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ORIGINAL ARTICLE

A comparison of dosimetric and clinical parameters between different IMRT boost techniques in preoperative rectal cancer

Sibel Karaca[1,2], Kadriye Aysenur Arli Karacam[1,3]

[1]Erzurum Regional Training and Research Hospital, Department of Radiation Oncology, Turkey. [2]Department of Radiation Oncology, Akdeniz University Faculty of Medicine, Turkey. [3]Department of Radiation Oncology, Marmara University Faculty of Medicine, Turkey.

Summary

Purpose: *In this study we compared the clinical and dosimetric outcomes of simultaneous integrated boost intensity modulated radiation therapy (SIB-IMRT) and sequential boost (SEQ-IMRT) techniques in preoperative rectal cancer (RC).*

Methods: *We analyzed 67 preoperative RC patients who received RT with Helical TomoTherapy (HT) device. 27 of patients were irradiated with SEQ-IMRT and 40 were irradiated with SIB-IMRT technique. The primary tumor and involved lymph nodes were simultaneously treated using the SIB-IMRT (50.4Gy/25 fraction). SEQ-IMRT delivered 45Gy/25 fractions to primary tumor (involved lymph nodes) and 5.4Gy/3fractions to boost volume. Dosimetric parameters, acute toxicities and 5year overal survival (OS), disease-free survival (DFS) and local control (LC) between two techniques were compared.*

Results: *In the SIB-IMRT group planning treatment volume (PTV) homogeneity index (HI) was better than in the SEQ-IMRT group. PTV doses of Dmax for SEQ-IMRT group were higher than the SIB-IMRT group ($p<0.05$). The bladder doses of Dmax in the SIB-IMRT group were higher than SEQ-IMRT group ($p<0.005$). There were no significant differences in other dosimetric parameters between groups. Median follow up was 29.06 months (range 4.3-92.07) and 36.46 months (range 8.7-79.6) in the SIB-IMRT and SEQ-IMRT groups, respectively. No significant difference was found between the SIB-IMRT and SEQ-IMRT groups in acute toxicity ($p=0,909$). Five-year OS, DFS and LC were 73.15%, 66.75% and 75.55% in SIB-IMRT group and 65.19%, 55.53% and 60.22% in the SEQ-IMRT group, respectively. No statically significant differences were found between the two groups regarding 5-year OS, DFS and LC.*

Conclusions: *SIB-IMRT and SEQ-IMRT tecniques provided similar outcomes for dosimetric and clinical results for RC in HT treatment.*

Key words: *preoperative rectal cancer, SIB-IMRT, SEQ-IMRT, helical tomotherapy, radiotherapy*

Introduction

Global rectal cancer (RC) rates are increased dramatically over the last years. Nearly 704000 new cases are expected in 2018. RC is the 10th most lethal cancer among all cancers [1]. The main therapeutic goal is to provide a cure in the treatment of RC, to prevent recurrence of disease, to improve overall survival (OS), disease-free survival (DFS), as well as to maintain intestinal function and patient quality of life. In parallel with the developments in RC surgery, significant advances have been made in the adjuvant treatment options aimed at providing a longer and higher quality life while reducing local recurrence. The importance of radiotherapy (RT) in RC treatment has increased in the last few decades. Studies have shown that preoperative neoadjuvant chemoradiotherapy (CRT), followed

Corresponding author: Sibel Karaca, PhD. Department of Radiation Oncology, Akdeniz University Faculty of Medicine, Pinarbasi, Akdeniz University Hospital, 07070 Bahtili/Konyaalto/Antalya, Turkey 07070.
Tel: +90 506 581 76 19; Email: sibeltuzlaci@gmail.com
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by total mesorectal excision (TME), has become the standard treatment for locally advanced RC [2-4]. Less toxicity, reduced local recurrence risk, increased sphincter preservation and resectability were achieved with this treatment method [5,6].

