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Dosimetric Comparison of Intensity Modulated Radiotherapy and Simultaneous Integrated Boost Techniques in the Treatment of Glioblastoma Multiforme

Glioblastoma Multiform Tedavisinde Yoğunluk Ayarlı Radyoterapi ve Simultane Entegre Boost Tekniklerinin Dozimetrik Karşılaştırılması

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ABSTRACT

Aim: The aim of this study was to compare dosimetric advantages of using intensity-modulated radiation therapy (IMRT) and simultaneous-boost (SIB-IMRT) techniques for glioblastoma multiform (GBM).

Materials and Methods: Ten patients with GBM were retrospectively selected between the years of 2020 and 2021. For all patients, two treatment plans were created. The plans were calculated using anisotropic analytical algorithm with 6 MV photon energy. Treatment doses were 50 Gy for planned target volume (PTV) (50 Gy), 10 Gy for PTV (60 Gy) and 60 Gy for PTV (60 Gy), which is planned as 2 Gy per daily fraction in IMRT technique. In the SIB-IMRT technique, which provides different dose levels in target volumes simultaneously in 25-day fractions, was used. All plans were compared with respect to the doses received by PTV and the organ at risk including brain system, optic chiasma, optic nerves, eyes, the dose homogeneity index (HI), conformity indexes (CI) and total monitor unit counts required for the treatment.

Results: The average doses for PTV were 60.62±0.33 Gy for the IMRT technique and 60.58±0.32 Gy for the SIB-IMRT technique. The average doses for PTV, for both techniques were found to be similar. The average HI value for PTV (60 Gy) was 0.05±0.009 in IMRT, 0.13±0.197 in SIB-IMRT, 0.97±0.02 in IMRT, and 0.35±0.06 in SIB-IMRT, respectively. As a result of the statistical comparison, a significant difference was observed in HI and CI values between IMRT and SIB-IMRT in the analysis of the values of PTV (p=0.004, p=0.001). When the SIB-IMRT plans were compared with the IMRT plans, it was observed that the mean doses received by critical organs such as optic chiasma, optic nerve, and eye were significantly decreased in the SIB-IMRT technique (p=0.000).

Conclusion: When the IMRT technique for GBM treatment was compared with the SIB-IMRT technique, SIB-IMRT provided better protection for organ at risk. SIB-YART plans may be clinically acceptable treatment modalities for GBM cancers.

Keywords: Glioblastoma multiform, intensity-modulated radiation therapy, simultaneous integrated boost method

ÖZ

Amaç: Bu çalışmanın amacı glioblastoma multiform (GBM) tedavisinde yoğunluk ayarlı radyoterapi (YART) ve simultane entegre boost (SIB-YART) tekniklerini dozimetrik olarak karşılaştırmaktır.

Gereç ve Yöntem: Bölümümüzde 2020-2021 yılları arasında RT tedavisi alan 10 GBM hastası çalışmaya dahil edildi. Her hasta için aynı tümör ve kritik yapılar kullanılarak YART ve SIB-YART tekniklerinde planlar yapıldı. Tedavi dozları YART tekniğinde günlük fraksiyon başına 2 Gy olacak şekilde planlanan hedef hacime (planned target volume-PTV) (50 Gy) 50 Gy ve PTV'ye (60 Gy) 10 Gy ve toplamda PTV'de (60 Gy) 60 Gy'yi tamamlayacak şekilde planlandı. SIB-YART tekniğinde ise 25 günlük fraksiyonda eş zamanlı olarak hedef hacimlerde farklı doz seviyelerinin sağlandığı SIB tekniği kullanıldı. Planlar 6 MV foton enerjisi kullanılarak, anisotropik analitik algoritması ile Eclipse tedavi planlama sisteminde hesaplatıldı. PTV, beyin sapı, optik kiazma, optik sinir ve göz gibi risk altındaki organlar (RAO), doz homojenite indeksi (HI), konformite indeksi (CI), monitör üniteleri açısından YART planları SIB-YART planları ile karşılaştırıldı.

