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## Original Article

### Which technique is better for planning parametrial boost for cervical carcinoma?

### A dosimetric comparison study about new radiotherapy techniques vs classic method

Zeliha Güzelöz<sup>a, †, </sup>, Ahmet Çalışır<sup>a, </sup>

<sup>a</sup> Department of Radiation Oncology, Health Science University Tepecik Training and Research Hospital, İzmir

#### ABSTRACT

**Objective:** The idea of this study was based on the question of which technique should be used to plan parametrial boost in clinics that treat cervical carcinoma with external beam radiotherapy (EBRT), but send their patients to other centers for brachytherapy, and who wish to prepare all EBRT plan before brachytherapy.

**Materials and Methods:** Intensity Modulated Radiotherapy (IMRT), Volumetric Arc Therapy (Vmat) and Antero-Posterior (AP-PA) plans with Simultaneous Integrated Boost (SIB) or sequential boost of 10 patient target volume and organ at risk doses were evaluated. Forty-five Gy were administered for the pelvis and 54 Gy were administered for the parametrium.

**Results** The conformity and homogeneity indexes were found to be better in SIB for both the pelvis and the parametrial volumes. In the evaluation of V45 and V54 in the rectum and the bladder, it was observed that the SIB plan was statistically significantly lower ( $p=0.01$ ,  $p<0.001$ ,  $p=0.02$ ,  $p<0.01$  respectively) and for the V54 AP-PA plan was higher than the others ( $p<0.01$  for both rectum and bladder).

**Conclusion:** SIB is considered to be a preferable method due to better CI, HI, dose coverage and lower normal tissue tolerance doses than the other techniques. A sequential boost can be applied in patients where a higher daily pelvic dose is desired.

**Keywords:** cervical carcinoma, radiotherapy, parametrial boost, simultaneous integrated boost, radiotherapy techniques

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## Introduction

The parametrium (PM) is a fibrous connective tissue that is located at the supravaginal part of the cervix. This tissue surrounds the uterus. It separates the bladder from the cervix [1]. Due to its close location, parametrium is usually the first place that extra cervical invasion is seen. That is why gynecological examination under anesthesia is recommended to evaluate both the cervix and the parametrium [2].

Pelvic external beam radiotherapy (EBRT) and concurrent chemotherapy followed by intracavitary brachytherapy (ICBT) is the standard treatment for advanced-stage cervical cancer [3]. Parametrial boost (PMB) is an important part of EBRT. It is known that an additional boost dose given to the parametrium prevents local recurrences in this area [4]. A total 50-60 Gy dose is recommended for PMB [5].

Midline blocks have been traditionally recommended during EBRT to protect the midline structures [5]. Blocks improve the dose distribution in brachytherapy by lowering the dose in the midline (rectum, bladder, small bowel) and at the same time, it allows safe dose distribution of PMB. However, today, instead of midline blocks, technological innovations in radiotherapy planning such as Intensity Modulated Radiotherapy (IMRT) and Volumetric Arc Therapy (Vmat) provide improvements in dose distribution and less toxicity [6-8].

Traditionally, a parametrial boost is planned where sufficient dose cannot be reached in the parametrial area after the ICBT dose distribution.

However, it is difficult to plan parametrial boost for radiotherapy centers without brachytherapy equipment, just as in our case.

The idea of this study was based on the question of how to plan parametrial boost in clinics that treat cervical cancer with EBRT but send their patients to other centers for brachytherapy or who wish to prepare all EBRT plans before the ICBT. Therefore, in the current study, we aimed to plan the parametrial boost within EBRT sessions and to compare different new methods (not using midline blocks) such as IMRT, Vmat, SIB and AP-PA field in this planning by SIB or sequential.

Our goal was to reveal the treatment method that would affect the brachytherapy dose distribution at least, have low organ risk doses, preserve midline structures, but provide a sufficient dose to the parametrium.

## Material and methods

### Patient selection

10 patients diagnosed with Stage IIB according to the FIGO 2018, who had intact uterus cervical cancer treated with radical chemoradiotherapy in our department between April 2018 to April 2019 were enrolled.

<sup>†</sup> Corresponding author.