Due to the horseshoe shape of the planning target volume (PTV) in RC, the use of intensity-modulated radiation therapy (IMRT) techniques for protection organs at risk (OARs) can be very appropriate [7,8]. Two fractionation schemes can be applied with the IMRT technique. In sequential boost IMRT (SEQ-IMRT) technique, the target volume and elective nodal region are initially irradiated, and then the required treatment dose is added to the smaller boost region. In simultaneous integrated boost IMRT (SIB-IMRT) technique doses for target volume, elevated nodal region and boost region are delivered in the same number of fractions [9,10]. The 2 different IMRT methods have some advantages and disadvantages. Some studies found the SIB-IMRT method superior, while others found the SEQ-IMRT technique superior.

Helical tomotherapy (HT) is a RT method for IMRT combined with image guided radiation therapy (IGRT) based on megavoltage computed tomography (MVCT). The gantry rotates around the patient to treat from many angles in HT. HT system has 6MV in-line linear accelerator. There are a total 64 tungsten leaves on multileaf collimator (MLC). Due to the rapid opening and closing of leaves in the collimator, HT can give more homogeneous radiation doses to complex shaped tumor areas [11,12]. Clinical studies have also shown that HT produces precise dose distribution and decrease the irradiated volume of normal tissue during high-dose RT for RC [13].

Few institutions used HT for a long time and few studies have focused on the application of preoperative HT for RC. We present a single center's experience with this study and we aim to compare the dosimetric and clinical treatment results of preoperative RC patients between SIB-IMRT and SEQ-IMRT techniques. This study could help decision making about the optimal delivery technique (SIB-IMRT or SEQ-IMRT) to be applied in the case of a standard and consensus-based treatment of preoperative RC.

Methods

Eligibility criteria

The eligibility criteria were as follows: histopathologically confirmed rectal adenocarcinoma, T stage was T3-T4 and the region was high, mid and low rectum. Patients with unresectable metastatic disease at diagnosis were excluded. Patients received preoperative RT (10 patients) or chemo-RT (CRT) (57 patients). Most of the patients (n=46) received surgery after concurrent CRT. A selection was made among patients with similar treatment dose schedules (total 50.4Gy) irradiated with SIB-IMRT and SEQ-IMRT technique on the HT device. This study was approved by the Ethics Committee (Erzurum BEAH KAEK 2019/15-144).

Treatment protocol

Patients were immobilised in supine position and scanned with 3 mm slice thickness. All patients drank 500 cc of water 30-60 min before CT (with full bladder). The planned CT was performed from the L1 vertebra level to femur 1/3 proximal without giving contrast. Images were taken on a Siemens Somatom computed tomography (CT) scanner. The CT images were transmitted to the contouring workstation through Digital Imaging and Communications in Medicine (DICOM). Target organs and OARs were delineated first at the Focal Sim ver.4.62 (Elekta, Sweden) contouring workstation. Target volumes were defined according to Radiation Therapy Oncology Group (RTOG) consensus atlas [14].

In contouring, all patients' gross tumor volume (GTV) was determined by magnetic resonance imaging (MRI), positron emission tomography CT (PET-CT) and colonoscopic findings. While creating clinical target volume (CTV) 45 (standard risk volume), mesorectum + GTV-Tumor with 1-2 cm margin in radial, with a margin of 1.5-2 cm in superior-inferior, retained lymph node for GTV-Node, internal iliac obturator lymph nodes, presacral lymph nodes and external iliac lymph nodes are included in T4 tumors. PTV45 was created by giving CTV45 margin in the range of 0.5-1 cm according to the clinician's decision. When creating CTV50.4 (high risk volume), the entire mesorectum, presacral lymph node (presacral space), GTV-Tumor with a margin of 1-2 cm radially, a margin of 1.5-2 cm in superior-inferior and a captured lymph node is included for the GTVNode. PTV50.4 was created by giving CTV50.4 margin in the range of 0.5-1cm according to the clinicians' decision and removed 0.5cm from the skin. The bowel, bladder and femoral heads were delineated as OARs.