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Bulgular: PTV için ortalama dozlar YART tekniği için 60,62±0,33 Gy iken, SIB-YART tekniği için 60,58±0,32 Gy'dir. Her iki teknik için PTV'nin aldığı ortalama dozlar benzerdir. PTV (60 Gy) için HI ortalama değeri sırasıyla YART'de 0,05±0,009 iken, SIB-YART'de 0,13±0,197, CI ise YART'de 0,97±0,02, SIB-YART için 0,35±0,06 olarak bulundu. Yapılan istatistiksel karşılaştırma sonucunda PTV'ye ait değerlerin analizinde YART ve SIB-YART arasında HI ve CI değerlerinde anlamlı bir fark görüldü (p=0,004, p=0,001). SIB-YART planları YART planları ile karşılaştırıldığında optik kiazma, optik sinir, göz gibi kritik organların aldığı ortalama dozların SIB-YART tekniğinde anlamlı olarak azaldığı görüldü (p=0,000).

Sonuç: GBM tedavisine yönelik YART tekniği SIB-YART tekniği ile karşılaştırıldığında, SIB-YART tekniğinin kritik organları daha iyi koruduğu görüldü. SIB-YART planları GBM kanserlerinde klinik olarak kabul edilebilir tedavi yöntemi olabilir.

Anahtar Kelimeler: Glioblastoma multiform, yoğunluk ayarlı radyoterapi, simultane entegre boost tekniği

INTRODUCTION

Glial tumors are the most common primary malignant brain tumors in adults[1]. Malignant gliomas (World Health Organization grade 3-4) constitute more than half of primary brain tumors, and approximately 75% of them are glioblastoma multiform (GBM) with grade IV[2,3]. It is known that malignant brain tumors, especially GBM, have lower survival rates and the worst prognosis due to their high progression potential[4]. The primary standard treatment for GBM treatment is surgery[5,6]. However, due to its high infiltrative character, GBM has high local recurrence rates even with the best surgical approach, which necessitates additional local treatments such as radiotherapy (RT). According to the results of phase III randomized studies, the standard adjuvant treatment of GBM is 60 Gy local RT ± alkylating agent-based chemotherapy[7]. In GBM RT, tumors can usually be located in or very close to critical radiation-sensitive structures such as the brain stem, optic chiasm, right optic nerve, left optic nerve, right orbit, and left orbit. The tolerance doses of these critical structures are lower than the targeted treatment doses, and this may cause damage to critical structures.

The aim in RT is to protect the critical structures around it in the best possible way, while giving the desired dose to the determined target volume[8]. Today, there are many RT options used in treatment. One of the most commonly used treatments in RT is intensity modulated RT (IMRT). In IMRT treatment techniques, the aim of treatment is determined in advance with the inverse planning system. In the optimization processes, it is tried to obtain a homogeneous and desired dose distribution in order to achieve these goals. In IMRT techniques, different fraction schemes can be applied to different target volumes simultaneously with the simultaneous integrated boost (SIB) method. In IMRT treatments for this purpose, organs at risk (OAR) and target volumes are displayed in three dimensions, and the most appropriate gantry angles and number of fields are determined, and treatment planning is made.

In this study, it was aimed to compare the current treatment plan of our patients with malignant glial tumors, who were treated with the IMRT technique, with the virtually created SIB-IMRT technique, dosimetrically.

MATERIALS AND METHODS

Patient Selection

For the study, 10 patients with malignant glial tumors who were treated with 60 Gy RT and CRT in the Department of Radiation Oncology, Faculty of Medicine Selçuk University between 2020 and 2021 were selected. Permission for this study was obtained from the Ethics Committee of Selçuk University Faculty of Medicine, with the decision dated 07 April 2021 and numbered 2021/198. The clinical and dosimetric characteristics of the patients selected for the study are given in Table 1.