E-mail: zelihaguzeloz@gmail.com  
ORCID ID: 0000-0003-3719-5748

### Target Delineation

Simulation tomography images of patients were downloaded from the contouring database Velocity version 3.2.1. All simulations were performed in the supine position with contrast enhancement and 3 mm slice thickness.

All contours were delineated by a single experienced radiation oncologist and all plans were made by a single physicist to avoid personal differences.

The bilateral parametria were contoured according to the RTOG consensus guideline [9]. The boundaries of the parametrium were defined in table 1.

Table 1: Anatomic boundaries of CTV<sub>pm</sub> according to the RTOG Guideline

Location	Anatomic definition
Anteriorly	Posterior wall of bladder or posterior border of external iliac vessel
Posteriorly	Uterosacral ligaments and mesorectal fascia
Laterally	Medial edge of internal obturator muscle/ ischial ramus bilaterally
Superiorly	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.
Inferiorly	Urogenital diaphragm

Target volumes were delineated as PTV<sub>pelvis</sub> according to the guideline [9]. The defined CTV and PTV contents have been demonstrated in table 2.

Table 2: Target volumes

PTV <sub>in</sub>	CTV <sub>in</sub> * +7 mm marj
PTV <sub>primary</sub>	CTV <sub>GTV,uterus,cervix</sub> +15 mm marj
PTV <sub>paravajen/pm</sub>	CTV <sub>paravajen,pm,ovvaries, proximal vagina</sub> +10 mm marj
PTV <sub>pelvis</sub>	PTV <sub>in</sub> +PTV <sub>GTV,uterus,cervix</sub> + PTV <sub>paravajen,pm,ovvaries, proximal vagina</sub>
PTV <sub>pm</sub>	CTV <sub>pm</sub> +5 mm

A 5 mm margin was given to the parametria in all directions except for the medial boundary to the CTV<sub>pm</sub> to avoid the maximum dose in the middle structure. We predicted that a sufficient dose would be reached with ICBT in this area.

### Treatment Planning

Forty-five Gy were administered for PTV<sub>pelvis</sub> and 54 Gy were administered for PTV<sub>pm</sub>.

In order to compare the different techniques in the parametrial boost plan, the PTV<sub>pelvis</sub> plan (up to 45 Gy) was planned to use the same arc technique in each plan. Two opposite full arcs were created using 6 Mvx energy. D95 (dose taking 95% of the volume) of the dose defined for PTV<sub>pelvis</sub> was aimed to cover 100% of the volume. The maximum dose was kept below 110%.

Four different boost plans were mentioned for PTV<sub>pm</sub>, (SIB, IMRT, Vmat and AP/PA) created up to 54 Gy. For each of the four plans, D95 of the dose defined for PTV<sub>pm</sub> was aimed to cover 100% of the volume. The maximum dose was kept below 110%. In the SIB plan, 3 full arc plans were designed, 2 of which were clockwise and one counterclockwise using 6 Mvx.

In the Vmat plan, 2 opposite full arcs were planned with 6 mvx. Seven area IMRT was created using 0°/51°/102°/153°/20° /255°/360° gantry angles with 6 MVX. The AP-PA plan was delivered using gantry 0°/180°

angles with 15 Mvx. The maximum value was permitted to be below 115% due to the thickness and 15 Mvx energy.

SIB comprised 27 fractions; the other plans were 25 fractions followed by 5 days of PMB, with a total dose of 54 Gy.

All plans were performed using the Varian Eclipse® Treatment Planning System version 15.5 for Varian Vital Beam® Linear Accelerator with 120-millennium multi-leaf collimator. Each leaf was 0.5 cm in the center and 1 cm in the outer part.

The mean, maximum, D95 and D98 (dose taking 98% of the volume) values of PTV<sub>pelvis</sub> and PTV<sub>pm</sub> were obtained from the dose-volume histograms with the recommendation of ICRU 98. Furthermore, the mean, maximum, V10-30-45-54 (percent of the volume taking 10-30-45-54 Gy dose), D2cc (minimal dose to 2 cm<sup>3</sup> of the OAR receiving the maximum dose) values for OAR were determined.