The IMRT plans were generated on the HT planning system (Accuray Inc., Madison, USA). For all cases, a field width of 2.5cm, a pitch ranged from 0.287 to 0.314, depending on the level of difficulty to achieve the OAR constraints, and a modulation factor of 2 to 3, depending on homogeneity and conformity were used during optimization. For SEQ-IMRT plans involved tumor and nodal volumes received 45Gy in 25 fractions of 1.8 Gy and then tumor region (mesorectum+ presacral space) received 5.4 Gy in 3 fractions of 1.8 Gy. For SIB-IMRT plans, involved the tumor and nodal volumes received 45 Gy in 25 fractions of 1.8 Gy and tumor region (mesorectum+ presacral space) received 50.4 Gy with the same fractions (25 fractions) of 2.016 Gy. RT was delivered in 5 days/week for SIB-IMRT and SEQ-IMRT techniques. The aim was to deliver at least 95% of the doses given to at least 95% of the PTVs but to keep volumes of irradiated OARs as low as possible. Dose constraints for the femoral heads' maximum doses were less than 50 Gy and doses were limited to V40 < 40%, V45 < 25%. Dose constraints

for the bladder maximum doses were less than 50Gy and doses were limited to V40 < 40%, V45 < 15% [15]. Treatment plans were compared by analyzing target and intersection volumes as well as DVH. The DVH for the PTV, bowel, bladder and femoral heads were analyzed in each patient.

The HT treatment was applied under the same conditions as planning CT and daily MVCT image was taken for registration.

Chemotherapy, follow up and toxicity

Patients received oral capecitabine or 5-fluorouracil-based chemotherapy simultaneously with RT. In the postoperative period, the patients with appropriate treatment tolerance continued with FOLFOX or CAPEOX chemotherapy. Patients were evaluated weekly during the RT and follow-up examinations every 3 months during the first 2 years, every 6 months during the next 3–5 years, and then once per year. The response to treatment (recurrence, response or stability) was also evaluated according to imaging and clinical criteria (volumetric reduction of the tumoral mass on MRI/CT/PET-CT).

Statistics

All data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, Ill, USA). OS was determined as the time from diagnosis to death for any reason. DFS was defined as the time from diagnosis to any type of recurrence or death for any reason. Local recurrence (LC) was defined as the time from diagnosis to recurrence in the primary or nodal region. OS, DFS and LC were estimated using the Kaplan-Meier method. Differences between SEQ-IMRT and SIB-IMRT groups were evaluated using the Log-Rank test. Dosimetric variables were compared using an independent *t*-test. Descriptive statistical analysis (numbers, percentages and mean values) was used to evaluate the data of demographic characteristics of patients and data of acute toxicity. P values <0.05 were considered statistically significant.

Results

Patient characteristics

We performed a retrospective chart review of consecutive patients who received RT in HT with preoperative RC (T3/T4 disease) between November 2013 and June 2019. RT was performed with a HT device (Tomotherapy Hi-Art System). This study included 67 patients (35 males, 32 females) with locally advanced RC. Twenty-seven patients were irradiated with the SIB-IMRT technique and 40 with the SEQ-IMRT technique. Patient and tumor characteristics are summarized in Table 1.

Dosimetric evoulation

Table 2 lists the dosimetric parameters of PTV and OARs for comparison of the two different IMRT techniques. The mean volume of the contoured PTV (45+5.4) in the SEQ-IMRT group was 1439.17±476.25 (cc) and the SIB-IMRT group it was 1391.48±412.72 (cc). When we look at the dose distribution of the PTV, we see that the SIB-IMRT group had a more homogeneous dose distribution compared to the SEQ-IMRT group (HI: 0.168±0.079 for SIB-IMRT, 0.289±0.1 for SEQ-IMRT). There was a statistically significant relationship between the SEQ-IMRT group of PTV maximum dose value and the SIB-IMRT group (p=0.03). The mean bladder volume was 190.48 cc±119.36 for the SEQ-IMRT group and 207.40 cc±172.80 for the SIB-IMRT group (p=0.142). There was a statistically significant relationship between bladder Dmax doses of the SIB-IMRT and SEQ-IMRT groups (p=0.001). The bladder Dmax of the SIB-IMRT group was higher than the bladder Dmax of the SEQ-IMRT group. Moreover, there was no significant differences in other OARs (bowel, femoral heads) dosimetric results between the SIB-IMRT and SEQ-IMRT groups.