Target Volume and Critical Organs

All patients were immobilized with a head and neck thermoplastic mask in the supine position. The images obtained by scanning 3 mm slice thickness over the area of interest in the computed tomography (CT) unit were transferred to the treatment planning system (Eclipse, version 15.1; Varian). Preoperative and postoperative axial T1 contrast and axial T2-FLAIR magnetic resonance (MR) images were fused to the planning CT image set for contouring. For gross tumor volume (GTV) determination, T1 contrast-enhanced and axial T2-FLAIR from preoperative MR images or the cavity and surrounding area of contrast on postoperative MR were defined as GTV_{50}.

The clinical target volume (CTV) CTV_{50} was created by adding an isometric 2-2.5 cm margin to the GTV_{50} to achieve the CTV, and the PTV_{50} was created by adding a 0.5 cm margin around the CTV_{50} for the planned target volume (PTV) definition. For the boost area, the GTV_{60} was contoured using preoperative MR axial T1 contrast-enhanced images. The CTV_{60} was created by adding an isometric 2-2.5 cm margin to the GTV_{60} and PTV_{60} was created by adding 0.5 cm margin around the CTV_{60}[9,10]. Brain stem, optic chiasm, right optic nerve, left optic nerve, right orbit and left orbita were contoured as critical organs. Target structures were removed with a 1 mm margin from each other in order to ensure sharp dose changes easily. By removing the parts of critical organs that intersected with the tumor with a margin of 2 mm, the mean dose values were reduced. The IMRT treatment technique was planned as PTV_{50}, 50 Gy from 2 Gy/25 fractions in phase 1, and then 60 Gy in total from PTV_{60} 2 Gy/5

fractions in phase 2. In the SIB-IMRT treatment technique, PTV_{60} was planned to be 2.4 Gy in 25 fractions.

Treatment Planning

In this study, the Varian Millennium 80-leaf collimators (Varian) treatment device available in our clinic was used. Dynamic IMRT and SIB-IMART treatment plans with 5 coplanar fields were created for GBM patients with IMRT and SIB-IMART techniques. IMRT plans were prepared with the inverse planning method using 6 MV X-rays. After the treatment plans were created, the optimization process was started. During the optimization process, minimum and maximum dose limitations were made to the target volumes, and it was aimed that 95% of the PTVs would receive 100% of the defined dose. Necessary dose limitations were made in order to give the lowest dose among the determined criteria to the organs at risk. Anisotropic Analytical Algorithm (v.15.1) was used for dose optimization and calculations of IMRT plans.

Plan Evaluation

Dose volume histograms (DVH) were used to compare the target volume and critical organ doses of the treatment plans. PTV and the doses taken by the OAR were evaluated by comparing DVHs from IMRT and SIB-IMRT plans. Homogeneity index (HI) and conformity index (CI) parameters are used to evaluate plans in different treatment options. The dose HI formula was defined according to the International Commission on Radiation Units report no: 83[11].

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

It is defined in the formula as "D_2 is the dose received by 2% of the target, D_{98} is the dose received by 98% of the target, and D_{50} is the dose received by 50% of the target". In cases where CI is equal to 1, we can talk about the ideal dose distribution. If CI is greater than 1, the irradiated volume is greater than the target volume, and if CI is less than 1, the target volume is partially irradiated. The CI index is used to estimate the degree of suitability of the plan[12]. It is calculated as the ratio of the volume of PTV receiving 98% of the dose to the total volume of PTV. This value was calculated automatically with the planning option. By using DVHs, D_{max}(Gy), D_{mean}(Gy) (maximum and mean doses at target volume), D_{98}, D_{95}, D_{50}, and D_2 data of PTV were compared. D_{max}(Gy) and D_{mean}(Gy) values were compared for optic nerves, brain stem, optic chiasm and orbits in critical organs. In addition, the monitor unit (MU) values of the plans were compared.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 25.1. The Paired samples t-test was used for statistical analysis of the difference between the two groups. A p value of <0.05 was considered statistically significant.

