



Dosimetric Comparison of Intensity-Modulated Radiotherapy and Volumetric Arc Therapy for Rectal Cancer

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OBJECTIVE

The aim of this study is dosimetric comparison of intensity modulated radiation therapy and volumetric arc therapy that are currently applied in the preoperative radiotherapy of locally advanced rectal cancer.

METHODS

Ten patients with locally advanced rectal cancer were recontoured according to defined protocol on computed tomography simulation that were previously scanned. Dosimetric comparison was done for each patients with 7 and 9 fields intensity modulated radiation therapy and volumetric arc therapy. Compared dosimetric parameters were determined as doses of organs at risk, the total duration of treatment, target coverage, conformity index, homogeneity index and the total monitor unit.

RESULTS

All plans provided comparable dosimetric parameters for target volumes. Arc plans demonstrated statistically significant benefit with lower doses on V15, Dmean of small bowel compared to intensity modulated radiation therapy. Arc plans were obviously superior relating to measured volumes of the whole body and plans with 7 field had the worst results. Besides the reduction in total treatment time by approximately 60% was achieved in arc plans.

CONCLUSION

Volumetric arc therapy with short treatment duration and low monitor units can be considered as providing a more comfortable and qualified treatment.

Keywords: Intensity-modulated radiotherapy; preoperative chemoradiotherapy; rectal cancer; volumetric arc therapy.

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Introduction

Neoadjuvant chemoradiotherapy has become the standard therapy in order to obtain the desired results in patients with local advanced (T3/T4) and lymph node

involvement (Stage II-III) rectal cancer in terms of local control and cure. Many studies have shown the superiority of preoperative radiotherapy in reducing the risk of local recurrence and toxicity compared to postoperative radiotherapy.[1-3] However acute and

chronic intestinal toxicity caused by preoperative treatment are still the most important causes of morbidity.[4]

It has been known the relationship between specific dose-volume constraints and organ toxicity.[5,6] The small bowel is a radiosensitive organ, as acute radiation enteritis occurs in many patients undergoing radiotherapy for rectal cancer. Many studies showed that the incidence of both acute and late effects is directly related to the maximum dose and total volume of irradiated bowel.[7,8] Grade 3-4 acute toxicity was reported in up to 23% of patients treated with preoperative radiotherapy with concurrent chemotherapy, escalating to 37% with doses >50 Gy to the pelvis.[9,10]

Accordingly highly conformal radiation therapy planning and delivery techniques such as intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT), that allows for a reduction of high doses to organs at risk, without compromising target coverage, are being investigated. Therefore there are several studies comparing the inverse planning system with the different IMRT and VMAT techniques and the clinical implications of the results are still unclear.[11,12] Thus we aimed to compare the organ at risks (OARs) sparing without compromising the target coverage among 7 field, 9 field IMRT and double arc VMAT, prospectively.

Materials and Methods

A. Patients Group

Ten locally advanced rectal cancer patients (5 women and 5 men), have been treated with the indication of preoperative chemoradiotherapy/radiotherapy in our clinic between 2012-2015 years were observed. Median age was 55 (min 33-max 69). The tumor length varied between 2 and 10 cm, with median lengths of 6 cm. All patients had stage III (cT3N+) disease.

B. Monitoring, Target Volume Determination, Dose Prescription

All patients were stabilized in a prone position using a carbon-fiber belly board. The planning CT was scanned at slice thickness of 3 mm were transferred to the Eclipse 10.0 treatment planning system. PET-CT and/or MRI images recorded were matched using fusion algorithms to determine target volume. Treatment volumes were recalibrated according to The Radiation Therapy Oncology Group (RTOG) consensus of conformal contouring atlas for anorectal cancer published online in 2008.[13] Fullness or empty bladder was not implemented. The organs at risk were bladder, right and left femur heads and small bowel. The dose to the OARs was at least com-

ply with the following constraints: bladder >65 Gy in <50% volume; small bowel (peritoneal cavity) >45 Gy in <195cc volume; femur heads >40 Gy in <10 % volume.