Dose constraints to the organ at risk were created based on the Quantitative Analysis of Normal Tissue Effect in the Clinic [10], but doses were kept lower for the rectum and the bladder. For the rectum, V50<50%, for the bladder, V50<50%. The other dose constraints were V45 <195 cc for the small bowel and V50<10% for the femoral heads. The Paddick conformity index was used to calculate conformity of PTV coverage to the prescribed doses for PTV<sub>pelvis</sub> and PTV<sub>pm</sub> [11]. In addition, the Homogeneity Index was evaluated for the homogeneity of the plans according to the ICRU 83. D2-D98/D50 was used for calculating the Homogeneity Index [12]. (D2: Dose of 2% of PTV, D98: Dose of 98% of PTV D50: Dose of 50% of PTV)

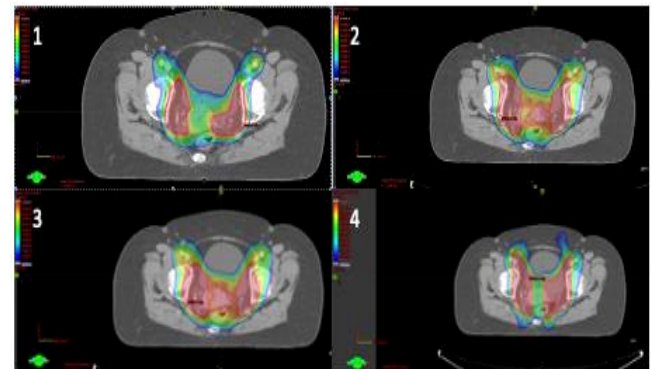
### Statistical analysis

Statistical analysis was carried out using the IBM® SPSS® 22 (SPSS Inc., Chicago, IL, USA) software. Descriptive analyses were given using the mean ± standard error for normally distributed variables, and median (median) and min-max, IQR for the non-normally distributed variables. The One-way ANOVA test was used to compare more than two groups. The homogeneity of variances was evaluated using the Levene test. In cases where there was a significant difference between the groups, the posthoc Bonferroni tests were used for the paired comparisons. Cases in which the p-value was below 0.05 were considered statistically significant.

## Results

The median tumor volume was 70 cc (25-102). The median right and left PM volumes were 49.5 cc and 49 respectively. Figure 1 shows the dose distributions of the SIB, IMRT, Vmat and AP-PA plans for a representative patient, respectively.

Figure 1. Dose distributions of the SIB, IMRT, Vmat and AP-PA



1; SIB plan, 2; IMRT plan, 3; Vmat plan, 4; AP-PA plan  
Dose distributions with colour wash image in Figure 1-4  
blue: PTV<sub>pelvis</sub>, magenta: PTV<sub>pm</sub>, red: GTV<sub>tumor</sub>

All results were obtained at the prescribed dose of 54 Gy. Table 3 summarizes the planning results of the target volumes (mean, maximum, minimum, D95, D98, CI, HI) Although the D95 value of PTVpelvis was not statistically significant, the SIB-D98, SIB-CI, SIB and HI values were statistically significant compared to the IMRT and Vmat plan. As shown in Table 3, the PTVpm CI and HI values were statistically significant for SIB compared to others (p<0.001 and p=0.05, respectively, with the Annova Test).

Table 3. Data of target volume parametres

Target Volume Parameters	SIB*	IMRT*	Vmat*	AP-PA*	p value
PTV <sub>pelvis</sub>					
Mean(Gy)	4859±23.8 <sup>b,c,d</sup>	4983±22.6	4986±22.9	5002±23.7	<0.001 <sup>a</sup>
Max (Gy)	5710±11.6	5690±13.8	5689±12.5	5723±23.1	0.812
Min (Gy)	3826±59.51 <sup>e,f,g</sup>	4044±35.6	4050±35.1	4038±34.5	0.001 <sup>a</sup>
D95	4546±3.5	4562±6.8	4563±7.1	4553±6.4	0.174
D98	4547±5.3 <sup>h,i</sup>	4530±5.8	4532±6.0	4522±5.6	0.016 <sup>a</sup>
CI (%)	0.887±0 <sup>i</sup>	0.777±0	0.770±0	0.739±0	<0.001 <sup>a</sup>
HI (%)	0.222±0 <sup>k,l,m</sup>	0.204±0	0.200±0	0.215±0	<0.001 <sup>a</sup>
PTV <sub>pm</sub>					
Mean (Gy)	5502±5.3	5498±4.9	5495±5.0	5471±6.7	0.352
Max (Gy)	5710±11.6	5682±14.2	5685±12.3	5685±14.0	0.247
Min (Gy)	5114±21.8	5266±15.6	5273±20.5	5267±19.4	0.421
D95	5402±3.3	5436±4.5	5435±4.3	5356±91.4	0.576
D98	5376±3.3	5418±4.8	5418±4.5	5406±7.0	0.525
CI (%)	1.0±0 <sup>n</sup>	0.604±0	0.627±0	0.356±0	<0.001 <sup>a</sup>
HI (%)	0.041±0 <sup>o,p</sup>	0.030±0	0.029±0	0.032±0	0.005 <sup>a</sup>