RESULTS

In Table 2, the mean of dose values of PTV_{60} and PTV_{50} obtained from IMRT and SIB-IMRT treatment plans, the mean of HI and CI values, and the mean numerical values for MU values, and the results of binary statistical analysis between techniques for 10 GBM patients are given. IMRT plans are more advantageous than SIB-IMRT plans in terms of covering the PTV_{60} target volume with the defined dose. The comparison of the plans showing the dose covering 95% of the targeted volume in IMRT and SIB-IMRT techniques is shown in Figure 1. It was observed that similar results were obtained in IMRT and SIB-

Table 1. Patients' clinical and dosimetric characteristics

Patient	Age	Gender	Pathology	Grade	IDH	Anatomical localization	Size (mm)	Excision	Dose/W	Treatment protocol
1. A. Ö.	70	E	GBM	IV	Mutant	Temporal	55	Total	60 Gy/5W	Adjuvant RT+TMZ
2. N. M.	65	E	GBM	IV	Mutant	Temporal	40	Total	60 Gy/5W	Adjuvant RT+TMZ
3. A. Ş.	67	K	GBM	IV	Mutant	Basal ganglion +Temporal	85	Subtotal	60 Gy/5W	Adjuvant RT+TMZ
4. M. D.	80	K	GBM	IV	Mutant	Frontotemporal	55	Subtotal	60 Gy/5W	Adjuvant RT+TMZ
5. H. Y.	55	K	GBM	IV	Mutant	Frontal	36	Total	60 Gy/5W	Adjuvant RT+TMZ
6. Z. Y.	55	E	Geliosarcoma	IV	Mutant	Temporal	35	Total	60 Gy/5W	Adjuvant RT
7. A. B.	70	E	GBM	IV	Mutant	Temporal	70	Subtotal	60 Gy/5W	Adjuvant RT+TMZ
8. A. Ç.	62	E	GBM	IV	Mutant	Temporal	27	Total	60 Gy/5W	Adjuvant RT+TMZ
9. H. U.	76	K	GBM	IV	Non-mutant	Temporoparietal	30	Total	60 Gy/5W	Adjuvant RT+TMZ
10. İ. D.	52	E	GBM	IV	Non-mutant	Temporal	35	Total	60 Gy/5W	Adjuvant RT+TMZ
11. İ. G.	33	E	Anaplastic oligoastrocytoma	III DSO 2007	Non-mutant	Parietal	53	Total	60 Gy/5W	Adjuvant RT+TMZ

F: Female, M: Male, IDH: Isocitrate dehydrogenase, GBM: Glioblastoma multiforme, RT: Radiotherapy, TMZ: Temozolomide, PCV: Procarbazine, CCNU, and vincristine

IMRT plans in terms of covering the PTV_{50} target volume with the defined dose. Since the ideal value of HI was "0", the plans with the most homogeneous dose distribution were found in the IMRT technique (p=0.004). Since the ideal value of CI was "1", the most conformal technique was also found in the IMRT technique (p=0.001). The comparison of dosimetric values between techniques for critical organs is given in Table 3. When SIB-IMRT plans were compared with IMRT plans, the mean doses received by the brain stem, optic chiasm, optic nerves, and eyes were found to be significantly lower in the SIB-IMRT technique (p values: 0.006, 0.000, 0.000 and 0.000, respectively). In addition, the maximum doses received by the brain stem, optic chiasm, optic nerves and orbits were significantly reduced by the SIB-IMRT technique (p values: 0.000, 0.002, 0.000 and 0.000, respectively). The DVH of a patient whose treatment plan was prepared with IMRT and SIB-IMART is shown in Figure 2. The mean MU counts for the IMRT and SIB-IMRT techniques were 501±31 and 860±111, respectively. The MU value required for the IMRT technique was found to be significantly lower than for the SIB-IMRT technique (p=0.000).