C. Planning Techniques and Objectives

Planning target volumes (PTV1 and PTV2) were planned with the Eclipse 10.0 treatment planning system on the Trilogy linac and Millennium 120 MLC system using the simultaneous single boost method. The prescribed doses were 45 Gy to the PTV2 and 50.4 Gy simultaneous to the PTV1 in 25 fractions. Three plan were performed for each patient, including 7 field IMRT (IMRT7), 9 field IMRT (IMRT9) and double-arc VMAT (ARC). The maximum dose rate was optimized to 600 MU/min. 6 MV photons was used in all plans.

Plan optimization is defined as taking 100% of the prescription dose covered at least 95% of the PTV. The values of $D_{98\%}$ (Dose received by 98% of the PTV) and $D_{2\%}$ (Dose received by 2% of the PTV) for PTV were determined as the minimum and maximum doses (D_{mean} , D_{max}) according to the International Commission on Radiation Units and Measurements (ICRU 83). The conformity of the plans was evaluated with a conformity index (CI) defined as the ratio of the target volume receiving 95% of the prescribed dose divided by the total volume receiving that dose level. The homogeneity of the plans was measured in terms of the homogeneity index, which was expressed as $(D_{2\%} - D_{98\%})/D_{50\%}$. Eclipse system was not able to calculate the estimated treatment time per fraction. Therefore monitor units (MU) values were used in VMAT plans to compare treatment times ('beam on'). The duration of treatment was determined by the ratio of the total MU to the maximum dose rate (MU/dose rate). In IMRT plans, 'beam on' times were obtained from the system. Plan QA (Quality Assurance) was done for total treatment periods. Data were obtained using dose-volume histograms (DVHs). Anisotropic Analytical Algorithm (AAA version 10.0.028) was used as the planning algorithm and Dose Volume Optimizer (DVO version 10.0.028) was used for the optimization algorithm.

1. IMRT Plans

The IMRT plans were calculated with seven fixed gantry angles (0°, 52°, 104°, 154°, 208°, 260°, and 312°) and nine fixed gantry angles (0°, 41°, 82°, 123°, 164°, 205°, and 328°).

2. VMAT Plans

Each plan with double arc was consisted of two complete arcs set from 181° to 179° and from 179° to 181°

(clockwise and counterclockwise), respectively. The collimator angles were defined as 30° and 330° for all plans.

D. Organ at Risk

Organ at risk for each plan was evaluated with the following including; $V_{<12}$ (the volume receiving under 12 Gy), V_{15} , D_{min} , D_{max} for small bowel; V_{30} , V_{40} , D_{mean} for bladder; D_{15} , V_{30} , D_{max} , D_{mean} for each femoral heads; V_{10} , V_{20} , V_{30} , V_{40} for normal tissue which is excused PTV2 from whole body (NTV).

E. Statistical Analysis

All dosimetric results from different irradiation techniques were compared with each other. Repeated measures analysis of variance (ANOVA) was used in

comparison of plans. Bonferroni correction was used for post hoc analysis. Intraclass correlation coefficient (ICC) was used to determine the correlation between measurements. Results were considered statistically significant with $p < 0.05$.

Results

The statistical dosimetric evaluation and comparison of the three planning techniques were listed in Table 1.

Target Coverage and Dose Distribution

The mean volume of the PTV was 1452.9 ± 115.1 cc, the minimum was 286.9 cc and the maximum was 603.6 cc. For PTV1, IMRT9 achieved better homogeneity in-

