



Research Article

Dosimetric Comparison of Adjuvant Pelvic Radiotherapy for Endometrial Cancer using Intensity-Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Helical Tomotherapy (HT)

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Abstract

Objectives: The purpose of the present study is to compare dosimetrically IMRT, VMAT, HT techniques in endometrium cancer adjuvant radiotherapy practice.

Methods: The 10 patients to whom we had applied Pelvic RT due to endometrium cancer previously were selected retrospectively. All patients had received TAH+BSO+BPLND. Three different plans were made for the patients as IMRT, VMAT, and HT.

Results: The rectum V40 was found to be 53%, 54%, 45% ($p=0.002$), respectively; and the bladder V45 was 27%, 26%, 20% ($p=0.002$), respectively. Bowel V40 was found to be 15%, 17%, 12%, respectively ($p<0.001$). Total monitor unit (MU) and beam-on times were found superior at VMAT (<0.001). Bone marrow V40 was found to be 27%, 26%, 33%, respectively ($p<0.001$).

Conclusion: It was found that the three techniques were suitable in terms of planning criteria and OARs. HI and CI were found to be superior at HT. In risky organs, in rectum, bowel and bladder, HT was found to be superior than the others; in terms of bone marrow, IMRT was found to be superior; and in terms of bone, VMAT was found to be superior. VMAT has the advantage of having short treatment time and low MU.

Keywords: Endometrial cancer, radiotherapy.

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Endometrial Cancer (EC) is the most common cancer of the female genital system in developed countries. The most common histopathologic type is adenocarcinoma.^[1] Surgical excision is accepted as the primary approach to treatment.^[2] However, in many Phase 3 studies, adjuvant Whole Pelvic Radiotherapy (WPRT) has been shown to contribute to pelvic control in the presence of various risk factors, including high grade tumor, lymphovascular invasion, deep myometrial invasion, and presence of histological types such as serous or clear cell carcinoma.^[3–5] There are

several modalities utilized for the application of adjuvant radiotherapy in patients with EC: 3-Dimensional Conformal Radiation Therapy (3DCRT), Intensity-Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Helical Tomotherapy (HT) techniques.

Intensity-Modulated Radiation Therapy (IMRT) is a technique that allows the application of high-dose radiotherapy to the target area, while protecting surrounding tissues. In recent years, this method has found increased use in gy-

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necologic cancers,^[6] as it has been shown to have very few side effects when compared with conventional techniques.^[7, 8] This advantage has been demonstrated by Mundt et al.^[9] who compared the IMRT and 4-Field Box techniques and found that IMRT had fewer acute and chronic gastrointestinal system (GIS) side effects while there were no differences between the techniques in regard to the genitourinary (GU) system. Additionally, the RTOG 0418 Study, which was the first multicenter Phase 2 study on this topic, has also reported the efficacy and safety of IMRT.^[10]

Volumetric modulated arc therapy is an improved form of IMRT and has gained increased use in gynecologic tumors, primarily due to its several advantages including better handling of dosage via gantry rotation, less total MU, and faster treatment.^[11]

Helical Tomotherapy is a novel method and arc-based application of IMRT. During the application of this technique, the gantry constantly rotates 360° at a fixed speed to apply RT. During Helical Treatment, while the Linac rotates constantly, the total 360° is divided into 51 projection angles and the MLC order changes during each projection. With the help of this rotational movement, it allows target dose conformity and reduced dosages on organs at risk (OAR).^[12]

The purpose of the present study was to compare the IMRT, VMAT and HT techniques used in the treatment of postoperative endometrium cancer in terms of dosimetry findings of Organ at Risk (OARs). We also aimed to evaluate PTV coverage, Conformity index and Homogeneity index with these methods.

Methods

Patient Selection

A total of 10 patients who had underwent Pelvic RT in the Tomotherapy device due to early-stage endometrium cancer, but did not receive Paraortic RT were selected retrospectively for the present study. All patients had undergone Total Abdominal Hysterectomy+Bilateral Salpingo-Oophorectomy+Bilateral Pelvic Lymph node Dissection/Sampling (TAH+BSO+BPLND) surgeries. None of the patients had residue mass, surgical margin positivity or involvement of lymph nodes. Tomotherapy plans and LINAC plans were made by separate medical physicists. The study was approved by local Ethics Committee in accordance with Helsinki Declaration. Patient characteristics are given in Table 1.

