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Which radiotherapy technique is better for neoadjuvant treatment of rectal cancer: A dosimetric comparison

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ABSTRACT

Objective: Our aim was to compare helical tomotherapy (HT) and volumetric modulated arc therapy (VMAT) plans with 3-dimensional conformal radiotherapy (3D-CRT) considering the planning target volume (PTV) and organs at risk (OARs) in rectal cancer patients treated with neoadjuvant radiotherapy.

Patients and Methods: Thirty patients, previously treated with intensity modulated radiotherapy (IMRT) or 3D-CRT from January 2014 to February 2020 were selected and 3 plans were generated for each patient using VMAT, HT and 3D-CRT. Dosimetric comparisons were made for each plan regarding PTV and OARs. Integral dose (ID) was calculated and beam on times were analyzed.

Results: The homogeneity index (HI) was significantly better in HT plans compared with VMAT and 3D-CRT plans ($p<0.001$), conformity index (CI) was better in VMAT plans. For small bowel, high doses were higher in 3D-CRT plans ($p <0.001$). HT produced lower doses for the bladder as compared to VMAT and 3D-CRT ($p<0.005$). The mean and maximum doses of bilateral femoral heads were higher in 3D-CRT plans. Beam on times were longer and IDs were higher in HT plans ($p<0.001$).

Conclusion: Both VMAT and HT improved target homogeneity and conformity and decreased OAR doses compared to 3D-CRT. Although, VMAT was the best method to decrease ID, HT produced better bladder sparing.

Keywords: Rectum cancer, Volumetric modulated arc therapy, Helical tomotherapy, 3-dimensional conformal radiotherapy, Plan comparison

1 INTRODUCTION

Colorectal tumors are the third most common tumors among men and women, not only in Europe but also in Turkey [1]. Rectal tumors account for approximately 20 % of all colorectal tumors. Preoperative chemoradiotherapy (CRT) is the standard neoadjuvant treatment in patients with locally advanced rectal cancer (LARC); T3-T4 and/or N+ since 2004 [2,3]. Conventionally fractionated radiotherapy (50.4 Gy/28 fx/6 weeks) is the most widely accepted regimen. Pathologic complete response (pCR) after CRT is associated with improved local and distant control, overall survival (OS) and disease free survival (DFS) [4]. However relatively low rate of PCR (13% to 20%) and high rate of distant metastases have led to re-evaluation of the role of treatment intensification by intensifying chemotherapy (CT) regimens or radiotherapy (RT) dose (>50 Gy). So far, six randomized trials comparing fluoropyrimidine CRT with or without oxaliplatin reported [5]. However, this treatment not only did not improve the outcome but also showed an increase in grade 3-4 toxicity. In a meta-analysis investigating the effect of radiotherapy boost on pathologic response rate it was shown that dose escalation above 60 Gy for LARC, results in high pCR-rates and grade 3 early toxicity ranges between 10%-42.6% [6]. Please note that none of the studies used IMRT. A recent randomized study about intensification of CRT by either radiotherapy dose escalation or multidrug CT also showed improved pathologic

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response rates in the escalated dose arm [7]. The standard 45-50.4 Gy RT dose may change in the future albeit at the expense of increased toxicity, and there will be an increased interest in the safe and tolerable administration of preoperative high dose CRT. In the majority of the studies reported, the most common RT technique is 3D-CRT with either AP-PA opposing fields or a four-field-box technique. Because of the concave shape of the planning target volume (PTV) to cover lymphatics, sparing of the normal tissue (bladder, small bowel, and femoral heads) is rather limited with this technique. The most common Grade 3 or 4 toxicity is mainly gastrointestinal, and the volume of small bowel receiving at least 15 Gy (V15) was found to be strongly associated with the degree of toxicity [8]. To reduce the toxicity, modern RT techniques, such as IMRT, VMAT, and HT have increasingly been used for pelvic radiotherapy. However, dosimetric studies comparing VMAT, HT, and 3D-CRT techniques concerning target volume coverage and (OAR) are lacking.

In this study, we compared the dosimetric parameters between VMAT, HT and 3D-CRT techniques in a relatively large number of rectal cancer cases who received preoperative radiotherapy.

