Comparing Treatment Plans for Bladder Cancer: FIF, IMRT and SIB: A Dosimetric Study

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Abstract

Aim: The purpose of this study is to compare plans for bladder cancer using field-in-field (FIF), intensity modulated radiotherapy (IMRT) and simultaneous integrated boost (SIB) technique.

Method: FIF, IMRT and SIB treatment plans were created using tomography images of 20 patients diagnosed with bladder cancer. Two separate planning target volume (PTV) were defined for each patient: PTV1 and PTV2. For the FIF and IMRT plans, PTV1 and PTV2 received treatment doses of 50.4 Gray (Gy) and 60 Gy in 33 fractions, respectively. In 28 daily fractions, the SIB method was used in which different doses were delivered simultaneously in the target volumes. In the SIB technique, the daily treatment dose was determined as 2.14 Gy. The plans were compared in terms of PTV, organs at risk (OARs) such as rectum, bowel, femoral heads, homogeneity index (HI), conformity index (CI) and monitor unit values (MU).

Results: All plans were designed to cover 95% of the dose in the target volume. The CI for SIB plans showed significantly favourable results compared to FIF and IMRT plans. The V_{45} and V_{30} doses for the rectum in the SIB plans were statistically significantly lower compared to the FIF ($p<0.05$). The biologically effective doses (BED) values of rectum V_{30} were found to be 57.01±11.94 in SIB plans and 56.37±10.95 in IMRT plans. MU counts were significantly lower in FIF plans ($p<0.05$).

Conclusion: The SIB technique demonstrated better sparing of critical organs compared with FIF and IMRT in bladder radiotherapy. BED analysis, however, indicated higher doses with SIB. Overall, SIB appears to be a feasible option for appropriate patients, provided that dose to critical organs is carefully monitored.

Keywords: Bladder cancer, radiotherapy, simultaneous integrated boost.

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Mesane Kanseri İçin Tedavi Planlarının Karşılaştırılması: FIF, YART ve SIB: Dozimetrik Bir Çalışma

Öz

Amaç: Bu çalışmanın amacı, alan içi alan (FIF), yoğunluk ayarlı radyoterapi (YART) ve eşzamanlı entegre boost (SIB) tekniği kullanılarak mesane kanseri için yapılan planları karşılaştırmaktır.

Yöntem: Mesane kanseri tanısı almış 20 hastanın tomografi görüntüleri kullanılarak FIF, YART ve SIB tedavi planları oluşturuldu. Her hasta için iki ayrı planlama hedef hacmi (PTV) tanımlandı: PTV1 ve PTV2. FIF ve YART planları için, PTV1 ve PTV2'ye sırasıyla 33 fraksiyonda 50,4 Gray (Gy) ve 60 Gy tedavi dozları verildi. 28 günlük fraksiyonda hedef hacimlerde farklı dozların eş zamanlı olarak verildiği SIB yöntemi kullanıldı. SIB tekniğinde günlük tedavi dozu 2,14 Gy olarak belirlendi. Planlar PTV, rektum, bağırsak, femur başları gibi kritik organlar, homojenlik indeksi (HI), konformite indeksi (HI) ve monitör unit değerleri (MU) açısından karşılaştırıldı.

Bulgular: Tüm planlar, hedef hacimdeki dozun %95'ini kapsayacak şekilde tasarlandı. SIB planlarının CI'si FIF ve YART planlarına kıyasla anlamlı derecede daha iyi sonuçlar gösterdi. SIB planlarında rektum için V45 ve V30 dozları, FIF planlarına kıyasla istatistiksel olarak anlamlı derecede daha düşüktü ($p<0,05$). Rektum V_{30} BED değerleri, SIB planlarında 57,01±11,94 ve YART planlarında 56,37±10,95 olarak bulundu. MU sayıları, FIF planlarında anlamlı derecede düşüktü ($p<0,05$).

Sonuç: SIB tekniği, mesane radyoterapisinde FIF ve YART tekniklerine kıyasla kritik organları daha iyi korumuştur. Ancak BED analizi, SIB ile daha yüksek dozlara işaret etmektedir. Genel olarak, kritik organlara verilen dozun dikkatlice izlenmesi koşuluyla, SIB uygun hastalar için uygulanabilir bir seçenek gibi görünmektedir.