Simulation and Contouring of Targets and OARs

All patients were provided with 500 cc water to drink in the supine position 30 minutes before CT imaging was performed. All scheduled CT imaging studies were performed from the L3 vertebra level until 1/3 proximal of the femur

with and without contrast at 3 mm thickness. The images were sent to Velocity Contouring Station version 2.8.1 (Varian, USA).

The same physician performed all patients' contouring. Clinical Target Volume (CTV) and Organs at Risk (OARs) were contoured in line with the RTOG Map.^[13] OARs were determined on the basis of the Dose Constraints RTOG 0921 Study and were defined as follows: rectum, bladder, bowel bag, femoral heads, bone marrow and bones Table 2.^[14] Bone marrow and bones were contoured to include the entirety of the bone and bone marrows 2 cm below and above the PTV.

Treatment Planning

PTV was obtained by adding a 0.5 cm margin to the CTV. Prescription dose was determined as 45 Gy to be delivered in 25 fractions. The dose was prescribed to cover 95% of the PTV. Further dose definitions were as follows: A volume of 0.03 cc within any PTV should not receive >110% of the prescribed dose, No more than 0.03 cc in the PTV should receive <93% of prescribed dose, and a dose exceeding 110% of the prescribed dose for PTV was not allowed in any 0.03 cc volume outside of the PTV.

In VMAT and IMRT planning, the Varian Eclipse planning

Table 1. Patient characteristics

Age	Mean 64 (range 57-79)
BMI	Mean 34.6 kg/m ² (range 26.6-44.4)
Histology	
Adenocarcinoma	8
Serous carcinoma	1
Clear cell carcinoma	1
Grade	
1	2
2	4
3	4
FIGO Stage	
1A	2
1B	4
2	2
3	2

Table 2. Dose constrains

Structures	Dose Constraints
PTV	≥95% of PTV receiving 45 Gy
Rectum	≤60% of rectum receiving ≥40 Gy
Bladder	≤35% of bladder receiving ≥45 Gy
Bowel Bag	≤30% of bowel receiving ≥40 Gy
Femoral head	≤15% of femoral head receiving >35 Gy

system version 13.7 (Varian Medical Systems, Palo Alto, USA) was used; and in HT planning, the Tomotherapy Planning System (Hi-Art Tomotherapy, version 5.1.2, Accuray, Madison, WI, USA) was used. For IMRT and VMAT plans, the structures contoured in the Velocity Contouring Station were transferred to the Eclipse Planning System DICOM (Digital Imaging and Communication in Medicine) format.

In IMRT plans, 7 Coplanar Beams (0° - 51° - 102° - 153° - 204° - 255° - 306°), with 3° Collimator Angle and Sliding Window Technique were used. The Isocenter was determined as the midpoint of the PTV volume. Dose constrains were defined for PTV and OARs.

In both the IMRT and VMAT techniques, a 1 cm-thick shell was drawn 5 mm beyond PTV. Anisotropic Analytical Algorithm (AAA) photon dose calculation algorithm was used and the maximum dose rate was defined as 400 MU/min. The dose calculation grid was 2.5 mm.

In all VMAT plans, one dual arc 181° - 179° clockwise and 179° - 181° counterclockwise rotation were used. For all plans, the number of MLC apertures were 177, which were spaced every 2 degrees for one full arc. The PO (Photon Optimizer version 13.7) algorithm was used to optimize leaf position, dose rate and gantry speed. The maximum dose rate was set at 600 MU/min. Dose calculation grid was set to 2.5 mm and AAA was applied for final dose calculations. The collimator was rotated 30° and 330° to reduce overlapping tongue and groove effects.

In IMRT and VMAT techniques, a 120-leaf (central 20-cm of the field uses 0.5-cm-wide leaves, while the outer field uses 1-cm-wide leaves) dynamic multileaf collimator (MLC) was used. The maximum leaf speed was 2.5 cm/s.

For HT plans, a field width of 2.5 cm, pitch values of 0.287, modulation factor of 3 and a fine dose calculation grid was used. 6MV energy was used in all VMAT, IMRT and HT plans.

Evaluation Tools

Plan evaluation was performed by examining all slides one-by-one and by assessment of Dose Volume Histograms (DVHs).