2. PATIENTS and METHODS

Thirty patients with pathologically proven and previously treated with pelvic radiotherapy for locally advanced rectal cancer from January 2014 to February 2020 were randomly selected for this study. The research protocol was reviewed and approved by Ethics Committee of Kocaeli University School of Medicine (15.04.2021). All patients were simulated in supine position with full bladder. Computed tomography (CT) simulation scanning was done using the Siemens Definition AS (Siemens Healthcare, Erlangen, Germany) CT machine with 3-mm slice thickness through the L1 vertebral body to 2 cm below the perineum.

Treatment planning

Target volumes were defined according to the recommendations of the international commission on radiation units and measurements report No.62 [9]. The clinical target volume (CTV) included the gross tumor volume-tumor (GTV-T), the mesorectum, pre-sacral nodes, the common and internal iliac lymph nodes. PTV was generated with a 1-cm symmetrical expansion around the CTV. The bowel bag, bladder and femur neck were delineated as OAR and OARs dose constrains were determined based on the RTOG 0822 Study [10]. To avoid possible inconsistencies for the CTVs, the same physician created a new contouring task for each patient. Three sets of plans for 3D-CRT, HT and VMAT were generated for each patient for the dosimetric comparisons. The prescribed dose to planning target volume (PTV) was 50.4 Gy in 28 fractions. For 3D-CRT and VMAT planning Eclipse Planning System V13.6 (Varian Medical Systems. Palo Alto, CA), and for HT planning TomoTherapy Planning Station V5.1.1.6 (Accuray) was used. The tomotherapy plans were all helical IMRT plans with field widths of 2,5 cm, 0.287 pitch value and 2.00 planning modulation factor. 3D-CRT technique was planned with four field technique, using beam angles 0, 90, 180, 270 with 15 MV photon energy. VMAT technique was planned using 2 full arcs. Arc rotations were 181°-179° clockwise and 179°-181°counterclock wise. In order to minimize leaf leakage in the created arc areas, 30 degrees and 330 degrees collimator angles were used for each arc. All of the plans were normalized to cover 100% of the PTVs with ≥95% of the prescribed dose. No planning objective was created for OARs.

Plan Evaluation

Dose Volume Histogram (DVH) was used for PTV and OAR dose comparison. PTV D98% (Dose received by 98% of the PTV), PTV D2% (Dose received by 2% of the PTV), PTV D50% (Dose received by 50% of the PTV), HI {(PTV D2% – PTV D98%) /PTV D50%}and, CI {PTVvol / IRvol 95% (Irradiated volume enclosed by the 95% of isodose line)} were evaluated for target coverage. While a greater HI value indicates poorer uniformity of the dose distribution, the value of CI varies between 0 and 1, with a value closer to 1 indicates better conformity of the dose to the PTV. OAR (small bowel, bladder, femoral head) avoidance was evaluated using the following parameters: Dmean, Dmax, VnGy (volume receiving radiation dose ≥ n Gy). ID formula (Eintegral=Vb * pb* Db; V:Volume of body, p: density of body, D:Mean dose of body) was used to calculate the total dose delivered to the whole patient body [11-13].

Statistical Analysis

Statistical analyses were performed using the SPSS soft-ware version 20. The paired, two-tailed Wilcoxon signed-rank test was applied for statistical analysis. All p values reported were two-sided, and p value <0.05 was considered statistically significant.

3. RESULTS

Target coverage, conformality, dose homogeneity and beam on time

The average maximum doses for PTV (represented by D2) were significantly higher in 3D-CRT plans than VMAT and HT plans (p<0,001). Minimum PTV doses (represented by D98) were significantly lower in VMAT plans compared with 3D-CRT and HT plans. Although, HI was significantly better in HT plans than VMAT and 3D-CRT plans (p<0,001), CI was better in VMAT plans. The average CI of the VMAT plans was 0.9, and the average CI of 3DCRT and HT plans were 0.6 and 0.8, respectively, (p <0.001). The dosimetric parameters for target volumes and beam on times are summarized in Table I and Figure 1 shows the axial, sagittal and coronal CT slides of a patient representing the isodose distributions for the three modalities.

