 gray (Gy). Target and OAR parameters, conformity, and homogeneity indices were evaluated. P value under 0.05 was considered statistically significant.

RESULTS

Objectives for target volumes were achieved. No significant differences were found in conformity index, maximum dose (D_{max}), or integral dose. Homogeneity index was better with IMRT (1.06 vs. 1.07; $p<0.01$). Dose received by 2% volume of PTV ($D_{2\%}$), $D_{5\%}$, the volume receiving 107% of prescribed dose ($V_{107\%}$), and $V_{105\%}$ were lower with IMRT ($p<0.05$). PTV $D_{98\%}$, percent volume receiving ≥45 Gy ($V_{45\ Gy}$), and clinical target volume $V_{45\ Gy}$ were higher with VMAT ($p<0.05$). Regarding OARs, only rectum $V_{40\ Gy}$, rectum PTV $V_{40\ Gy}$, and dose volume parameter D_{2cc} were lower with VMAT ($p<0.05$). VMAT was superior with respect to monitor units and beam-on time per fraction: 465 vs. 1689 and 166 vs. 338 seconds, respectively ($p<0.001$).

CONCLUSION

Static IMRT is superior to VMAT regarding homogeneity, Dmax and OAR sparing, except for the rectum and the bladder. However, it is a marginal benefit with small differences. VMAT remains an attractive solution due to low number of monitor units needed and shorter treatment duration, which allows more time for patient imaging and positioning.

Keywords: Intensity-modulated radiotherapy; volumetric modulated arc therapy; endometrial cancer; radiotherapy; gynecological neoplasms.

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Dr. Şefika Arzu ERGEN
İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
İstanbul-Türkiye
E-mail: ergenarzu@yahoo.com

Introduction

Endometrial cancer is the most common gynecologic cancer in women between ages 55 and 85 in developed countries.[1,2] Only 5% of patients are younger than 40 years old.[2] According to actual guidelines, standard treatment consists of surgery±radiotherapy±chemotherapy in case of non-metastatic operable cases.[3] Technological advancements in radiotherapy made 3D conformal (3DCRT) and intensity modulated radiotherapy (IMRT) techniques available. The use of these new techniques allow sparing the organs at risk (OARs) situated in the proximity of target volume from ionizing radiation better, therefore reducing the acute and late toxicity.

Today, treatment of endometrial cancer in the postoperative setting is widely done with 3DCRT. Free contouring atlases for the delineation of OARs and target volumes are available online.[4–6] IMRT is reported to be even superior to 3DCRT regarding acute gastrointestinal and hematological toxicities.[7,8] A study performed with 36 mixed gynecologic cases showed less chronic gastrointestinal toxicity and complication rates with IMRT, and RTOG 0418 is the first published multicenter phase II study proving the feasibility of IMRT for this group of patients in routine practice.[9,10]

Volumetric Modulated Arc Therapy (VMAT) is an advanced form of IMRT where irradiation continues while the gantry is rotating around the patient. Studies including various gynecological malignancies showed dosimetric superiority of VMAT to static IMRT regarding OARs.[11,12] However the number of published studies and endometrial cancer cases included are limited. Moreover, the methods used and parameters evaluated do not match our standard clinical practice. Therefore we needed to compare static IMRT technique with double-arc VMAT on previously treated cases having only endometrial cancer in postoperative setting.

Materials and Methods

Patient selection criteria

Twelve previously treated early stage endometrial cancer cases who had previous post-operative pelvic external beam radiation without para-aortic treatment indication were selected for the analysis. The study was approved by the local Ethics Committee in accordance with the Helsinki Declaration. All patients had proper surgery in accordance with oncological principles without any residual mass, involved lymph node or positive surgical margin (no indication of external beam boost dose). Computerized Tomography (CT) images were acquired in supine position with 2.5 mm slice thickness using General Electric Lightspeed model CT simulator (General Electric Company, Easton Turnpike, US). All patients were scanned with empty rectum and full bladder. The cranial and caudal borders of the CT scan were the upper border of L3 vertebra and proximal third of femurs, respectively.