Table 1. Patient and tumor characteristics

Characteristics	*SIB-IMRT Group N=27 (40.3%) n (%)*	*SEQ-IMRT Group N=40 (59.7%) n (%)*
Age, years, median	62 (27-85)	61 (22-87)
Sex		
Male	13 (48.1)	22 (55)
Female	14 (51.9)	18 (45)
Pretreatment tumor stage		
T3	18 (66.7)	31 (79.5)
T4	9 (32.3)	8 (20.5)
Pretreatment node status		
N0	5 (18.5)	7 (17.5)
N1	16 (59.3)	27 (67.5)
N2	6 (22.2)	6 (15)
Primary tumor location		
Low rectum	10 (37)	19 (47.5)
Mid rectum	10 (37)	9 (22.5)
High rectum	7 (25.9)	12 (30)
ECOG		
0	9 (33.3)	20 (50)
1	12 (44.4)	13 (32.5)
2	3 (11.1)	6 (15)
3	3 (11.1)	1 (2.5)
Chemotherapy		
5-fluorouracil	8 (29.6)	6 (15)
Capecitabine	16 (59.2)	27 (67.5)
Radiotherapy only	3 (11.11)	7 (17.5)
Surgery		
Yes	19 (70.4)	27 (67.5)
No	8 (29.6)	13 (32.5)

Acute toxicity

The acute toxicities were assessed according to the grading of toxicities presented in Table 3 between the two groups. Diarrhea was the most common acute toxicity with Grade 1,2 and 3 noted in 24 (35.8%) cases, followed by dermatitis in 14 cases and other urologic toxicities in 17 cases. Acute toxicity information of 11 cases was not available. No significant difference was found between the SIB-IMRT and SEQ-IMRT groups in acute toxicity (p=0.909).

Follow-up and Outcome

Nineteen patients (70.3%) with SEQ-IMRT and 27 patients (67.5%) with SIB-IMRT group underwent surgery after RT. Eleven patients died (6 patients; 15%) in the SIB-IMRT group, 5 patients; 18.5% in the SEQ-IMRT group, and 56 patients were still alive with a median follow-up time of 30.46 months (4.3-92 months) (SIB-IMRT group: 29.06 ±18.95 months (4.3-92.07 months); SEQ-IMRT group: 36.46 months (8.7-79.60 months). The first case of death occurred in the 38th month in the SIB-IMRT group, and in the 21st month in the SEQ-IMRT group. Five-year OS, DFS and LC were 73.15% ±7.07% (95%CI:59.26-86.98), 66.75% ±6.44% (95% CI:54.13-79.37) and 75.55% ±5.59% (95% CI:64.59-86.51) in the SIB-IMRT group and 65.19% ±5.4% (95% CI:54.47-75.90), 55.53% ±7.07 % (95% CI: 41.67-69.39) and 60.22% ±6.9% (95% CI: 46.68-73.75) in the SEQ-IMRT group, respectively.

Table 2. Evaluated dosimetric parameters of PTV and OARs for comparison of two different IMRT techniques