Anahtar Sözcükler: Mesane kanseri, radyoterapi, eş zamanlı integral boost.

Introduction

Bladder cancer is the second most common cancer of the urogenital system[1]. It is stated that bladder cancer is associated with both genetic and environmental factors[2]. Non-muscle invasive cancers tend to recur. The risk of death due to distant metastasis is high in muscle invasive cancers[3,4]. More sensitive and specific imaging techniques are being developed for earlier diagnosis[5]. Multifaceted treatment applications including radiotherapy and chemotherapy are used in the treatment of bladder cancer. Radiotherapy aims to destroy cancer cells using high-energy radioactive rays. In addition, it is aimed at providing local control by giving the highest possible dose in a way that causes the least possible damage to the surrounding healthy tissues[6]. In three-dimensional conformal radiotherapy (3D-CRT), the four-field technique is generally widely used. However, with 3D-CRT, larger areas are included in the treatment area, causing healthy tissues to receive more radiation. One of the effective ways to reduce the amount of critical organ dose with 3D-CRT is the field-in-field (FIF) technique. In this technique, tissues that receive unnecessary excess dose are tried to be protected with the subfield method. Intensity modulated radiotherapy (IMRT) is one of the most frequently used modern methods in bladder cancer treatment today. IMRT treatment is an advanced form of 3D-CRT. It is a method that can make dynamic dose changes within the treatment area and allows the tumor dose to be increased without giving excessive

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dose to tissues other than the target tissues. In this treatment approach, the dose distribution becomes more conformal, and normal tissues are better protected by optimally adjusting the beam intensity in each radiation field[7]. The advantage of this type of dose distribution over conventional treatments is that critical organs are better protected and higher doses can be achieved in the target[8,9]. If all target volumes are treated simultaneously using different fraction sizes, it can become the most conformal. This treatment strategy is called simultaneous integrated boost (SIB)[10,11]. The SIB technique has been reported to allow higher doses per fraction delivery to the target volume while maintaining lower dose levels to normal tissues from a radiobiological perspective[12]. The aim of this study was to compare the dosimetric performance of FIF, IMRT, and SIB techniques in bladder radiotherapy by evaluating target coverage, organ-at-risk doses (OARs) and biologically effective dose (BED) values. This comparison was intended to clarify the relative advantages of the different techniques in clinical practice.

Material and Methods

Patient selection and Contouring

For this study, 20 bladder cancer cases who were treated at the Radiation Oncology Department of Selcuk University Faculty of Medicine Hospital between 01.01.2020 and 30.12.2021 were selected. Patient characteristics were given in Table 1. Bladder filling instructions have been standardized. Patients were instructed to drink 500 ml of water 30 minutes before simulation and treatment to comfortably achieve a full bladder. Computed tomography (CT) planning scans were performed using a CT scanner with a 3 mm slice thickness. All clinical target volumes (CTVs) were contoured according to recommendations of consensus guidelines by the same radiation oncologist using Varian Eclipse Operation version 15.1 TPS. CTV included all regions of potential microscopic disease and PTV was generated by expanding the CTV 10 mm isotropically. Normal tissues including the rectum, bowel, right femur, left femur and sacral plexus were contoured as OARs.

Table 1. Patients characteristics

Characteristics	**Subgroup**	**Number (n)**	**Percentage (%)**
Sex	Male	19	95
	Female	1	5
Mean age (years) (range)	67.43 (54-80)	-	-
Tumor diameter	**<3 cm**	8	40
	≥3 cm	12	60
Tumor grade	Low-grade	1	5
	High-grade	19	95
T category	T2	12	60
	T3	6	30

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	T4	2	10
Comorbidities	No	11	55
	HT and/or DM	9	45