DISCUSSION

Currently, the standard treatment for GBM tumors is surgery, chemoradiotherapy and adjuvant chemotherapy[13]. In high-grade astrocytomas, no matter how extensively the tumor

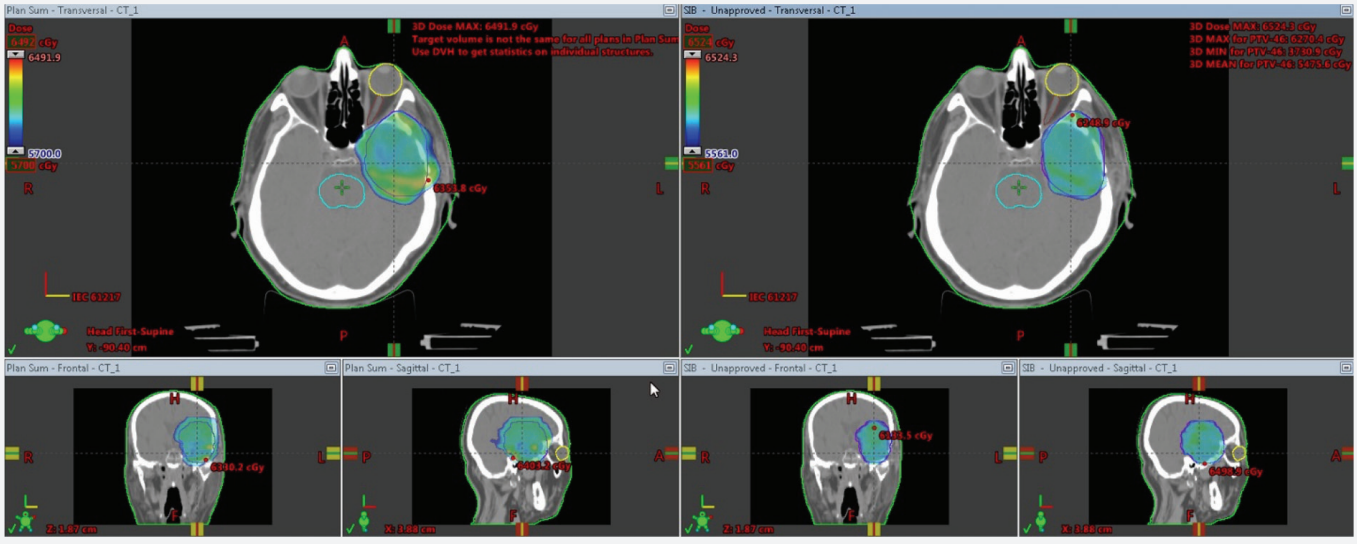

Figure 1. Plan comparison of IMRT and SIB-IMRT techniques

Table 2. Dosimetric values at planned target volume

OAR	IMRT (Mean±SD) (Gy)	SIB-IMRT (Mean±SD) (Gy)	Δ Mean±SD (IMRT SIB-IMRT)	p
PTV60				
$D_{98\%}$ (Gy)	59.87±0.30	57.80±0.20	2.06±0.38	**0.000**
$D_{95\%}$ (Gy)	60.44±0.39	58.42±0.15	2.02±0.40	**0.000**
$D_{50\%}$ (Gy)	60.77±0.54	60.42±0.15	0.34±0.46	0.489
$D_{2\%}$ (Gy)	62.80±0.37	62.32±0.21	0.47±0.41	0.547
D_{max} (Gy)	63.61±0.42	63.60±0.44	0.01±0.06	0.589
D_{mean} (Gy)	60.62±0.33	60.58±0.32	0.04±0.04	0.485
CI	0.97±0.02	0.35±0.06	0.62±0.08	**0.001**
HI	0.05±0.009	0.13±0.197	-0.08±0.19	**0.004**
MU	501±31	860±111	-359±101	**0.000**
PTV50				
$D_{98\%}$ (Gy)	48.97±0.32	48.38±0.41	0.59±0.40	0.001
$D_{95\%}$ (Gy)	49.68±0.18	49.41±0.31	0.26±0.37	0.050

*p<0.005.

SD: Standard deviation, OAR: Organ at risk, IMRT: Intensity-modulated radiation therapy, SIB: Simultaneous integrated boost, HI: Homogeneity index, CI: Conformity indexes, MU: Monitor unit, PTV: Planned target volume

tissue is surgically removed, the neoplastic cells at the microscopic level reproduce in the normal brain tissue due to their infiltrative structure. Therefore, RT is recommended to prevent the increase of residual cells or to eliminate the macroscopic tumor remaining after subtotal resection[14]. RT is an important treatment option in the treatment of malignant glial tumors. In this study, IMRT and SIB-IMRT plans were made for 10 cases diagnosed with malignant glial tumors, and they were compared dosimetrically in terms of target volume coverage, risky organ doses and MU.