The Homogeneity index (HI) was calculated as: $HI = D2 - D98 / Dp$. In this Formula D2 is the minimum dose applied to 2% of the target volume, D98 is the minimum dose applied to 98% of the target volume, and Dp is the prescribed dose. This is the most commonly used formula in the literature. Equation 1 shows that lower HI values cause a more homogeneous target dose distribution.^[15]

The Conformity index was calculated as: Conformity index $RTOG = VRI / TV$. (VRI: volume of the reference dose, and TV: target volume. A conformity index equal to 1 shows ideal dose coverage and high conformity.^[16]

Statistical Analysis

Analyses were performed using the Statistical Package for Social Science version 22.0 software (SPSS, Chicago, IL, USA). Data were summarized by mean \pm standard deviation (SD). The Shapiro-Wilk test was used to assess the normality of distribution. Normally-distributed data were analyzed by Repeated measures analysis of variance and post-hoc corrections were performed via the Bonferroni method. Data that did not show normal distribution were analyzed with the Friedman test and the Bonferroni adjusted pairwise comparison. In all analyses, significance level was considered to be the demonstration of a p-value lower or equal to 0.05.

Results

Mean PTV volume was 992 ± 110 cc. The PTV coverage was acceptable and prescribed dose covered 95% of the PTV for each of the 3 plans used in all 10 patients. The PTV coverage comparison is shown in Table 3. DVH is shown in Figure 1.

Table 3. PTV coverage comparison

Parameter	n	IMRT (Mean \pm SD)	VMAT (Mean \pm SD)	HT (Mean \pm SD)	p
Dmean (Gy)	10	46.04 \pm 0.013	46.21 \pm 0.016	45.71 \pm 0.016	<0.001
Dmax (Gy)	10	47.83 \pm 0.040	48.51 \pm 0.019	47.45 \pm 0.042	<0.001
Dmin (Gy)	10	42.32 \pm 1.22	41.82 \pm 0.47	40.10 \pm 0.84	0.002
Conformity Index	10	1.317 \pm 0.06	1.22 \pm 0.052	1.2 \pm 0.069	<0.001
Homogeneity Index	10	0.043 \pm 0.009	0.05 \pm 0.006	0.0395 \pm 0.006	<0.001
MU/fx	10	1949 \pm 223	442 \pm 45	6646 \pm 529	<0.001
Beam on time/fx (sc)	10	351 \pm 40	265.2 \pm 65	464.3 \pm 36	<0.001
PTV 95 (%)	10	99.5 \pm 1.3	99.9 \pm 0.006	99.7 \pm 0.1	0.001
PTV 100 (%)	10	96.7 \pm 1.2	94.8 \pm 0.85	95.2 \pm 0.3	0.002
PTV 105 (%)	10	0.88 \pm 2.2	2.98 \pm 3.03	0.02 \pm 0.04	0.01

IMRT: Intensity-Modulated Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy; HT: Helical Tomotherapy.