\*Mean Values±%standard error  
<sup>a</sup> Statistically significant difference between four groups with Annova test.  
<sup>b-p</sup> are evaluated with repeated measures analysis of variance and post hoc analyses with Bonferroni correction test  
 Statistically significant difference in comparison of <sup>b</sup> SIB and IMRT (p=0.03), <sup>c</sup> SIB and Vmat (p=0.03), <sup>d</sup> SIB and AP-PA (p=0.01), <sup>e</sup> SIB and IMRT (p=0.005), <sup>f</sup> SIB and Vmat (p=0.004), <sup>g</sup> SIB and AP-PA (p=0.007), <sup>h</sup> SIB and IMRT (p=0.043), <sup>i</sup> SIB and Vmat (p=0.026), <sup>j</sup> SIB and IMRT, Vmat, AP-PA (p<0.001 for all three values), <sup>k</sup> SIB and IMRT (p=0.02), <sup>l</sup> SIB and Vmat (p<0.001), <sup>m</sup> Vmat and AP-PA (p=0.015), <sup>n</sup> SIB and IMRT, Vmat, AP-PA (p<0.001), <sup>o</sup> SIB and IMRT (p=0.018), <sup>p</sup> SIB and Vmat (p=0.008).

Table 4 summarizes the data on organ at risk (OAR). The mean values for all OAR except the small intestine were found to be the lowest with the SIB method.