Treatment planning

CT images were transferred to Varian Eclipse software (version 8.6.15 - Varian Medical Systems, Palo Alto, CA – US). Contouring of the Clinical Target Volume (CTV) and organs at risk (OARs) were done by the same physician in accordance with RTOG atlases.[5,6] OARs included: rectum, iliac crests, small bowel, femoral heads and bladder. In addition to OARs, OAR minus Planning Treatment Volume (PTV) structures were also created. Iliac crests were delineated for assessment of dose to iliac bone marrow (BM) where contouring was done including the whole bony structure. Following dose constrains were used for planning: rectum $V_{40\ Gy}$ <50%, D_{max} <50 Gy; BM $V_{10\ Gy}$ <90%, $V_{20\ Gy}$ <75 Gy; small bowel $V_{45\ Gy}$ ≤200 cc, D_{max} <50 Gy; femoral heads D_{max} <50 Gy, $V_{40\ Gy}$ <40%, $V_{45\ Gy}$ <25%; bladder $V_{40\ Gy}$ <50%, D_{max} <50 Gy.

PTV was automatically created with 1 cm margin added to CTV. Dose prescription to PTV was set as 45 Gy in 25 fractions. No more than 0.03 cc in a confluent volume was allowed to receive more than 110% of prescribed dose. There was an exception in the vaginal cuff region where we set the upper limit to 115%. No more than 0.03 cc of PTV was allowed to receive less than 93% of the target dose. 6 MV photon energy was used. All static IMRT plans were made with 7 field arrangement and VMAT plans with double-arc.

For the standardization of integral dose calculation, external body contours were restricted to 3.5 cm above and below the PTV volume. PTV was subtracted from this cropped body contour. The resulting volume was used for integral dose calculation.

Planning optimization and dose calculations were done with Eclipse software (version 8.6.15). For both techniques, multi-leaf collimators (MLC) were used in dynamic mode. MLCs consist of 120 leaves which are 0.5 cm thick at the isocenter for the central 20 cm, and 1 cm in the outer 2x10 cm (maximum leaf speed 2.5 cm/s and leaf transmission of 1.6%; maximum gantry speed of 5.54°/s).

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Table 1 MU/fx, beam on time/fx, integral dose and global dose distribution

Parameter (unit or ratio*)	n	IMRT Mean±SD	VMAT Mean±SD	t	M	S	p
Conformity Index	12	1.08±0.04	1.09±0.04			19	0.151
Homogeneity Index	12	1.06±0.01	1.07±0.01	3.94			**0.002**
D_{max}	12	1.09±0.02	1.09±0.01			22	0.092
D_{max} (Gy)	12	49.14±0.74	49.43±0.59			22	0.092
Integral dose (Gy x cc)	10¥	329837±99295	328068±87985	-0.27			0.792
MU/fx	12	1689±341	465±38	-12.84			**<0.001**
Beam on time/fx (sec)	12	338±68	166±0.67		-6		**0.001**

t, M and S: Results of Student's t, Sign and Wilcoxon Signed-Rank tests, respectively; *: Parameters without a unit are ratios. ¥: Two patients had CT images with a cranial border of less than 3.5 cm above the PTV; D_{max}: maximum dose; fx: Fraction; VMAT: Volumetric modulated arc therapy; IMRT: Intensity modulated radiotherapy; MU: Monitor units; SD: Standard deviation.

IMRT

For the IMRT plans; 7 gantry angles were chosen (30°, 80°, 130°, 180°, 230°, 280°, 330°) using sliding window technique. Isocenter was the center of the PTV volume. Maximum dose rate was 300 MU/min. Dose constrains were defined for PTV, OARs and OAR-PTV volumes in accordance of priority, where rectum had the maximum priority among OARs. Body-PTV volume had also dose constrains in order to limit any hot spots. Anisotropic Analytical Algorithm (AAA) photon dose calculation algorithm was used for all plans. [13–15] The dose calculation grid was set to 2.5 mm.

VMAT

Same photon energy, isocenter point and dose constrains as for the IMRT were used for VMAT plans to achieve the optimal solution. Progressive Resolution Optimization (PRO) algorithm used for the optimization process calculates in 177 control points with 2° intervals. After the optimization dose calculation grid was set to 2.5 mm and AAA was used.