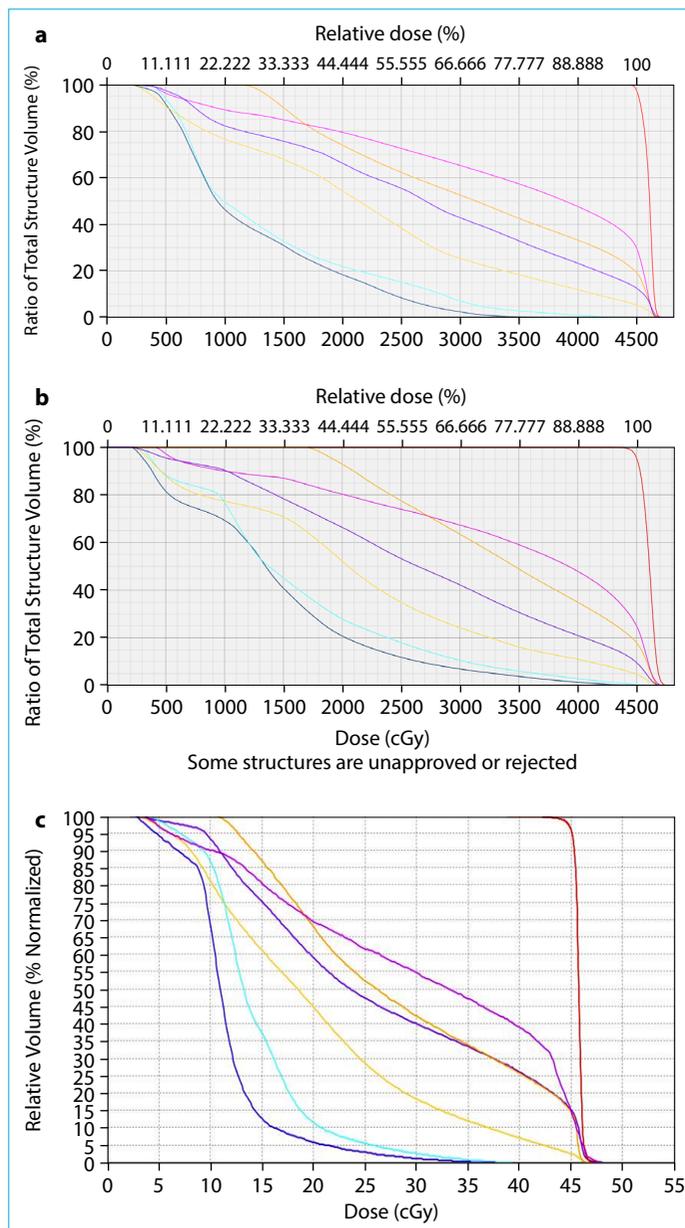


Figure 1. DVH of representative patient (a) IMRT, (b) VMAT, (c) HT. PTV (red), bladder (orange), bowel bag (yellow), right femoral head (blue), left femoral head (light blue), rectum (purple), pelvic bones (navy blue).

The Mean Dmean dose and Dmin dose were found to be lower in HT compared to the other methods. The Mean Dmax dose was found to be higher with the VMAT technique compared to the other methods. The Mean PTV95 (%) (the PTV volume including 95% of the prescribed dose) was lower than the others with the HT technique, while IMRT and VMAT values were similar. The PTV100 (%) in IMRT and the PTV105 (%) in VMAT, were found to be significantly higher than the corresponding values obtained with other techniques. The mean CI value was found to be higher with the IMRT technique, while Mean HI was found to be higher with the VMAT technique. Overall, HT was found to be su-

perior to the other methods in terms of HI and CI.

The Mean MU was found to be lower with the VMAT technique at a significant level. The Mean beam-on time per fraction in IMRT and VMAT were found to be significantly lower than the HT technique.

Rectum: The Mean Dmean, V20, V30, V40, V45 doses were found to be lower with the HT technique compared to the other methods, while V10 doses were found to be similar in all three methods.

Bowel: The Mean Dmean, V20, V30, V40 and V45 doses were found to be lower with HT, while V10 doses were found to be similar in all three methods.

Bladder: The Mean V45 doses were found to be lower with HT, the Dmean and V20 doses were lower with IMRT, and the V10, V30, V40 doses were found to be equal with all three methods.

Bone Marrow: The Mean V10 value was found to be at the lowest level with IMRT, V20 and V45 doses were lowest with VMAT (followed by IMRT), and the V30, V40, Dmean values were lower with HT.

Whole Bones: The Mean V10, V20, V30, V40, V45 values were found to be at the highest level with the HT method, while other techniques showed similar results. Only the Dmean values were found to be lower with the HT technique compared to the other techniques.

Right-Left Femoral Head: The VMAT Mean V30 and V35 values were found to be significantly higher than the other techniques. The Dmax dose was found to be at the lowest level with HT. The dose comparison of OARs are shown in Table 4.

Discussion

In this study, our purpose was to investigate the differences regarding PTV coverage, HI, CI values and OAR dose with the IMRT, HT and VMAT techniques in a group of 10 patients who had received postoperative radiotherapy after surgical treatment of EC. The HI and CI values obtained with the HT technique were found to be superior to the values obtained with IMRT and VMAT. Furthermore, OAR dose values were lower with the HT technique in the majority of comparisons.