Table 4. Data of OAR parameters

Organ at Risk Parameters	SIB	IMRT	Vmat	AP-PA	p value <sup>a</sup>
Rectum					
Mean (Gy)	4469±60.4	4944±55.5	4853±50.4	4846±77.4	0.383
Max(Gy)	5450±41.4 <sup>r</sup>	5504±36.2	5508±24.2	5633±33.1	0.005
V <sub>10</sub> (%)	100±0	100±0	100±0	100±0	
V <sub>30</sub> (%)	98.9±0.7	99.7±0.1	99.8±0.1	99.8±0.1	0.313
V <sub>45</sub> (%)	62.7±5.4 <sup>s,t</sup>	79.7±4.2	82.3±4.2	83.0±4.2	0.010 <sup>u</sup>
V <sub>54</sub> (%)	0.5±0.3	2.1±0.6	4.1±1.3	17.1±5.0 <sup>v,w</sup>	<0.001 <sup>a</sup>
Mesane					
Mean (Gy)	4053±86.0 <sup>x,y</sup>	4406±83.8	4461±92.8	4627±96.4	0.001 <sup>a</sup>
Max(Gy)	5618±10.6	5619±12.2	5615±11.0	5687±20.7 <sup>z,aa,ab</sup>	0.002 <sup>a</sup>
V <sub>10</sub> (%)	100±0	100±0	100±0	100±0	
V <sub>30</sub> (%)	81.0±2.8	89.1±3.3	89.6±3.1	92.8±2.5	0.053
V <sub>45</sub> (%)	43.3±4.1 <sup>ac,ad</sup>	57.3±3.6	59.7±3.6	65.3±3.9	0.002 <sup>a</sup>
V <sub>54</sub> (%)	5.3±1.3	10.6±1.5	10.5±2.1	28.6±3.8 <sup>ae</sup>	<0.001 <sup>a</sup>
Small bowel					
Mean (Gy)	2387±135.9	2377±135.2	2381±136.6	2412±142.7	0.998
Max(Gy)	5137±106.4	5121±132.2	5101±130.0	5168±148.6	0.987
V <sub>10</sub> (%)	83.0±5.1	82.9±4.8	84.9±5.0	82.9±4.8	0.990
V <sub>30</sub> (%)	30.3±3.5	29.5±3.8	36.4±8.0	33.8±4.7	0.787
V <sub>45</sub> (%)	7.1±1.7	7.6±2.0	16.5±8.7	8.8±2.1	0.458
V <sub>54</sub> (%)	0.2±0.1	0.6±0.3	0.7±0.4	1.8±1.0	0.273
Right femoral head					
Mean (Gy)	2934±56.1	3073±85.8	3124±80.5	3159±303.7	0.782
Max(Gy)	4893±39.2 <sup>af</sup>	5273±27.0	5321±34.6	5465±226.9	0.011 <sup>ag</sup>
V <sub>10</sub> (%)	100±0	100±0.1	100±0.1	100±0.3	0.307
V <sub>30</sub> (%)	46.1±1.9	51.4±3.3	53.3±3.3	43.0±2.9	0.70
V <sub>45</sub> (%)	3.7±0.6 <sup>ah</sup>	13.3±1.3	14.3±1.3	7.3±0.8 <sup>ai</sup>	<0.001 <sup>a</sup>
V <sub>54</sub> (%)	0±0	0±0	0±0	0±0	
Left femoral head					
Mean (Gy)	2865±56.1	3043±85.8	3027±80.5	2808±303.7	0.582
Max(Gy)	4978±39.2 <sup>aj</sup>	5208±27.0	5251±34.6	5201±79.9	0.033 <sup>ak</sup>
V <sub>10</sub> (%)	100±0	99.7±0.1	99.8±0.1	99.4±0.3	0.587
V <sub>30</sub> (%)	46.1±1.9	51.4±3.3	53.3±3.3	43.0±2.9	0.393
V <sub>45</sub> (%)	3.7±0.6 <sup>al</sup>	13.3±1.3	14.4±1.3	7.3±0.8	0.004 <sup>am</sup>
V <sub>54</sub> (%)	0±0	0±0	0±0	0±0	0.593

<sup>a</sup> Statistically significant difference between four groups.  
<sup>r-aa</sup> are evaluated with repeated measures analysis of variance and post hoc analyses with Bonferroni correction test  
 Statistically significant difference in comparison of <sup>r</sup> SIB and AP-PA (p=0.004), <sup>s</sup> SIB and Vmat (p=0.027), <sup>t</sup> SIB and AP-PA (p=0.02), <sup>u</sup> SIB and AP-PA (p=0.001) <sup>v</sup> IMRT and AP-PA (p=0.002), <sup>w</sup> Vmat and AP-PA (p=0.008), <sup>x</sup> SIB and Vmat (p=0.017), <sup>y</sup> SIB and AP-PA (p<0.001), <sup>z</sup> SIB and AP-PA (p=0.008), <sup>aa</sup> IMRT and AP-PA (p=0.011) <sup>ab</sup> Vmat and IMRT (p=0.006), <sup>ac</sup> SIB and Vmat (p=0.03), <sup>ad</sup> SIB and AP-PA (p=0.002), <sup>ae</sup> AP-PA and SIB, IMRT, Vmat (both two p values<0.001), <sup>af</sup> SIB and AP-PA (p=0.009), <sup>ag</sup> SIB and IMRT, Vmat (both two p values<0.001), <sup>ah</sup> AP-PA and IMRT (p=0.003), <sup>ai</sup> AP-PA and Vmat (p=0.003), <sup>aj</sup> SIB and Vmat (p=0.046), <sup>ak</sup> SIB and IMRT(p=0.041), <sup>al</sup> SIB and Vmat (p=0.007)

A similar situation was seen for the maximum value, except for the bladder Vmat plan. The V10 value of all OAR was seen as %100, except for the small intestine.