Table 1 Dosimetric Results for PTV and OARs

| | IMRT7 | IMRT9 | ARC | IMRT7 vs IMRT9 | IMRT7 vs ARC | IMRT9 vs ARC |
|--|-------------|-------------|-------------|----------------|--------------|--------------|
| PTV1 Volume (cc): 452.9±115.1 (286.9-603.6) | | | | | | |
| $D_{2\%}$ (Gy) | 52.93±0.16 | 52.76±0.23 | 52.88±0.18 | n | n | n |
| $D_{98\%}$ (Gy) | 50.10±0.19 | 50.19±0.13 | 49.97±0.11 | 0.043* | n | 0.020* |
| D_{mean} (Gy) | 51.54±0.12 | 51.43±0.13 | 51.52±0.12 | n | 0.002** | n |
| $V_{95\%}$ (%) | 99.85±0.07 | 99.93±0.05 | 99.94±0.0 | n | n | n |
| HI | 0.054±0.005 | 0.050±0.005 | 0.056±0.003 | 0.031* | n | n |
| CI | 0.994±0.004 | 1.013±0.034 | 0.995±0.003 | n | 0.024* | n |
| Small bowel Volume (cc): 822.2±340.7 (430.2-1394.3) | | | | | | |
| $V_{<12(cc)}$ | 43.5±15.8 | 44.0±9.4 | 45.9±11.4 | n | n | n |
| $V_{15(cc)}$ | 57.8±11.8 | 50.8±8.9 | 49.7±12.1 | n | 0.030* | n |
| $V_{30(cc)}$ | 30.9±21.9 | 17.5±7.4 | 22.5±18 | n | n | n |
| D_{mean} (Gy) | 16.48±2.73 | 16.93±2.97 | 16.24±3.09 | n | n | 0.035* |
| D_{max} (Gy) | 48.21±2.40 | 48.65±2.20 | 49.04±1.96 | n | n | n |
| Bladder Volume (cc): 180.5±129.7(62.6-517) | | | | | | |
| $V_{30(cc)}$ | 35.2±6.8 | 28.9±8.8 | 26.3±3.8 | 0.031* | 0.020* | n |
| $V_{40(cc)}$ | 13.2±4.3 | 12.2±4.9 | 11.2±3.6 | n | n | n |
| D_{mean} (Gy) | 27.52±1.84 | 27.11±2.06 | 24.83±1.82 | n | n | n |
| Femur Heads R. Volume (cc): 173.55±35.53(118.9-228.7) L. Volume (cc): 174.8±35.6(119.9-226.3) | | | | | | |
| R. D_{mean} (Gy) | 16.76±2.03 | 13.17±0.92 | 12.37±1.33 | 0.001* | 0.001* | n |
| R. D_{max} (Gy) | 47.36±2.45 | 45.07±2.86 | 38.94±2.48 | n | 0.001* | 0.001* |
| R. $V_{30(cc)}$ | 11.1±3.4 | 5.6±2.2 | 2.4±0.7 | 0.001* | 0.001* | 0.004* |
| R. D_{15} (Gy) | 28.26±2.16 | 23.65±1.23 | 22.42±1.22 | 0.001* | 0.001* | n |
| L. D_{mean} (Gy) | 15.77±2.14 | 13.02±1.13 | 11.90±1.13 | 0.003* | 0.001* | 0.004* |
| L. D_{max} (Gy) | 47.94±1.93 | 43.44±4.62 | 38.73±3.24 | 0.022* | 0.001* | 0.017* |
| L. V_{30} (cc) | 9.1±3 | 5.1±2.6 | 2.5±1.2 | 0.001* | 0.001* | 0.023* |
| L. D_{15} (Gy) | 26.65±1.67 | 23.51±1.20 | 22.54±0.87 | 0.005* | 0.001* | n |
| Normal tissue | | | | | | |
| V_{10} (cc) | 20.8±3.6 | 21.8±4 | 21.4±4.2 | 0.004* | n | n |
| V_{20} (cc) | 13.8±2.5 | 11.9±2 | 9.8±1.5 | 0.001* | 0.001* | 0.001* |
| V_{30} (cc) | 5±0.7 | 4.6±0.6 | 3.9±0.5 | 0.003* | 0.001* | 0.001* |
| V_{40} (cc) | 1.9±0.3 | 1.9±0.3 | 1.5±0.2 | n | 0.001* | 0.001* |

*Letter stated when comparison of both tested groups was significant different ($p < 0.05$). P value of n means no statistically significant.

dex (HI) than IMRT7 and ARC ($p=0.026$). Although the $D_{98\%}$ was higher for IMRT9 than ARC ($p=0.001$), there were no significant differences between all plans on CI values ($p=0.188$). For PTV2, did not show any

difference for all the evaluated dosimetric parameters (Table 1). Dose distributions of the three planning techniques for two patients in axial slices were showed in Figure 1.