In previous studies, the comparison of 3DCRT and IMRT have shown that IMRT technique is superior, both in terms of dose distribution and side effects.^[9] The RTOG 0418 Study was the first Phase 2 Study which utilized and assessed postoperative IMRT techniques in EC. Among the 43 patients included, 12 (28%) developed Grade ≥ 2 bowel adverse events; 9 of which were Grade 2, and 3 were Grade 3.^[10,17] The superiority of IMRT was also supported by Yang

Table 4. OARs comparison

	IMRT (Mean±SD)	VMAT (Mean±SD)	HT (Mean±SD)	p
Rectum				
V30	68.8±5.8	74.8±10	65±10	0.008
V40	52.9±5.4	54.1±5.5	45.3±7.7	0.002
V45	35.9±5.9	32.6±4.1	22.3±5.5	<0.001
Dmean	35.15±1.65	36.30±2.48	33.6±2.8	<0.001
Bladder				
V45	27.2±4.3	26.1±4.6	20.2±3.8	0.001
Dmean	34.54±1.99	36.74±2.54	35.1±3.6	0.024
Bowel				
V40	15.2± 8	17.7±9.4	12.2±6	<0.001
V45	7.7±5.1	7.9±5	4.2±3.4	<0.001
45 Gy (cc)	144.12±82.5	153.3±95.5	77.4±52.9	<0.001
Bone Marrow				
V10	80±3.5	87.5±3.4	96±2	<0.001
V40	27.4±4	26.2±3	33±3	<0.001
Dmean	27.99±11.6	28.14±9.8	30.5±0.8	<0.001
Whole Bones				
V45	12.4±2	10.6±1.2	14.4±2.7	0.002
Dmean	27.41±11.2	28.07±9.9	29.5±0.9	<0.001
Femoral Head (Right)				
V30	5.6±2.3	14.8±4.5	7.7±4.3	<0.001
V35	2.8±1.8	8.2±2.6	3.6±2.4	<0.001
Dmax	43.6±28.5	45.5±11.5	42.7±2.2	<0.001
Femoral Head (Left)				
V30	6.7±3.4	12.5±4.1	7.5±3.3	<0.001
V35	3.7±2.5	7.4±3.6	3.5±1.7	<0.001
Dmax	45.33±19.4	42.4±10.5	43±1.1	<0.001

IMRT: Intensity-Modulated Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy; HT: Helical Tomotherapy.

et al.,^[18] who found that the IMRT technique was superior to the 3DCRT technique in terms of dose conformity and dosage applied to normal tissue and OARs.

The VMAT technique has gained an increased frequency of use in recent years, which has led to various studies investigating its efficacy and safety compared to other methods. For instance, Wong et al.^[19] compared VMAT, IMRT and 3DCRT in 5 postoperative EC cases and reported that VMAT and IMRT had similar effects; whereas, both were reported to be superior to 3DCRT in terms of dosage applied to the small bowel and iliac bone. In the present study, 8-field IMRT and 300°-30° and 330°-60° angles were used.

In another study by Elicin et al.,^[20] the VMAT and Static Field IMRT techniques were compared. Static IMRT was found to be marginally better than VMAT in terms of homogeneity, and IMRT was also better in terms of OAR dose-sparing, except for the dose applied to the bladder and rectum. Rectum Dmax was found to be lower in IMRT, whereas rectum

V40, rectum-PTV, and D2cc values were found to be lower with VMAT. However, the VMAT technique was found to be vastly superior to IMRT in terms of monitor units and beam-on time. The authors concluded that, although Static Field IMRT had marginally better results in several comparisons, the advantages of the VMAT technique (lower MU and shorter treatment) make it an important treatment choice. In the current study, the HI was computed with a different formula and was found to be higher in the VMAT technique compared to the IMRT technique (0.05 vs 0.043); CI was computed according to the RTOG Protocol and found to be higher in IMRT than VMAT (1.3 vs 1.2). The Dmean was found to be similar in both techniques; however, Dmax was higher with VMAT. Furthermore, PTV100 (%) was found to be higher in IMRT (96.7 vs 94.8). In regard to dosage applied to OARs, bone marrow V20 and V45 doses were found to be lower with VMAT, while right-left femur V30 and V35 values were higher with VMAT compared to IMRT.