Treatment Planning

All plans were created using the Varian DHX linear accelerator in the Eclipse v15.1 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). FIF plans were created from four main beam fields, with subfields added to reduce temperature in hot dose regions. For each field, a corresponding multi-leaf collimator subfield was created in the beam's eye view projection. If the maximum dose was still too high, additional subfields and weights were created using the same procedure. Seven different gantry angles were used in the IMRT and SIB plans and optimized using inverse planning. For the FIF and IMRT plans, treatment doses of 50.4 Gray (Gy) and 60 Gy were administered to PTV1 and PTV2, respectively, in 33 fractions. The daily treatment dose was planned at 1.80 Gy for PTV1 and 2.00 Gy for PTV2. In SIB plans, two dose levels were defined under the same optimization weights: 2.14 Gy per fraction for high-risk volumes and 1.8 Gy for low-risk volumes. 6 MV photon energy was used in all techniques. The Anisotropic Analytical Algorithm (AAA) was selected for dose calculations, and the dose calculation grid resolution was set to 2.5 mm. During the optimization process, the same dose constraints and planning objectives were applied equally to all techniques.

For target volumes, plan acceptance requires that at least 95% of the PTV receives 95% of the prescribed dose, and the maximum dose does not exceed 107% of the prescription. The same parameters were used to evaluate all techniques: PTV coverage ratio, maximum hot spot, homogeneity index (HI), and conformity index (CI). Optimization constraints for critical organs (OARs) were set according to international guidelines in the literature. During planning, the following limits were used for the rectum: $V_{45} < 50\%$, $V_{40} < 60\%$, and $D_{mean} < 40$ Gy; for both femoral heads: $D_{mean} < 40$ Gy and $D_{max} < 50$ Gy.

Dose volume histograms (DVH) obtained from FIF, IMRT, and SIB plans were compared and doses received by PTV and OAR were evaluated. HI and CI parameters were evaluated. HI was defined according to International Commission Radiation Units (ICRU) Report No:83[13].

$$HI=\frac{(D_{2\%}-D_{98\%})}{D_{50\%}}$$

The formula defines the dose received by 2%, 98%, and 50% of the PTV. When the CI value is equal to 1, it defines the ideal dose distribution[14]. The CI index is used to estimate the suitability of the plan. CI values were automatically obtained from DVH in the Eclipse TPS. Using DVHs, D_{max}, D_{mean}, D_{98}, D_{95}, D_{50}, and D_2 data were compared in the PTV. In critical organs, D_{mean}, V_{45}, V_{30} and V_{20} for rectum, D_{mean}, V_{45} and V_{30} for bowel, D_{mean} and

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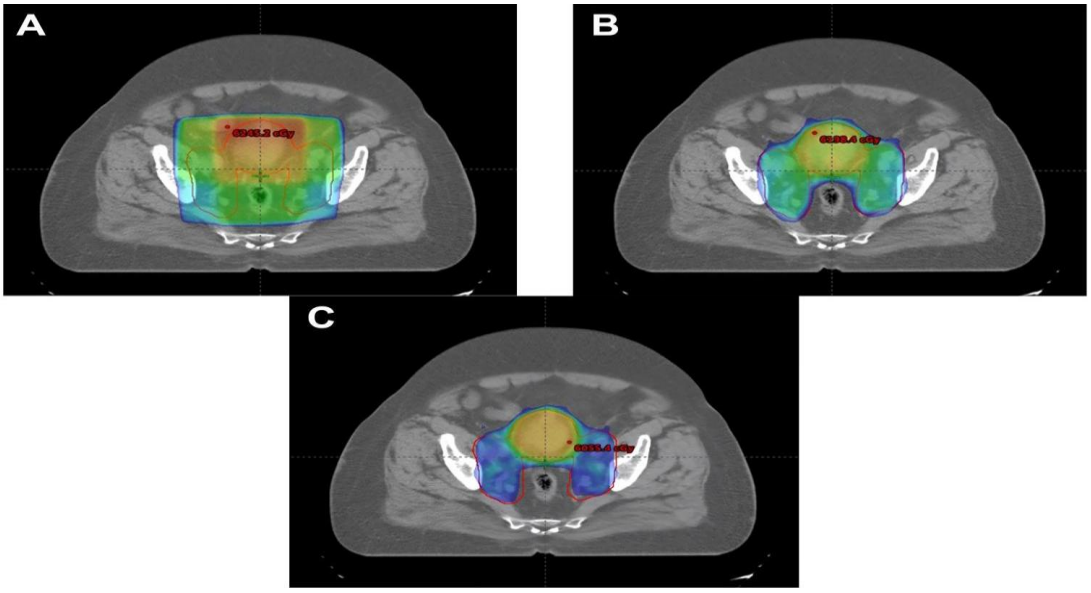
V_{20} for femoral heads and D_{max} for sacral plexus were compared. Monitor unit (MU) values in the plans were compared.