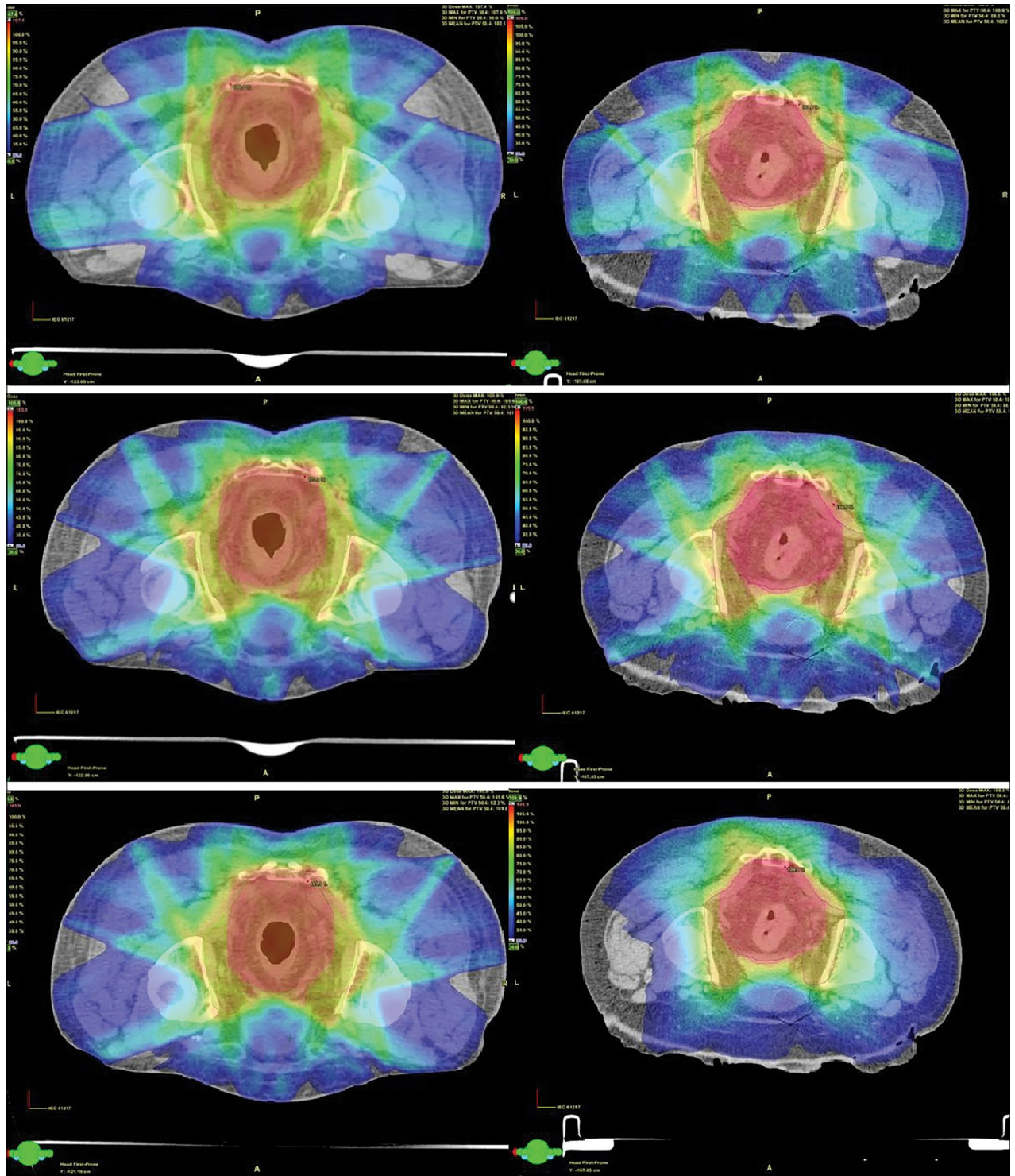


Fig. 1. For two patients comparative dose distribution in IMRT7, IMRT9 and ARC plans in axial slices, respectively.