In a study conducted by Yang et al.,^[21] the SmartArc (VMAT-S), IMRT and HT techniques (with a total dose of 50 Gy that was applied in 25 fractions) were compared in 9 patients. The average MU values were found to be 823, 1105 and 8403, and the beam-on times were found to be 156, 516 and 570 seconds, respectively. In the current study, MU values were found to be 442, 1949 and 6646, respectively. However, the beam-on times were found to be 265, 351 and 464 seconds, respectively, indicating that VMAT beam-on time was shorter in the current study. Yang and colleagues also found HI values as 1.06, 1.10 and 1.07, respectively. Thus, VMAT was better than IMRT and similar to HT in terms of HI. No differences were determined in terms of CI. In our study, HI and CI were computed with a different formula, and HI values were found to be closer to 0 with HT (0.05, 0.04, 0.03, respectively); and CI values were found to be closer to 1 with the VMAT and HT techniques compared to the IMRT technique (VMAT CI: 1.22, HT CI: 1.2, and IMRT CI: 1.3). In the above mentioned study, the rectum, bladder and pelvis bone V40 doses were found to be reduced with the VMAT technique compared to IMRT. In our study, HT was found to apply a lower dose than the other techniques in terms of rectum and bowel V40 doses, which are crucial advantages; however, whole bones V40 dose was found to be lower with VMAT. Lian et al.^[22] conducted a study in 10 patients with 3C Stage EC, and compared the dosimetric results of 3DCRT, IMRT and HT. The IMRT and HT techniques were found to be better than 3DCRT in terms of PTV coverage and dosage sustained by OARs. When IMRT was compared with HT, the two techniques were found to demonstrate similar PTV coverage; however, HT had the advantage of lower OAR dose and integral dose.

In this study, we investigated the dosimetric characteristics of 3 frequently used techniques for adjuvant radiotherapy in patients treated for EC. The majority of doses sustained by OARs in all 3 techniques were found to fulfill the RTOG 0921 and RTOG 0418 criteria. Although rectum V30 doses of $\leq 60\%$ were not achieved in the current study, the rectum V40 $\leq 60\%$ criterion was met by each of the three techniques used in this study. However, the V10 $\leq 90\%$ dose level required for the bone marrow were met by VMAT and IMRT, but not by the HT technique which was found to have lower dose values for the majority of OARs assessed in this study.

In the RTOG 0418 Study, it was reported that the median percentage volume of bone marrow receiving 10, 20, 30, and 40 Gy was 96%, 84%, 61%, and 37%, respectively. In cervix cancer cases, a V40 value of $>37\%$ and a median dose of >34.2 Gy was found to be significant in terms of

hematologic toxicity.^[17] In our study, the median volumes sustaining V40 dose with HT, IMRT and VMAT were found to be 34%, 27% and 26%, while median doses were 30.7, 28 and 28 Gy, respectively.

In the current study, the small bowel was not drawn separately and was contoured as the bowel bag (also referred to as the peritoneal cavity), as is the case in many prior studies. In the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) analysis, the recommended dose-volume constraints of bowel bag are V45 ≤ 195 cm³.^[23] In our study, this value was determined with the three techniques. V45 found 144, 153 and 77 cc for IMRT, VMAT and HT respectively. Additionally, considering the nature of radiotherapy treatment, it may be feasible to suggest that the positioning of the patient (supine vs. prone) may have a significant effect on bowel dose. However, Beriwal and colleagues conducted a study in which patients were treated in 2 different positions (prone and supine). Their results indicated that the two positions were similar in terms of dosimetry and toxicity.^[24]

The findings of our study show that the HT technique has crucial advantages in the application of RT to patients with EC, especially in terms of OAR doses, while providing similar (or marginally better) dose to the PTV. Therefore, we believe that the HT technique is a very interesting choice in the adjuvant RT treatment of patients who have undergone surgery for EC. However, it is also evident that the other techniques assessed in this study (IMRT and VMAT) do not demonstrate significant disadvantages and even have various advantages; thus, it is important to decide on the treatment approach based on various factors, including physician experience, specific disease characteristics, and, at a certain level, patient requests.

Conclusion

In our study, all 3 techniques compared were found to be suitable in terms of OARs and planning criteria. Since there is the characteristics of performing Cone Beam CT (CBCT) or MV CT before the treatment, IGRT is performed without problems. Our results show that HT is better in terms of dose levels sustained by the rectum, bladder and bowel which are important OARs. However, it is crucial to note that total MU and beam-on times were lower with the VMAT technique. In our routine clinical practice, the majority of such patients are treated via HT. However, patients who refuse to be placed in the RT device for extended periods of time, patients who have fear of entering enclosed places (the gantry), and patients who have high risk for hematological toxicity, may benefit from being treated with other techniques.

Disclosures

Ethics Committee Approval: The study was approved by local Ethics Committee in accordance with Helsinki Declaration.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – O.T.; Design – O.T.; Supervision – M.D.; Materials – M.S.S.; Data collection &/or processing – O.T.; Analysis and/or interpretation – O.T.; Literature search – O.T.; Writing – O.T.; Critical review – M.D.

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