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Organs at risk doses, whole body integral dose

All details of the organ at risk doses are given in Tables II – IV.

Small Bowel

High doses (V50.4, V45, V40 and V30) were statistically higher in 3D-CRT plans than VMAT and HT plans (p <0.001), while there was no difference between VMAT and HT plans. V20 was lowest in VMAT plans; however V10 values were comparable between groups.

Bladder

HT produced significantly lower V50.4Gy, V45Gy, V40Gy, V30Gy, V20Gy, V10Gy and mean values for the bladder as compared to the VMAT and 3D-CRT (p<0.005). V10 value as representing the low dose volume did not differ between VMAT and 3D-CRT (p=0.593).

Right-left femoral head

The mean and maximum doses of both femoral heads were higher in 3D-CRT plans compared to VMAT and HT plans. There was no statistical difference between HT and VMAT plans regarding V50.4 values, while V45, V40 and V30 values were significantly lower in VMAT plans; however V20 values were comparable between VMAT and HT plans (p<0.005).

Whole body integral dose

ID was lowest in VMAT plans, and HT produced the highest as shown in Table I.

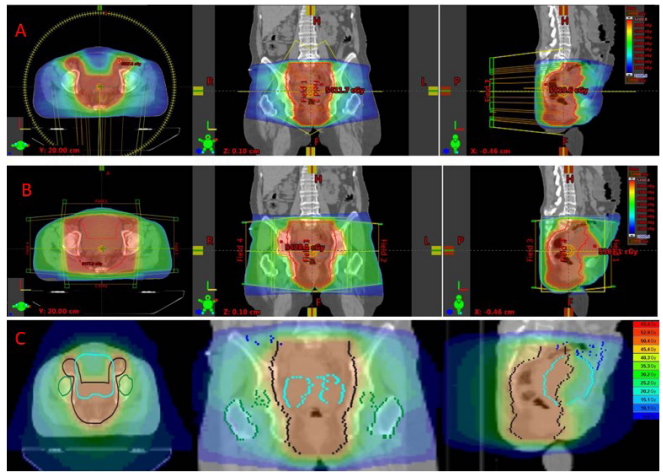

Figure 1. *Isodose distributions of a patient in the axial, coronal and sagittal plan for VMAT (A), 3D-CRT(B) and HT(C).*
VMAT: volumated modulated arc therapy, 3D-CRT: 3-dimensional conformal radiotherapy (3D-CRT), HT: helical tomotherapy

Table I. *Dose volume histogram parameters for PTV comparing 3D-CRT, HT, and VMAT Techniques (Values are presented as mean ± standard deviation)*

Parameters	VMAT	HT	3D-CRT	p-value (HT vs 3D-CRT	p-value (VMAT vs 3D-CRT	p-value (VMAT vs HT)
D2%(Gy)	53.24±6.38	51.63±0.36	54.22±7.02	0.00	0.00	0.00
D50%(Gy)	51.95±3.93	50.92±0.25	52.48±4.82	0.00	0.00	0.00
D98%(Gy)	49.54±1.86	49.64±0.32	49.68±1.84	0.00	0.003	0.00
HI	0.07±0.01	0.03±0.01	0.08±0.01	0.00	0.00	0.00
CI	0.92±0.02	0.87±0.03	0.6±0.06	0.00	0.00	0.00
Beam On Time(minute)	0.85±0.08	5.69±0.79	0.36±0.01	0.00	0.00	0.00
Body ID	375.53±112.49	410.06±91.52	404.06±92.56	0.012	0.001	0.001

PTV: planning target volume; CRT: conformal radiotherapy, HT: helical tomotherapy, VMAT: volumated modulated arc therapy, HI: homogeneity index, CI: conformity index, ID: integral dose

Table II. *Comparison of small bowell dose parameters between 3D-CRT, HT, and VMAT (Values are presented as mean ± standard deviation)*