Small Bowel and Bladder

The mean volume of small bowel was 822.2 ± 340.7 cc (ranged from 430.2 to 1394.3 cc). There were no significant differences between all three plans on $V_{<12}$, V_{30} and D_{max} . However the V_{15} and D_{mean} was lower for ARC than IMRT7 and IMRT9, respectively (ARC-IMRT7 $p=0.030$ and ARC-IMRT9 $p=0.035$). The volume of the bladder ranged from 62.6 ile 517 cc with a mean of 180.5 ± 129.7 cc. The results for plans were comparable but the V_{30} was lower for IMRT7 than both IMRT9 and ARC ($p=0.031$, $p=0.02$) (Table 1).

Femur Heads

Areas of 40 Gy receiving in each of three plans were excluded from the analysis because of evaluated only linearly on the DVHs. In general, IMRT7 revealed the highest irradiated volumes, whereas IMRT9 and ARC could achieve comparably better results (Table 1).

Normal Tissue

V_{10} , V_{20} , V_{30} , V_{40} was evaluated for normal tissue which was excluded PTV2 from whole body (Table 1). The results for the ARC were obviously superior relating to measured volumes and IMRT7 plans had the worst results (ARC<IMRT9<IMRT7).

Monitor Units and Durations of Treatment

ARC plans had the lowest monitor unit values, as expected ($p=0.01$). There was no significant difference between the 'beam on' times. However, when the total treatment time was considered, the superiority of ARC plans was observed according to the data obtained with QA. The mean treatment periods were measured as 6.83 ± 0.61 minutes in IMRT7, 8.21 ± 0.74 minutes in IMRT9 and 3.09 ± 0.31 minutes in ARC.

Discussion

Dosimetric benefits of IMRT and VMAT compared to 3-dimension radiation therapy (3DRT) for preoperative treatment of rectal cancer are well established. These highly conformal radiation therapy planning and delivery techniques are based on the delivery of highly modulated dose fluence from multiple directions in order to limit high-dose volumes outside the treatment target. In this way, concave/convex isodose lines can be formed. This advantage means a reduction of high doses to organs at risk, that creates lower acute and late toxicity expectations in clinical implication. There are several prospective studies using IMRT/VMAT for preoperative radiotherapy in rectal cancer.

However studies demonstrating clinical benefits are limited to phase I/II, and late toxicity data are few.

The primary reason of using these technologies is to decrease acute and late toxicity for treatment tolerability and long-term quality of life. Most common acute toxicity is radiation enteritis, occurs in many patients undergoing radiotherapy for rectal cancer. Grade 3–4 acute toxicity was reported in up to 23% of patients treated with preoperative chemoradiotherapy, escalating to 37% with doses >50 Gy (9-10). These data suggested that the small bowel volume receiving 15 Gy (V_{15Gy}) is strongly associated with the degree of toxicity.[9] Also Robertson JM et al.[14] showed that V_{15} , V_{20} and V_{25} were associated with grade 3-4 diarrhea. Urbano et al.[15] reported a 64% reduction in intestinal volume by 45-50 Gy with IMRT compared to 3DRT in dosimetric analysis with patients with rectal cancer simulated in the prone position with full bladder. In this study, three different IMRT schemes, as 5, 7, and 9 field IMRT, were compared. Although the superiority of IMRT to 3DRT was shown, no significant difference was found in the effect of field count on the irradiated intestinal volume. In our study although there was a decrease in the average V_{15} and V_{30} values in IMRT9 compared to IMRT7 plans, there were no significant differences (V_{15} , $p=0.067$; V_{30} , $p=0.107$). ARC showed superior dosimetric results to IMRT7 on V_{15} and to IMRT9 on D_{mean} ($p=0.030$, $p=0.035$).