Two arcs with 181°–179° clockwise and 179°–181° counterclockwise rotations were used with maximum dose rate of 600 MU/min. To minimize the 'tongue and groove' effect 45° collimator angle was used.

Evaluation and statistical analysis

Evaluation of plans was done over standard dose-volume histograms (DVHs) and with examination of all slices. Homogeneity and conformity indices were calculated with the formulas proposed by RTOG: Homogeneity Index (HI)=[maximum isodose in the target]/[reference isodose], Conformity Index (CI)=[volume of reference isodose]/[target volume].[16] Normal distribution pattern of each parameter was measured with Saphiro-Wilk Test. Two-tailed paired Student's t Test was used for normally distributed data, and two-tailed non-parametric paired tests for the remaining (Wilcoxon Signed-Rank and Sign Test for symmetric and asymmetric distributed data, respectively). All statistical analysis were performed using JMP 9.0 (SAS Institute Inc. North Carolina, US). Two-sided p values under 0.05 were considered as statistically significant.

Results

Mean PTV volume was 1477±130 cc. Comparative results of IMRT and VMAT techniques are presented in Tables 1–3. Because of the abundance of normally distributed data, standard deviation was preferred to interquartile range in the tables. A retrospective analysis revealed that the study had 88% power to detect 1 Gy difference between two techniques for the OARs.

Target Coverage, Dose Distributions, MU and Beam-on-time (Tables 1, 2)

Between IMRT and VMAT, there was no significant difference in mean CI, D_{max} (global maximum dose), integral dose and PTV $V_{95\%}$ (volume receiving 95% of the prescribed dose) or CTV_{min} (minimum point dose CTV receives). Mean HI, PTV $D_{2\%}$ (highest dose covering 2% of PTV), PTV $D_{5\%}$, PTV $D_{98\%}$, PTV $V_{107\%}$, PTV $V_{105\%}$, PTV $V_{45\ Gy}$ (percent of volume receiving at least 45 Gy) and CTV $V_{45\ Gy}$ were significantly lower with IMRT. MU and beam-on-time per fraction were markedly lower with VMAT technique. It shall be also noted that each IMRT field setup required additional time (not measured).

Organs at Risk (Table 3) (Only results with p<0.05 are presented in Table 3)

Small bowel: Slight but statistically significant mean dif-

Table 2 Dosimetric comparison of target volume parameters

Parameter (unit or ratio*)	n	IMRT Mean±SD	VMAT Mean±SD	t	M	p
PTV $D_{2\%}$ (Gy)	12	47.7±0.42	48.35±0.52	3.94		**0.002**
PTV $D_{5\%}$ (Gy)	12	47.41±0.42	48.09±0.49	4.07		**0.002**
PTV $D_{98\%}$ (Gy)	12	44.49±0.34	44.74±0.3	2.71		**0.020**
PTV $V_{107\%}$	12	0.01±0.02	0.08±0.08		4	**0.039**
PTV $V_{105\%}$	12	0.13±0.14	0.40±0.25		5	**0.006**
PTV $V_{95\%}$	12	0.998±0.002	0.998±0.002		-3	0.146
PTV V_{45} Gy	12	0.96±0.01	0.97±0.01	3.34		**0.007**
CTV $_{minimum}$ (Gy)	12	43.98±0.71	44.48±0.28	2.03		0.068
CTV V_{45} Gy	12	0.99±0.01	0.999±0.002		4	**0.039**

t, and M: Results of Student's t and Sign Test, respectively; *: Parameters without a unit are ratios; CTV: Clinical treatment volume; $D_{x\%}$: Maximum dose covering x% of the volume; VMAT: Volumetric modulated arc therapy; IMRT: Intensity modulated radiotherapy; PTV: Planned treatment volume; SD: Standard deviation; $V_{x\%}$: Volume covered by at least x% of the dose; $V_{x\ Gy}$: Volume covered by at least x Gy isodose.