The formula of the biologically effective dose (BED) used in this study was as follows: BED=nd×[1+d/(α/β)], which was based on the linear-quadratic (LQ) model[15,16]. To convert the prescription dose to the BED, we set the α/β ratio= 10 for tumors and the α/β ratio= 3 for the OARs in this study. Paired samples t-test was used in the comparisons in the study, and $p<0.05$ was considered to be significant.

Figure 1. Comparison of plans showing dose coverage of 95% of the planning target volume **A:** Field in field technique **B:** Intensity modulated radiotherapy technique. **C:** Simultaneous integrated boost technique



Ethical Statement

Ethical approval for the study was granted by the Selcuk University, Faculty of Medicine, Ethics Committee with the decision number 2022/67 dated 03 February 2022. The study adhered to the principles outlined in the Declaration of Helsinki.

Results

The doses of PTV and OAR according to plans are tabulated in Table 2. and Table 3. respectively. The mean doses for the target were 59.56±0.77, 60.18±1.32 and 60.26±0.60 for FIF, IMRT and SIB plans, respectively. There was not found any significant difference concerning maximum and mean doses for the target. Figure 1. shows the evaluation of the plans and Figure 2. shows DVH comparison for FIF, IMRT and SIB plans. The CI values were 1.11±0.28, 0.47±0.23 and 0.26±0.18 for FIF, IMRT and SIB. Although CI values are less than 1 in IMRT and SIB plans, this is expected due to the irregular geometry of the bladder PTV and the simultaneous delivery of different dose levels in the SIB technique[17]. The HI values for FIF was 0.09±0.01, for IMRT was 0.05±0.02 and for

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SIB was 0.05±0.01, respectively. The IMRT and SIB plans showed significant results because of the smaller HI, which means more homogeneous dose distribution to PTV. The MU for FIF, IMRT and SIB plans were 253±9.10, 1234±74.94 and 1411±142, respectively. FIF technique delivered fewer MUs than other plans ($p < 0.05$).

The rectum D_{mean}, V_{45} and V_{30} dose were significantly lower in SIB and IMRT plans than FIF ($p < 0.05$). When the bowel was examined, V_{30} and V_{15} doses in SIB and IMRT plans were significantly lower than FIF plans ($p < 0.05$). Also concerning the femur heads D_{mean} doses were significantly lower in SIB plans ($p < 0.05$). The BED values of PTV and OARs were listed in Table 4. In SIB plans, D_{mean}, V_{45}, and V_{30} BED doses for the rectum and bowel were found to be significantly higher than in IMRT and FIF plans. When we examined the D_{mean} doses for the femoral heads, it was found to be higher in the FIF plans.