Values (%)	VMAT	HT	3D-CRT	p – value (HT vs 3D-CRT	p-value (VMAT vs 3D-CRT	p – value (VMAT vs HT)
V50.4 Gy	6.46±8.5	6.01±7.84	20.4±15.68	0.00	0.00	0.216
V45 Gy	14.52±12.19	14.15±10.93	26.91±17.24	0.00	0.00	0.718
V40	19.76±14.28	21.53±13.74	30.34±18.14	0.002	0.00	0.07
V30	36.14±19.1	41.01±18.22	47.07±20.65	0.046	0.00	0.013
V20	56.70±21.91	72.02±23.14	71.58±17.81	0.889	0.016	0.012
V10	82.77±17.09	81.63±31.58	81.64±16.72	1	0.144	0.655
Mean	25.78±6.9	28.38±6.47	29.78±8.21	0.14	0.00	0.00

Vn Gy: percentage of the volume receiving radiation ≥ n Gy, CRT: conformal radiotherapy, HT: helical tomotherapy, VMAT: volumated modulated arc therapy

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***Table III**. Comparison of bladder dose parameters between 3D-CRT, HT, and VMAT (Values are presented as mean ± standard deviation)*

Values (%)	VMAT	HT	3D-CRT	p-value (HT vs 3D-CRT	p-value (VMAT vs 3D-CRT	p-value (VMAT vs HT)
V50.4	20.01±19.32	16.27±14.79	68.28±16.45	0.00	0.00	0.111
V45	44.29±23.30	32.66±19.26	81.08±16.07	0.00	0.00	0.024
V40	54.49±24.22	41.07±20.87	84.69±15.48	0.00	0.00	0.017
V30	70.28±22.29	59.53±25.16	95.51±9.87	0.00	0.00	0.00
V20	89.29±17.7	55.18±35.93	99.91±0.49	0.00	0.02	0.00
V10	99.85±0.69	70±46.60	99.99±0.03	0.04	0.593	0.004
Mean	38.72±7.3	3441±7.36	48.39±3.44	0.00	0.00	0.00

Vn Gy: percentage of the volume receiving radiation ≥ n Gy, CRT: conformal radiotherapy, HT: helical tomotherapy, VMAT: volumated modulated arc therapy

***Table IV**. Comparison of femoral head dose parameters between 3D-CRT, HT, and VMAT (mean ± standard deviation)*

Values(%)	VMAT	HT	3D-CRT	p-value (HT vs 3D-CRT	p-value (VMAT vs 3D-CRT	p-value (VMAT vs HT)
Right Femur						
V50.4	0.02±0.09	0.06±0.24	2.08±2.71	0.00	0.00	0.176
V45	0.58±1.19	1.64±2.44	4.37±3.71	0.01	0.00	0.02
V40	2.06±2.59	5.59±4.48	6.18±4.44	0.254	0.00	0.00
V30	13.12±7.02	20.53±8.45	38.24±19.93	0.00	0.00	0.00
V20	42.06±15.75	44.38±15.85	74.77±19.65	0.00	0.00	0.877
V10	75.59±21.76	81.63±21.67	82.39±17.09	0.495	0.00	0.14
Mean	18.19±4.55	20.59±3.98	25.30±5.44	0.00	0.00	0.00
Max	46.53±4.4	48.94±2.48	51.56±2.57	0.00	0.00	0.00
Left Femur						
V50.4	0.0±0.03	0.02±0.7	2.10±3.49	0.00	0.00	0.214
V45	0.58±1.55	1.83±2.25	4.35±4.57	0.01	0.00	0.00
V40	1.96±2.87	5.88±4.42	6.20±5.32	0.94	0.00	0.00
V30	13.18±7.2	22.81±13.05	36.52±16.43	0.001	0.00	0.00
V20	45.54±20.47	45.79±15.62	75.04±19.5	0.00	0.00	0.727
V10	76.17±22.64	86.71±15.66	83.45±16.10	0.00	0.001	0.00
Mean	18.41±4.9	21.49±4.71	25.39±5.21	0.00	0.00	0.00
Max	47.05±4.13	49.27±2.23	51.23±32.7	0.00	0.00	0.00

Vn Gy: percentage of the volume receiving radiation ≥ n Gy, CRT: conformal radiotherapy, HT: helical tomotherapy, VMAT: volumated modulated arc therapy