Table 3 Dosimetric comparison of OAR parameters (only significant values)

Parameter (unit or ratio*)	n	IMRT Mean±SD	VMAT Mean±SD	t	M	p
Bowel D_{max} (Gy)	12	48.35±0.85	49.09±0.60	3.16		**0.009**
Bowel $D_{2\%}$ (Gy)	12	46.27±1.31	46.94±1.62		4	**0.039**
Bowel D_{2cc} (Gy)	12	47.5±0.62	48.22±0.64	3.76		**0.003**
Bowel-PTV D_{2cc} (Gy)	12	45.67±0.06	46.48±1.53	2.76		**0.018**
Bowel-PTV $V_{45\ Gy}$ (cc)	12	8.01±9.07	25.87±21.22		5	**0.006**
BM $D_{2\%}$ (Gy)	12	46.93±0.3	47.45±0.47	3.21		**0.008**
BM $V_{10\ Gy}$	12	0.95±0.06	0.99±0.02		5	**0.006**
BM-PTV $D_{2\%}$ (Gy)	12	44.83±1.2	47.45±0.47	6.45		**<0.001**
BM-PTV $V_{10\ Gy}$	12	0.95±0.07	0.99±0.02		5	**0.006**
Rectum D_{max} (Gy)	12	47.79±0.54	48.45±0.58	2.96		**0.013**
Rectum $V_{40\ Gy}$	12	0.59±0.14	0.51±0.144	-3.4		**0.006**
Rectum-PTV D_{2cc} (Gy)	12	42.22±4.2	40.66±5.39		-4	**0.039**
Rectum-PTV $V_{40\ Gy}$	12	0.21±0.13	0.12±0.11		-6	**0.001**
Left femur D_{2cc} (Gy)	12	42.81±1.76	44.61±1.97	3.56		**0.004**
Left femur $D_{2\%}$ (Gy)	12	41.96±2	43.93±2.42	3.29		**0.007**
Left femur $V_{45\ Gy}$	12	0.006±0.008	0.02±0.02		5	**0.006**

t, and M: Results of Student's t and Sign tests, respectively; *: Parameters without a unit are ratios. D_{max}: Maximum dose; $D_{x\%}$: Maximum dose covering x% of the volume; $D_{x\ cc}$: Maximum dose covering x cc of the volume; OAR: Organ at risk; SD: Standard deviation; $V_{x\ Gy}$: Volume covered by at least x Gy isodose.

ferences were observed in small bowels D_{max}, $D_{2\%}$, D_{2cc} and in favor (lower) of IMRT. D_{2cc} and $V_{45\ Gy}$ of 'small bowel – PTV structures' were also lower with IMRT.

Iliac BM: D_{max}, $D_{2\%}$, D_{2cc} of BM and D_{2cc}, $V_{45\ Gy}$ of BM-PTV were significantly lower with IMRT

Bladder: No significance found in mean difference of parameters regarding bladder.

Rectum: Results related with the parameters of rectum were against the general trend. Only rectum D_{max} was lower with IMRT. On the contrary; rectum $V_{40\ Gy}$, rectum-PTV $V_{40\ Gy}$ and D_{2cc} were lower with VMAT, all reaching statistical significance.

Femoral heads: D_{2cc}, $D_{2\%}$ and $V_{45\ Gy}$ of only left femoral heads were significantly lower with IMRT. However there was also a trend towards statistical significance (p=0.079) in D_{2cc} and $D_{2\%}$ of the right side.

Discussion

In this study, 7-field static IMRT and double-arc VMAT techniques are compared using image sets of 12 previously treated patients having endometrial cancer in post-operative setting. Retrospectively, dosimetric and clinical superiority of IMRT to 3DCRT regarding small

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bowel, pelvic BM, bladder, rectum and femoral heads is already investigated and shown in gynecologic malignancies having indication for external pelvic radiation.[7–9,17–21] Likewise, dose coverage of PTV, integral doses, HI and CI were compared in these former studies.[12] All taken into consideration, it can be clearly stated that IMRT is superior to 3DCRT especially regarding toxicity and CI. Therefore we did not need to include the 3DCRT technique into consideration in our study. In phase II RTOG 0418 study it is reported that IMRT technique for endometrial cancer in post-operative setting is practically feasible and should be preferred with proper education and standardization.[10]