Table 2. Dosimetric values in the target

Parameters	(A) FIF (Mean ±SD)	(B) IMRT (Mean ±SD)	(C) SIB (Mean ±SD)	p A vs. B	p A vs. C	p B vs. C
PTV_{60} D_{98}(Gy)	56.48±1.24	58.21±1.63	58.20±0.76	**0.000**	**0.000**	0.980
PTV_{60} D_{95}(Gy)	57.16±1.10	58.94±1.49	58.98±0.66	**0.000**	**0.000**	0.901
PTV_{60} D_{90}(Gy)	57.78±1.02	59.42±1.37	59.51±0.61	**0.000**	**0.000**	0.739
PTV_{60} D_{50}(Gy)	59.62±0.77	60.16±1.30	60.27±0.58	0.122	**0.008**	0.673
PTV_{60} D_{2}(Gy)	62.22±0.96	61.66±1.43	61.74±0.82	0.167	0.135	0.792
PTV_{60max}(Gy)	62.99±1.07	63.06±1.59	63.02±0.74	0.876	0.898	0.916
PTV_{60mean}(Gy)	59.56±0.77	60.18±1.32	60.26±0.60	0.090	0.007	0.749
PTV_{50} D_{95}(Gy)	54.35±3.41	53.84±3.05	53.11±3.20	0.438	0.165	0.382
CI	1.11±0.28	0.47±0.23	0.26±0.18	0.000	0.000	0.005
HI	0.09±0.01	0.05±0.02	0.05±0.01	0.000	0.000	0.840
MU	253±9.10	1234±74.94	1411±142	0.000	0.000	0.000

FIF: field-in-field, IMRT: intensity-modulated radiation therapy, SIB: simultaneous integrated boost, PTV: planned target volume, CI: conformity index, HI: heterogeneity index, MU: monitor unit, SD: Standard deviation p: paired sample t-test, *p <0.05

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Figure 2. Dose volume histogram comparison of a patient. ▲: FIF: field-in-field ●: SIB: simultaneous integrated boost ■: IMRT: intensity-modulated radiation therapy (red: planned target volume, brown :rectum, yellow: sacral plexus, blue:bowel)