In the evaluation of V45 and V54 in the rectum and the bladder, it was observed that the SIB plan was statistically significantly lower (p=0.01, p<0.001, p=0.02, p<0.01 respectively), and for the V54 AP-PA plan, it was higher than the others (p<0.01 for both the rectum and the bladder). Similarly, in the bilateral femoral heads, it was noteworthy that the V45 value was statistically significantly lower in the SIB plan and higher in the AP-PA plan (p<0.01 for right femoral head, p=0.04 for left femoral head)

Table 5 shows that the rectum D2cc value was statistically significantly lower in the SIB plan than in the other plans [Statistically significant difference in comparison of SIB vs IMRT (p=0.002), SIB vs Vmat (p=0.001), SIB vs AP-PA (p<0.01)]

Table 5. Datas of D2cc values

D2cc	SIB	IMRT	Vmat	AP-PA	p-value <sup>a</sup>
Rectum	5090±48.7 <sup>b, y</sup>	5316±39 <sup>u, z</sup>	5335±32.3	5510±35.2	<0.001
Bladder	5505±9.5	5532±10.7	5523±10	5615±17 <sup>a</sup>	<0.001
Small Bowel	4955±117.6	4963±131.9	4972±127.8	5067±151	0.925

<sup>a</sup> Statistically significant difference between four groups.  
 Statistically significant difference in comparison of <sup>y</sup> SIB and IMRT (p=0.002), <sup>z</sup> SIB and Vmat (p=0.001), <sup>u</sup> SIB and AP-PA (p<0.001), <sup>v</sup> IMRT and AP-PA (p=0.008), <sup>w</sup> Vmat and AP-PA (p=0.02), <sup>x</sup> AP-PA and SIB, IMRT, Vmat (p<0.001)

## Discussion

Sufficient dosing to the parametria is an important parameter in terms of local control in the treatment of cervical cancer. In the study of Chao et al, 343 local advanced cervical cancer patients treated with radiotherapy were evaluated and 83 patients were verified as clinically positive with uterosacral involvement. The doses of EBRT were 18.02-33.20 Gy for the central pelvis and 48.22- 59.40 Gy for the lateral parametrium. The lateral parametrium dose was on average 10 Gy higher in patients with verified uterosacral involvement. Although the 5-year central/marginal recurrences of patients with uterosacral involvement were higher than the group without involvement (36% and 21% respectively p=0.002), the recurrence in the lateral parametrium was the same in both groups due to the use of PMB (39% and 38% respectively p=0.42) [4].

As it was mentioned in the introduction part, using midline blocks was a traditional method. In the study of 191 patients by Huang et al., incomplete MB was found to cause radiation proctitis [13]. In another study, 50% dose leakage was reported in OAR due to inappropriate blocks [14]. Furthermore, according to the information we received from 3D brachytherapy, while midline block caused the tumor to take lower doses, it caused higher doses with organs such as the bladder and the rectum [15]. That is the reason for new approaches to pm boost having been developed, namely image-guided brachytherapy with interstitial needles [16-18], stereotactic IMRT boost, etc. [19]. Although these methods are technically successful, they are not cost-effective, because they are invasive, impractical and costly.

Since the dose distribution in MB is not as desired, new approaches are invasive and need expensive equipment; hence, the idea of planning PMB with external RT has emerged. This method seems to be fast, cheap and technically feasible, especially for departments that have to refer brachytherapy patients to other centers.

At this point, it is important to know which method to choose when boosting with external beam RT. There are many

studies in the literature that draw attention to the SIB technique, because with this method, you can irradiate both the primary site and the area you will boost on the same day. Thus, you can shorten the treatment time, and in cervical cancer, shortening the treatment period returns as a survival advantage [20].

In the study of Chen et al., the IMRT-MB, IMRT-SIB, Vmat-SIB technique were compared for PMB plans. Dose coverage was found to be better in the model combined with SIB in both the pelvis and the parametria (PTV45-V100 are 98.7%, 98.53%, 98.90%, respectively,  $p < 0.001$ ; PTV50-V100 are 91.79%, 99.31%, 99.08%  $p < 0.001$ , respectively). Similarly, the CI values were found to be better in plans with SIB. The same is true for OAR.

In the study of Marnitz et al., the SIB and the sequential boost method were compared using helical tomotherapy. According to the study, boosting with the SIB technique was a good alternative and the clinical toxicity results were acceptable [21].

In the study of Giolda et al., it was emphasized that boost planning by image-guided helical tomotherapy was successful inhomogeneity and reducing the maximum doses in a small volume of OAR [22].