VMAT techniques were developed after implementation of IMRT. Over the past ten years they were compared to IMRT and 3DCRT, Wong et al., compared VMAT, IMRT and 3DCRT.[11,12] The study included 5 post-operative endometrial cancer cases, some of them treated with para-aortic volumes as well. The arc technique consisted of 30–300° and 60–330° gantry arrangements and the IMRT was delivered with 8 fields. There were no significant difference between IMRT and VMAT. Both of them were superior to 3DCRT regarding the small bowel and iliac BM doses. Unlike that, we used 7-field IMRT setup and did not restrict the angular arrangement of VMAT. With the use of static IMRT we observed significant reduction in doses to small bowel (D_{max}: 48.35 vs. 49.09 Gy, $D_{2\%}$: 46.27 vs. 46.94 Gy, D_{2cc}: 47.5 vs. 48.22 Gy, V_{45}: 180.97 vs. 219.31 cc) and iliac BM ($D_{2\%}$: 46.93 vs. 47.45 Gy, $V_{10\ Gy}$: 95% vs. 99%) compared to VMAT. In our study, formula defined by RTOG was used for HI calculation (maximum isodose volume/reference isodose volume) and HI was better with static IMRT over VMAT (1.06 and 1.07, respectively). Wong et al., used a different formula (dose difference between $D_{5\%}$ and $D_{95\%}$ of PTV) and their results were in favor of IMRT against VMAT as well (7.5% dose difference vs. 11%, respectively).[11]

Cozzi et al., compared single-arc VMAT and IMRT in 8 cases with cervix cancer who were treated with chemo-radiation.[12] The prescription was 50.4 Gy in 28 fractions to PTV. Results were in favor of static IMRT both for CI and the doses to OAR. They reported significant reduction in $V_{40\ Gy}$ of small bowel and 'small bowel-PTV' with VMAT in contrast to our study which resulted with better D_{max}, $D_{2\%}$, D_{2cc} of small bowel and D_{2cc}, $V_{45\ Gy}$ of 'small bowel-PTV' with IMRT (Table 3). We could not find any difference in parameters of bladder whereas Cozzi et al., reported reduction in $D_{2\%}$ of 'bladder-PTV', $V_{40\ Gy}$ of bladder and 'bladder-PTV' with VMAT.[12] Both studies showed reduction in $V_{40\ Gy}$ of rectum, $V_{40\ Gy}$ and D_{2cc} of 'rectum-PTV' with VMAT (51% vs. 59%, 12% vs. 21% and 40.66 Gy vs. 42.22 Gy respectively in our study). Although there is a decrease in dose to femoral heads in our study, it does not have any clinical importance.

For the parameters of PTV, Cozzi et al., reported no difference in $D_{98\%}$ and $V_{95\%}$ between two techniques but a superiority of VMAT for in $D_{2\%}$.[12] In our study parameters representing maximal doses like $D_{2\%}$, $D_{5\%}$, $V_{107\%}$ and $V_{105\%}$ were lower with IMRT. On the other hand, with higher $D_{98\%}$, PTV $V_{45\ Gy}$, CTV $V_{45\ Gy}$ and CTVmin, VMAT was capable of delivering better dose coverage (Table 2). We think that the main underlying reason for this distinction is the difference of PTV and anatomy between cervical and post-operative endometrial cancers. Additionally, it should be noted that Cozzi et al., did not define the pelvic BM as OAR and used another formula than RTOG for the calculation of CI and HI.

Yang et al., also compared 3DCRT, IMRT and a conformal double-arc technique on 10 cases with post-operative endometrial cancer.[22] They made plans with an optimization for 50 Gy to ≥95% of the PTV. Regarding OAR parameters, arc plans had better results than 3DCRT and worse results than IMRT plans. But the arc technique used in this study was a rotational conformal modality with neither inverse planning nor intensity modulation. Mean MU for 3DCRT, arc and IMRT was reported as 240, 451 and 877 MU, respectively. Our results for MU/fraction and 'beam on time' (IMRT/VMAT: 1688.58/465.5 MU and 337.72/166.42 seconds) are in concordance with the results of Cozzi et al., showing a marked advantage of VMAT.[12] Risk of secondary malignancy due to higher MU of IMRT versus slightly higher toxicity risk with VMAT (except for rectum) is an issue open to discussion.