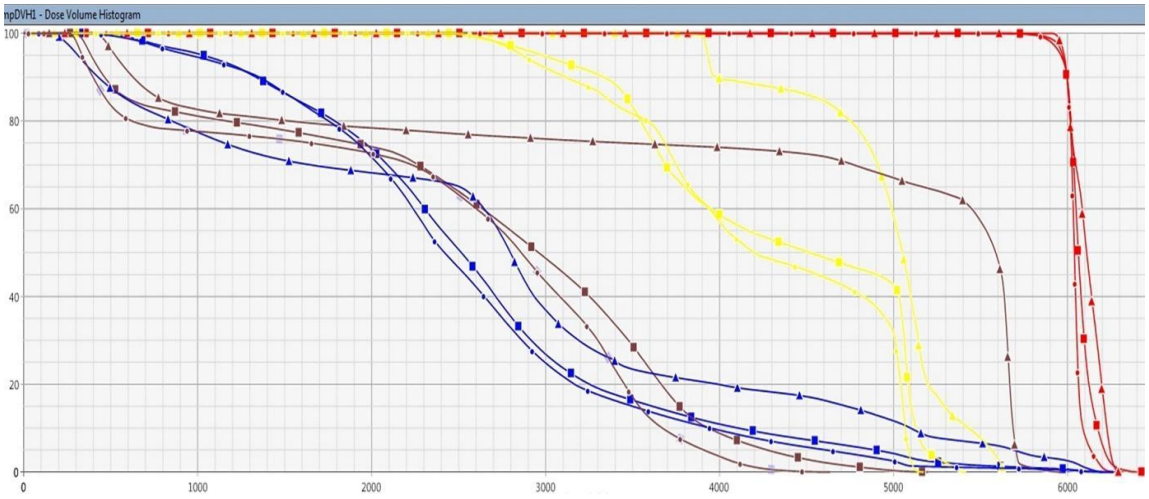

Table 3. Dosimetric values of organ at risks

Organ	Parameters	(A) FIF (Mean±SD)	(B) IMRT (Mean ±SD)	(C) SIB (Mean ±SD)	p A vs. B	p A vs. C	p B vs. C
Rectum	**D_{mean}(Gy)**	41.32±8.97	26.37±5.48	26.66±4.82	**0.000**	**0.000**	0.611
	V_{45}(Gy)	50.17±10.06	29.76±6.80	28.60±5.65	**0.000**	**0.000**	0.524
	V_{30}(Gy)	54.11±5.42	35.08±6.62	33.61±6.23	**0.000**	**0.000**	0.442
	V_{20}(Gy)	55.70±4.78	38.23±6.69	37.16±6.31	**0.000**	**0.000**	0.624
Bowel	D_{mean}(Gy)	24.62±12.65	19.61±7.16	19.76±7.70	0.040	0.042	0.998
	V_{45}(Gy)	22.75±12.45	19.67±10.59	19.22±10.86	0.000	0.001	0.628
	V_{30}(Gy)	29.25±13.50	25.25±10.38	25.45±11.71	0.002	0.016	0.888
Right Femur	D_{mean}(Gy)	25.61±9.38	17.72±7.34	17.02±6.72	0.000	0.000	0.034
	V_{20}(Gy)	40.53±7.10	28.60±4.94	27.98±4.51	0.000	0.000	0.153
Left Femur	D_{mean}(Gy)	26.47±9.37	17.01±6.93	16.30±6.65	0.000	0.000	0.036
	V_{20}(Gy)	41.85±7.45	27.41±4.19	28.10±7.95	0.000	0.000	0.690
Sacral Plexus	D_{max}(Gy)	55.37±2.64	52.95±2.48	51.98±1.37	0.001	0.000	0.041

FIF: field-in-field, IMRT: intensity-modulated radiation therapy, SIB: simultaneous integrated boost, D_{mean}: mean dose, D_{max}: maximum dose V: Volume, SD: Standard deviation p: paired sample t-test, *p <0.05

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Table 4. The biologically effective doses comparisons of target and organ at risks

Structures	Parameters	(A) FIF (Mean±SD)	(B) IMRT (Mean ±SD)	(C) SIB (Mean ±SD)	P		
					A vs. B	**A vs. C**	**B vs. C**
PTV_{60}	**D_{95}**	67.45±1.30	69.55±1.76	71.60±0.81	**0.000**	**0.000**	**0.000**
PTV_{50}	**D_{95}**	64.14±4.03	63.53±3.60	62.29±2.70	0.438	**0.000**	**0.000**
Rectum	**D_{mean}**	66.11±14.35	42.20±8.77	45.69±8.27	**0.000**	**0.000**	**0.001**
	V_{45}	80.28±16.11	47.61±10.89	48.46±10.61	**0.000**	**0.000**	**0.000**
	V_{30}	86.58±8.68	56.37±10.95	57.01±11.94	**0.000**	**0.000**	**0.002**
	V_{20}	89.12±7.65	61.49±11.17	63.04±12.32	**0.000**	**0.000**	**0.004**
Bowel	D_{mean}	39.40±20.24	31.38±11.46	33.41±13.91	0.040	0.172	0.000
	V_{45}	36.40±19.92	31.48±16.94	32.52±19.00	0.000	0.058	0.003
	V_{30}	46.80±21.61	40.41±16.61	43.35±20.45	0.002	0.434	0.000
Right Femur	D_{mean}	40.98±15.02	28.35±11.75	29.17±11.51	0.000	0.000	0.083
	V_{20}	64.85±11.36	45.77±7.90	47.94±7.74	0.000	0.000	0.005
Left Femur	D_{mean}	42.36±14.99	27.22±11.09	27.93±11.40	0.000	0.000	0.188
	V_{20}	66.97±11.93	43.85±6.70	48.14±13.63	0.000	0.000	0.156
Sacral Plexus	D_{max}	88.59±4.23	84.72±3.98	88.45±1.80	0.001	0.867	0.000

FIF: field-in-field, IMRT: intensity-modulated radiation therapy, SIB: simultaneous integrated boost, D_{mean}: mean dose, D_{max}: maximum dose V: Volume, SD: Standard deviation p: paired sample t-test, *p <0.05

Discussion

Radiotherapy applications to the bladder region may be complicated by the change in bladder volume. In order for patients to benefit from bladder radiotherapy, it is very important that the treatment as accurately and quickly as possible. The IMRT technique is an advanced form of 3D-CRT. The main beam is divided into smaller beamlets or segments that are adjusted to create different intensities in the target. In this treatment approach, which makes the PTV dose distribution more conformal and better protects normal tissues, the beam intensity in each radiation field is optimally adjusted. The advantage of this dose distribution over conventional treatments is that critical organs are better protected and higher doses can be reached in the target[18].