Parameters	*SEQ-IMRT (Summation Plan Values)*	*SIB-IMRT*	*p value*
PTV (45+5.4)			
Volume (cc)	1439.17±476.25	1391.48±412.72	0.528
HI	0.289±0.10	0.168±0.079	0.158
Dmax (Gy)	53.16±0.50	52.74±0.71	0.03
Dmean (Gy)	50.54±1.54	50.85±0.80	0.230
Dmin (Gy)	38.63±4.99	44.18±3.66	0.082
Bladder			
Volume (cc)	190.48±119.36	207.40±172.80	0.142
DMax (Gy)	50.44±2.06	51.82±1.44	0.001
DMean (Gy)	35.47±10.69	35.83±8.97	0.145
V15 (Gy)	45.61±7.30	47.00±5.43	0.415
V45 (Gy)	35.37±10.69	37.87±8.85	0.379
Bowel			
Volume	1410.95±678.57	1364.91±711.82	0.726
DMax (Gy)	47.83±5.78	50.56±2.97	0.376
DMean (Gy)	20.45±8.02	21.58±9.67	0.650
V15 (Gy)	38.87±8.43	40.06±9.12	0.581
V30 (Gy)	29.79±10.72	31.03±8.7	0.267
V45 (Gy)	22.69±9.48	20.04±7.86	0.459
Right Femur			
DMax (Gy)	44.41±4.82	43.65±4.88	0.310
DMean (Gy)	14.34±6.21	14.96±10.56	0.698
V5 (Gy)	32.79±7.19	33.97±7.57	0.358
V30 (Gy)	19.76±6.07	19.15±6.16	0.901
V45 (Gy)	14.79±5.63	12.98±4.98	0.298
Left Femur			
DMax (Gy)	44.57±4.77	43.62±4.85	0.564
DMean (Gy)	15.42±8.62	13.56±7.54	0.272
V5 (Gy)	31.90±8.80	33.80±7.98	0.608
V30 (Gy)	20.13±5.46	19.61±6.93	0.651
V45 (Gy)	14.69±2.29	13.35±4.98	0.539

HI= $(D_2-D_{98})/D_{med}$ (D2% is the highest dose delivered to 2% of the target volume, D98% is the dose delivered to 98% of the target volume and Dmedian is the median dose, the ideal HI value should be zero(ICRU-83) [16].

Recurrence was observed in 11 patients in the SIB-IMRT group and in 8 patients in the SEQ-IMRT group. Distant metastases were detected in 4 patients in the SIB-IMRT and in 2 patients in the SEQ-IMRT group. Local+distant metastases were detected in 3 patients in the SIB-IMRT and in 2 patients in the SEQ-IMRT group. Local metastases were detected in 4 patients in the SIB-IMRT and in 4 patients in the SEQ-IMRT group.

The first recurrence occurred in 1.7 months, and the last in 21.96 months for SIB-IMRT group, while the first recurrence occurred in 1.43 months and the last in 24.18 months for SEQ-IMRT group. The estimates of median recurrence was 9,27 months for SIB-IMRT (95% CI:7,46-11,065) and 3,73 months for SEQ-IMRT (95% CI:2,27-5,18). In Kaplan-Meier and log-rank analysis, there were no significant differences observed in DFS between SIB -IMRT and SEQ IMRT group (p=0.753). Kaplan-Meier curves are shown in Figures 1,2 and 3.

Discussion

HT is an advanced RT device used in the IMRT and IGRT method together. These methods reduce PTV and CTV margins and provide better critical organ protection [16-19]. The horseshoe shape of the target can make a RT challenge in RC. Studies have shown that the IMRT method can reduce acute and late toxicity with more homogeneous PTV dose distribution in RC [20,21]. IMRT offers different fraction schemes with SIB-IMRT and SEQ-IMRT techniques. SIB-IMRT and SEQ-IMRT techniques can provide comparable outcomes of

Table 3. Analysis of acutetoxities in patients with localy advance rectal cancer in SEQ-IMRT and SIB-IMRT groups

Acute toxicities	*SEQ-IMRT (N=27) n (%)*	*SIB-IMRT (N=40) n (%)*
Dermatitis		
Grade 1	6 (22.2)	3 (7.5)
Grade 2	3 (11.1)	2 (5)
Grade 3	-	-
Diarrhea		
Grade 1	4 (14.8)	9 (22.5)
Grade 2	5 (18.5)	4 (10)
Grade 3	2 (7.4)	-
Frequency/Urgency/Cystitis		
Grade 1	3 (11.1)	6 (15)
Grade 2	1 (3.7)	5 (12.5)
Grade 3	-	3 (7.5)
Not Available	3 (11.1)	8 (20)