A recent dosimetric study by Sharfo et al., compared different IMRT and VMAT strategies on 10 cervix cancer patients using automated in-house planning software.[23] The planning goal was to achieve highly conformal plans while sparing the OARs with a higher priority for the small bowel. The treatment delivery time was shorter with VMAT, but with IMRT superior plan quality was observed. Although performed on cervix and not on endometrial cancer patients, for us the results of this original work have profound importance, since they depend on an unbiased fully automated software solution where modern techniques were compared. In their conclusions, the authors also emphasized the importance of the trade-off between the plan quality and treatment delivery.

Two articles were published comparing 3DCRT, static field IMRT and helical tomotherapy using planning CT data of 10 endometrial cancer patients.[24,25] An interval from 95% to 110% was used for target coverage optimization. Lian et al., reported the results of extended-field radiotherapy for stage IIIC patients.[24] Target coverage was identical in both IMRT and tomotherapy plans. No difference in integral dose between tomotherapy and IMRT was shown. Yang et al., reported statistically insignificant differences in conformity among IMRT and tomotherapy plans.[25] Tomotherapy had 3.3% higher integral dose to normal tissue than static field IMRT ($p<0.01$).

In the present study, we could reach most of our dosimetric targets. Regarding the parameters of OAR, the objectives for bladder and femoral heads were achieved. Both techniques failed to keep $V_{10\ Gy}$ of BM under 90%, but the $V_{20\ Gy}$ target was easily reached. However it is important to emphasize for this group of patients that no hematologic toxicity is observed in our clinical routine. It was an unrealistic objective trying to keep $V_{40\ Gy}$ of rectum under 35% because of the large intersection of PTV and rectum. For the same reason, it prohibited achieving dosimetric goals for small bowel except for the maximum dose constrain. We think that the main reason behind this problem is our choice of +1 cm margin around CTV to create PTV. This relatively large margin could be reduced with daily instead of weekly Cone Beam CT (CBCT). The choice between a smaller PTV margin with high body kV X-ray exposure due to daily CBCT versus a larger margin with lower exposure due to less frequent CBCT is beyond the scope of this study.[26]

Even there is statistically significant difference between two techniques, one may find it as clinically unimportant. Thus, we did not observe any difference in toxicity profile during or after the treatment with IMRT or VMAT for post-operative endometrial cancer patients in our clinic so far. Acute toxicity is limited with genitourinary and gastrointestinal toxicity never higher than RTOG grade 2. Because of shorter treatment times compared to static IMRT, VMAT allows more time for patient set-up, daily image guidance and provides better patient comfort. Shorter treatment times also restrict intrafractional organ movement.[27]

As limitations, our study contains 12 pairs of plans for matched comparison, and although unique for endometrial cancer, the findings we present are not surprising based on previously published data on cancers of uterine cervix and anal canal. We also want to emphasize that statistical correction of p value due to multiple hypothesis testing was performed neither in any of the previously published studies nor in our study. If we were to interpret our results with a strongly conservative Bonferroni correction, results with $p>0.0008$ should be discarded. This would leave only the differences in MU/fraction, beam on time and BM-PTV $D_{2\%}$ parameters as statistically significant.

Conclusions

In this dosimetric study, we could achieve our primary objectives with both techniques for the treatment volumes regarding HI, CI, target dose, hot and cold spots. Static IMRT plans had slightly but significantly better results for some OAR parameters except for rectum. On the other hand, VMAT plans were clearly superior regarding lower MU and less treatment time. In our opinion, as we evaluate all the parameters from a clinical and holistic point of view, static IMRT technique provides only a statistical and marginal dosimetric benefit against the advantages of VMAT. VMAT remains to be an attractive solution for the adjuvant external beam treatment of endometrial cancer.

Disclosure Statement

The authors declare no conflicts of interest.

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