Çelen et al. compared the sequential IMRT and SIB techniques to the whole breast and boost area in patients who underwent breast-conserving surgery[19]. When the SIB and

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IMRT technique were applied to the ipsilateral lung, they found that the V_5 value was not statistically significant, while the V_{20} value was statistically significant. They found that V_{20} doses were lower in the ipsilateral lung with the SIB technique. Similarly, in our study, lower rectum V45 and bowel V30 dose values were observed in the SIB technique.

Nageeti et al. compared PTV and OAR in volumetric modulated arc therapy (VMAT) technique with SIB and sequential boost method for high-grade glioma[20]. In their study, they found similar results in critical organs for all plans. They stated that the SIB technique, which provides the total dose with fewer fractions, is the best option for patients with short survival without increasing toxicity. In our study, it was found that the SIB technique is suitable for the protection of critical organs.

Christine et al. compared the sequential IMRT and SIB techniques for treating pelvic targets[21]. They found that IMRT and SIB plans were comparable PTV coverage. They stated that the SIB technique significantly reduced the hot dose areas. They found that SIB plans provided good protection for critical organs overall but only significant results for rectum and small bowel doses. They also suggested that SIB technique reduces treatment time by facilitating the planning process. In our study, bowel D_{mean} and V_{45} doses and sacral plexus D_{max} and D_{mean} doses were not found to be statistically significant between SIB and IMRT plans. However, when we compared both plans with FIF, we found that SIB and IMRT techniques were more advantageous.

Li et al. compared the conventional IMRT and SIB technique for gastrointestinal stromal tumors[22]. They suggested that SIB may be a potential technique for achieving objective response and prolonging survival of selected GISTs patients. Moamen et al. compared the sequential (SEQ) and SIB techniques for breast radiotherapy[23]. They found that based on the DVH comparisons, the use of SIB reduced the biological breast mean dose by about 3%, the ipsilateral lung and heart by about 10%, and the contralateral breast and lung by about 7%. They suggested that SIB technique are dosimetrically more advantageous than SEQ in breast target volume and OARs. In our study, similar results were obtained with these studies.

Bakkal et al. evaluated the impact of SIB techniques on organs at risk in rectal cancer planning[24]. In a dosimetric comparison including 3D-CRT, IMRT and SIB-IMRT, it was reported that SIB-IMRT provided favorable dose distributions with improved sparing of organs at risk compared to conventional techniques. Similarly, in the present study, lower rectum and bowel dose parameters were observed in SIB and IMRT plans compared to FIF.

This study is based on dosimetric analysis, and no clinical conclusions can be drawn. According to the DVHs obtained from the study, the rectum and bowel V_{45} and V_{30} doses are significantly lower in IMRT and SIB plans. The results of the study demonstrated improved dose conformality and more favorable OAR dose distributions in SIB and IMRT plans compared to FIF. However, BED calculations have provided an additional benefit to these results. The BED values calculated for the rectum and bowel V_{45} and V_{30} doses were found to be slightly higher in SIB plans than in IMRT. This increase is due to

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the higher dose per fraction in the SIB technique. Therefore, although the SIB plans show lower doses for the rectum and bowel, biologically, these organ doses are seen to increase slightly. This indicates that although SIB plans result in higher calculated biological dose values in the target, careful attention should be paid to the biological dose received by critical organs. In addition to these results, in SIB technique, the reduction in the total number of fractions shortens the treatment time, thereby improving patient comfort, reducing the clinical workload, and increasing device utilization efficiency. This may potentially reduce overall treatment time and improve workflow efficiency, although these aspects were not directly evaluated in this study.

Conclusion

In our study, when the SIB technique was compared to other plans, it was seen that SIB had a significant advantage, especially against FIF plans. SIB plans increase biological efficacy due to their short treatment duration and high dose intensity; however, dose optimization must be performed with great care to avoid exceeding critical organ tolerances. Based on dosimetric findings, the SIB technique may be considered a feasible planning approach for bladder cancer; however, clinical outcome studies are required to confirm its safety and efficacy.

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