Moreover there are several studies that have focused on treatment intensification by using different chemoradiotherapy regimens with the aim of limiting treatment-induced toxicity using IMRT.[16-19] RTOG 0822 that have aimed 12% reduction of grade 2 and over gastrointestinal (GI) toxicity with IMRT applied to neoadjuvant CRT (concurrent capecitabine 825 mg/m² BID, 5 cycles of oxaliplatin 50 mg/m² weekly) compared to RTOG 0247 applied with 3BKRT, showed a 51.5 % rate of grade ≥ 2 GI toxicity, which exceeded the observed rate of 40 % in RTOG 0247.[19] Thus volume of the bowel receiving low-dose RT (e.g. 15 Gy) may be more important when using multi-agent chemotherapy, suggesting that low-dose constraints may need to be more compelling in order to produce a clinically optimal plan.

When the bladder tolerance doses are taken into account, dose prescriptions applied as preoperative for rectal cancer do not mean a significant risk for bladder toxicity. However, a volumetric or dosimetric threshold that can be associated with acute and late side effects in rectal cancer has not been established. Wolff HA et al stated in 2011, in that compared proton, VMAT, IMRT

and 3DRT in patients with locally advanced rectal cancer, only V_{40} volumes for bladder were statistically significantly higher in IMRT plans than VMAT.[20] In the same year, a similar comparison was published by S. Cilla et al.[13], V_{15} , V_{30} , V_{40} , V_{50} , V_{55} , D_{max} analyzes were performed for the bladder. However, PTV1 was defined as 57.5 Gy. Although lower doses were obtained for bladder in VMAT plans, no significant differences were found. Unlike the literature, in our study for bladder V_{30} was significantly lower for IMRT7 than for IMRT9 ($p=0.031$) and ARC ($p=0.02$). This results could be caused by used number of segments, different dose intensity on each fields or prone position.

One of the important parts of pelvic radiotherapy in terms of late toxicity is the femur heads because of its function. Dose-response relationship is not known but is more frequent at higher doses of 40 Gy. In this study, ARC showed superior dosimetric results to IMRTs. In addition, when IMRT plans are assessed within themselves, the superiority of IMRT9 plans is emphasized in all parameters. This may be due to the increased dose intensity compared to IMRT9 and because of coplanar beams (104° and 260°) used in IMRT7.

Although IMRT and VMAT have defined dosimetric advantages, clinical reflections have yet to be demonstrated. Both techniques limit the high dose areas taken by normal tissues when compared to 3DRT, while the low dose areas increase. This may lead to an increased risk of radiation-related cancer formation due to DNA mutations and carcinogenesis that increase in low and moderate dose values. As we assess the dosimetric comparison of normal tissue doses, V_{20} , V_{30} , V_{40} volumes were significantly lower in ARC plans (IMRT7> IMRT9> ARC). The number of field was only significant at lower doses (10 Gy), V_{10} was better in IMRT7 plans compared to IMRT9 ($p=0.004$; $p<0.01$).

The prolonged treatment increase the uncertainty due to the patient's movement and it has been stated that IMRT was successful in reducing the volume of irradiated bowel with prone position in many studies.[21,22] Uncertainties during interfraction and intrafraction can cause the target dose to fall below the desired dose due to sharp dose drops close to large target volumes at IMRT and VMAT. Considering all this, it can be said that VMAT's most important superiorities against IMRT are short duration of treatment and low monitor unit values. Volumetric-arc therapy resulted in a reduction of up to 60% in mean total treatment time (IMRT7 6.83+0.61 min, IMRT9 8.21+0.74 min, ARC 3.09+0.31 min).

Conclusion

Volumetric arc therapy with short treatment duration and low MU values can be considered as providing a more comfortable and qualified treatment for patients with rectal cancer. The superiority obtained in organ at risk may not be meaningful because of the uncertainty in clinical manifestations. There is a need for phase III dosimetric studies to be performed with more patients and clinical observation.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Ethics Committee Approval: This study was conducted in accordance with local ethical rules.

Financial Support: None.

Authorship contributions: Concept – S.O.; Design – S.O., H.A.; Supervision – S.O., M.Ü.; Materials – S.O., H.A., S.A., Y.S.; Data collection &/or processing – S.O., H.A.; Analysis and/or interpretation – S.O.; Literature search – S.O.; Writing – S.O.; Critical review – S.O., M.Ü.

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