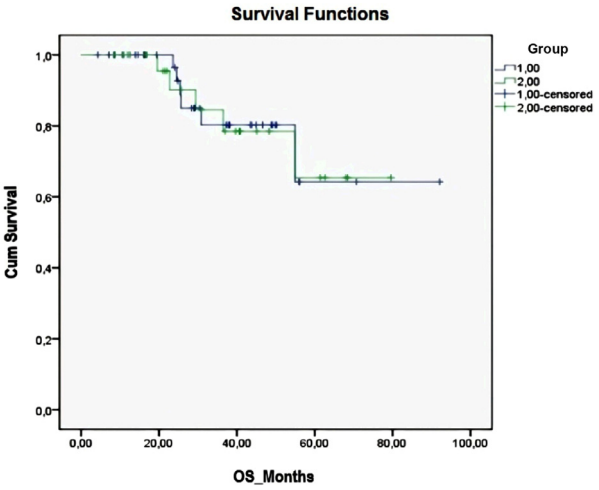

Figure 1. Kaplan-Meier estimates of overall survival for SIB-IMRT group (blue) and SEQ-IMRT group (green); p>0.05.

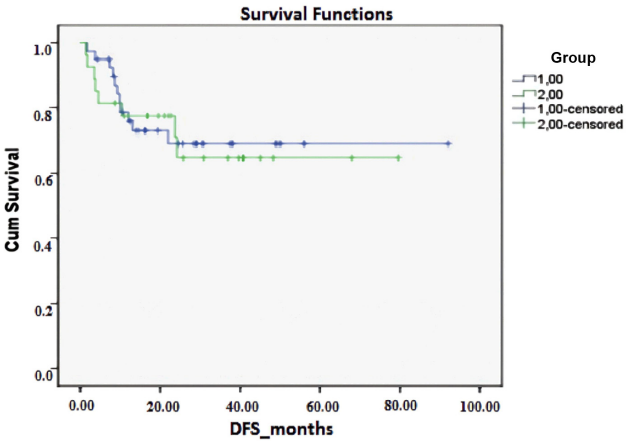

Figure 2. Kaplan-Meier estimates of disease-free survival (DFS) for SIB-IMRT group (blue) and SEQ-IMRT group (green); p>0.05.

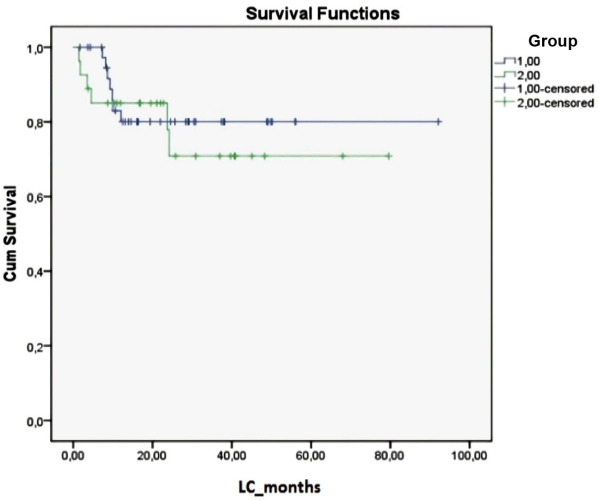

Figure 3. Kaplan-Meier estimates of local control (LC) for SIB-IMRT group (blue) and SEQ-IMRT group (green); p<0.05.

clinical effect in the treatment of RC patients. Our analysis determined that survival for preoperative RC including OS, DFS and LC is similar between SIB-IMRT and SEQ-IMRT techniques (p>0.05). Spiotto et al found similar results between SIB-IMRT and SEQ-IMRT techniques in a study comparing 2-year survival of head and neck (HN) patients [22].