4. DISCUSSION

In our dosimetric study we compared the standard and traditionally used 3D-CRT technique with VMAT and HT for patients with locally advanced rectal cancer treated neoadjuvantly. In the literature, there are studies comparing different IMRT techniques with 3D-CRT, as well as with each other but no study has been published comparing 3D-CRT, VMAT, and HT techniques at the same time [14-19]. Traditionally, 3D-CRT has been used for LARC targeting the primary tumor and mesorectum as well as lymph nodes. Gastrointestinal complications are the most common toxicity in 3D-CRT, leading to a decrease in treatment compliance. In the German Rectal Cancer Study Group study, there was 27% acute and 14% late grade ≥ 3 toxicity [2]. Braendengen et al., reported a study where acute and late toxicity rates were 28% and 17% respectively [20]. The 3D-CRT was used in both studies. There are notable number of studies that have shown dose-volume relationship between the irradiated small bowel volume and the severity of diarrheal toxicity at different dose levels [21,22]. A recent meta-analysis stated that V10Gy, V30Gy, V35Gy and V40Gy were found to be significantly predictive of the toxicity incidence in a univariate logistic regression model. In our study we showed that high doses (V50.4, V45, V40 and V30) were statistically higher in 3D-CRT plans than VMAT and HT plans ($p < 0.001$), while there was no difference between VMAT and HT plans . But V20 was also lowest in VMAT plans making

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VMAT one of the best choice for small bowel protection. This meta-analysis also reported that this dose-volume relationship and risk of toxicity is continuous, without a threshold below which the risk is unchanged, and hence the priority of all clinicians should be to ensure that normal tissue receives the lowest dose as possible [23]. In a dosimetric study comparing VMAT, 5F-IMRT and 3D-CRT, VMAT was found to be not only superior in normal tissue sparing, but also V35-V45 of small bowel were significantly less than in 5F-IMRT and 3D-CRT [17].

With the introduction of different IMRT planning techniques into clinical practice, reduction of OAR doses and better target dose conformity and homogeneity were obtained [14-15]. Yu et al., showed that the dose conformality of Tomotherapy was better than that of four-box field CRT [15]. Furthermore, the irradiated mean dose of the normal organs was found to be two-thirds of the 3-dimensional RT. A study reported by Arbea et al. comparing IMRT and 3D-CRT in LARC, showed that IMRT improves target conformity at the expense of target heterogeneity [14]. They also reported that HI was lower with HT compared to 3D-CRT. In our study both HI and CI were both better in VMAT and HT than 3D-CRT. HI was also significantly better in HT plans compared with VMAT and 3D-CRT plans ($p<0.001$), although, CI was better in VMAT plans.

Bladder should have been the second and femoral heads the third importance as an OAR that should be protected but often neglected in pelvic radiotherapy. In the study carried out by Temelli et al, the bladder was best protected by HT compared to IMRT and VMAT [24]. Similarly in our study HT produced significantly lower V50.4Gy, V45Gy, V40Gy, V30Gy, V20Gy, V10Gy and mean values for the bladder compared to VMAT and 3D-CRT ($p<0.005$) while femoral head doses mean and V45, V40 and V30 values were significantly lower in VMAT plans. Hip fracture after RT of pelvic tumors has been reported to be rare after mean doses of <40 Gy to the femoral neck, but a recent prostate cancer study suggest an increased risk of hip joint arthropathy [25-26].

It is generally accepted that as the total body ID increase, secondary malignancy risk increases. In our study ID was significantly lower in VMAT hugely beneficial for the protection of healthy tissue.

Conclusion

Future strategies in the preoperative treatment of rectal cancer will be based mainly on intensification of treatment with RT where toxicity will be an important issue. In National Comprehensive Cancer Network guidelines, IMRT is still advised only in the setting of a clinical trial or in unique clinical situations such as re-irradiation. This study shows that this statement should be changed since VMAT and HT provide better OAR sparing, and high dose conformity compared to 3D-CRT. Further investigation is required in the use of VMAT and HT techniques in the neoadjuvant treatment of rectal cancer.

Compliance with the Ethical Standards

Ethical Approval: The study was approved by the Ethics Committee of Kocaeli University, School of Medicine (15.04.2021).

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Conflict of Interest: The authors have no potential conflicts to disclose.

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