The sequential IMRT and Vmat boost mentioned in the study are seen as feasible options that are not superior to SIB. It is a good alternative when you want to give the pelvic daily dose higher than 1.66 Gy, total dose 45 Gy.

In the daily routine of our clinic, we prefer SIB doses as 45 Gy / 1.66 Gy daily for the pelvis and 54Gy / 2 Gy daily for the parametrium. However, we sometimes have doubts about how effective 1.66 Gy a day is. We do not recommend doses above 2 Gy per day due to the long-term side effects that may increase, especially for the small intestine and the rectum [23].

The pelvic target volume parameters in our study show that SIB plans are observed to be statistically significantly better in terms of D98, CI and HI than other plans. The minimum value in the SIB plan has been found to be statistically significantly lower than the sequential plans (SIB min value  $3826 \pm 59.51$   $p = 0.001$ ). Boost doses added in sequential plans lead to an increase in the doses within the area, causing the minimum dose to be higher. Although it was not statistically significant, the maximum values were found to be higher in the SIB plan due to the higher dose (2 Gy) given daily to the parametrium.

When the parametrial target volumes were evaluated, statistically significant values were found only in CI and HI with the SIB plan ( $p$  values  $< 0.001$  and  $0.005$  respectively). In the evaluation of organ at risks parameters, it was observed that small intestine doses did not change statistically with any planning technique. We would normally expect the intestinal doses to be higher, particularly in the AP-PA plan. That is why MLC reduces the effect instead of blocking applications used in old techniques.

The V10-30 values were found to be high in the bladder and the rectum due to the D95 values being almost 100% in target volumes and the good probability of dose coverage for all techniques.

It was seen that statistically significant lower doses were obtained in the rectum and the bladder with SIB for V45. We attribute this to the dose decrease in SIB after the target volume and the focusing of the dose without dispensing with the arc technique. Just like stereotaxy. The V54 doses were increased distinctly in AP-PA planning due to attempting to administer the required dose to the target tissue, especially in thick patients, depending on the increasing maximum doses.

Femoral heads in all four methods were not affected by the V54 dose. It was the SIB plan that made a statistically significant difference for the V45 parameter, and the AP-PA

doses were found to be high; 120% maximum dose was seen in some patients, due to the afore-mentioned reasons.

According to the current guidelines, the D2cc values should be reported for the bladder, rectum and the small bowel to evaluate the hot spots in cumulative EBRT and brachytherapy plan to avoid the late side effect. The recommendation of ABC limits for D2cc of the rectum and the bladder are  $\leq 75$  Gy and  $\leq 90$  Gy, respectively [24,25]. GEC\_ESTRO GYN and RetroEMBRACE recommended  $< 65$  Gy for the rectum,  $< 80$  Gy for the bladder and  $< 70$  Gy for small bowel [26,27]. We refer our patients to brachytherapy after EBRT with all plan data including the D2cc values. We try to keep the D2cc doses below 75 Gy for the rectum, bladder and small bowel in the cumulative plan according to our protocol. That is why we checked the D2cc in the EBRT plan and aimed for the lowest OAR dose. In the SIB plan, the rectum D2cc value was statistically significantly lower than the others. The SIB plan achieved a mean dose of approximately 3 Gy lower than IMRT, Vmat and 5 Gy lower than AP-PA. For the bladder, such an advance was not observed with SIB, IMRT or VMAT, but it was determined that it should not be preferred due to the high dose of AP-PA plans.

As a result, SIB is considered to be a preferable method, because it provides better CI, HI, dose coverage, and lower normal tissue tolerance doses than the other three sequential boosting techniques. Furthermore, the shortened treatment time appears to be cost-effective, both radiobiologically and financially. With this technique, we can refer the patient to brachytherapy with the EBRT plans completed. This is a cost-effective method, especially for the under-developed countries and inadaptible patients. The AP-PA plan, which is an old-fashioned method, should not be preferred if you are going to administer sequential therapy in patients who cannot be planned with SIB. If you have to choose it, doing this using with multi-leaf collimator will better preserve your normal tissue doses. Additionally, a sequential boost can be applied in patients where a higher daily pelvic dose is desired.

## Disclosure

Authors have no potential conflicts of interest to disclose.

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