In this study, we found that 5-year OS and DFS were 73.27% ± 4.97% (95% CI: 63.53-83.01) and 65.75 ± 5.08 (95% CI: 55.80-75.71), regardless of the group. Similarly, Rullier et al reported the OS and DFS were 74% and 64% at 5 years, with locally advanced RC who received preoperative CRT [23]. De Bari et al in their large series study determined that 4-year OS and DFS rates were 84.2% (95% CI 83.1-85.3%) and 74.6% (95% CI 73.0-75.0) for locally advanced RC patients treated with neoadjuvant CRT and HT [17]. In this study 10 (6.7%) patients were not operated due to older age and comorbidity and 21 (31.3%) patients received RT treatment only. Of the patients, 63.6% who died were not operated and did not receive chemotherapy. We think that this situation affected the survival time in our study.

The bowel is one of the most radiosensitive organs for RT. Acute toxicity can occur during bowel irradiation. Several previous studies have demonstrated that acute diarrhea is a common side effect of irradiation in RC [24-27]. De Felice et al reported that SIB-IMRT is a safe regimen and less genitourinary and gastrointestinal toxicity was observed compared to conventional IMRT fractionation [28]. Our results suggested that the most common acute toxicity was diarrhea followed by dermatitis. In their study Huang et al found that the most common acute adverse events encountered was dermatitis (75%), followed by diarrhea (69.5%), seen in the preoperative treatment of locally advanced RC patients undergoing CRT in HT [29]. In our study there was no significant difference between the SIB-IMRT and SEQ-IMRT groups concerning acute toxicity. Spiotto et al reported that the effect of IMRT techniques on toxicity remained uncertain [22].

In the dosimetric analysis of our study, the SIB-IMRT group had a more homogeneous dose distribution compared to the SEQ-IMRT. The maximum PTV dose value of the SEQ-IMRT group was greater than SIB-IMRT group (p=0.03). Similarly, the study of Dogan et al and Mohan et al emphasize that SIB-IMRT is more conformal than SEQ-IMRT [9,30]. Critical structures or other normal tissues may occur in high dose regions of the SIB-IMRT technique [9,31]. Similarly, we found the bladder Dmax doses of the SIB-IMRT group is higher than the SEQ-IMRT group (p=0.001). There were no significant differences between the SIB-IMRT and SEQ-IMRT groups' doses for bowel and femoral heads in our study.

Comparing studies of SIB-IMRT and SEQ-IMRT techniques we found that are generally concentrated on HN cancers [32-35]. However, there is still controversy over which method is better. As a result of Kuo et al determined that the SIB-IMRT technique is not much superior than the SEQ-IMRT technique [36].

There are some limitations of the current study. Firstly, there were a small number of patients in the two groups. The small group of patients may be inadequate to detect safe statistical differences. Second, in our study the follow-up was short in some patients, therefore, the long-term follow-up necessary to clarify the clinical effect is inadequate. Another limitation is that patients' data on acute toxicity were not fully available.

Conclusion

SIB-IMRT and SEQ-IMRT techniques are frequently used in RT of RC. Which of these techniques gives superior results (improve survival without increasing side effects and complications) needs to be investigated. Our study reported that dosimetrically the SIB-IMRT method had a more homogeneous dose distribution and no staticallly significant superiority was found between the two techniques. Also, according to result of the present study, we can claim that both IMRT techniques are preferable techniques for RC in the HT devices.

Authors' contributions

(I) Conception and design: All authors; (II) Administrative support: Kadriye Ayşenir Arli Karacam; (III) Provision of study materials or patients: Sibel Karaca; (IV) Collection and assembly of data: Sibel Karaca, Kadriye Aysemir Arlin Karacam (V) Data analysis and interpretation: Sibel Karaca; (VI) Manuscript writing: Sibel Karaca,; (VII) Final approval of manuscript: All authors.

Ethical statement

Our study was approved by the Erzurum Regional Training and Research Hospital Ethics Committee of Clinical Trials (Erzurum BEAH KAEK 2019/15-144). This study was a retrospective review so subject informed consent was not obtained.

Conflict of interests

The authors declare no conflict of interests.

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