Fogliata et al.[15] evaluated the potential benefits of IMRT and SIB-IMRT plans in head and neck patients in terms of planning and at a dosimetric level. Dose distributions were obtained with inverse planning IMRT for all plans and sliding window technique was used after IMRT optimization. They stated that the physical dose distribution and homogeneity were better for the plans obtained with the IMRT technique. They found that the V_{95} parameter was lower in SIB plans (p=0.002). They stated that the doses received by organs at risk, such as the spinal cord and parotid, were lower in the SIB-IMRT technique. Similarly, in our study, it was found that the plans obtained with the IMRT technique were more advantageous in terms of dose coverage, but the doses received by the OAR were lower in the SIB-IMRT technique.

Li et al.[16] compared IMRT and SIB-IMRT plans to deliver high doses to the prostate and lower doses to the pelvic region. They noted that the SIB-YART technique had potential advantages, including better preservation of critical structures, more efficient administration, shorter treatment time, and better biological efficacy. In parallel with this study, in this study conducted on 10 cases with a diagnosis of malignant glial tumor, it was observed that the mean doses received by the brain stem, optic chiasm, optic nerves and orbits were significantly lower in the SIB-IMRT technique when SIB-IMRT plans were compared with IMRT plans.

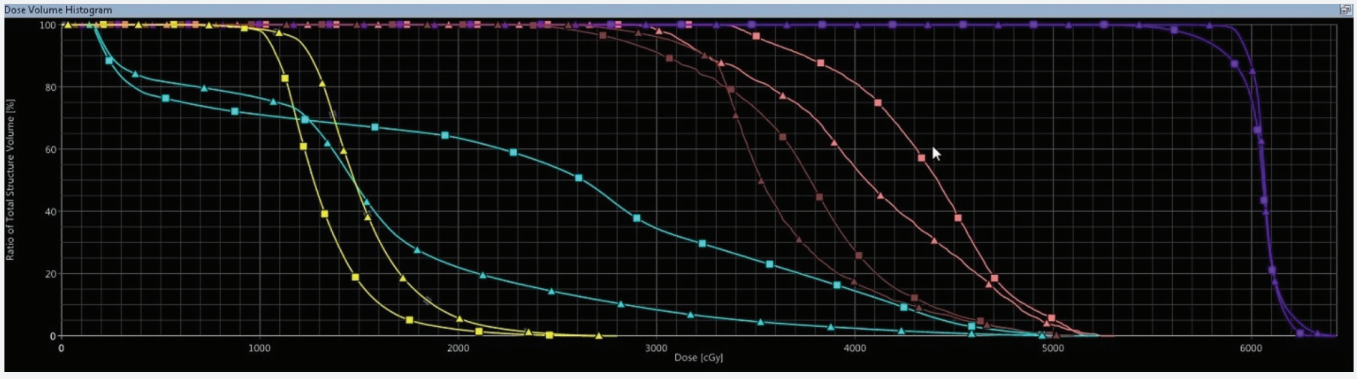

Figure 2. Dose volume histogram of a patient whose treatment plan was prepared with IMRT and SIB-IMRT (purple: PTV, blue: brainstem, pink: optic chiasm, brown: optic nerve, yellow: eye)

Table 3. Dosimetric values in organs at risk

OAR		IMRT (Mean±SD) (Gy)	SIB-IMRT (Mean±SD) (Gy)	Δ Mean±SD (IMRT SIB-IMRT)	p
Brainstem	D_{max}	52.88±1.58	51.43±1.04	1.44±0.70	**0.000**
	D_{mean}	19.87±5.61	19.18±5.86	0.68±0.60	**0.006**
Optic chiasm	D_{max}	44.67±6.23	42.41±7.23	2.26±1.68	**0.002**
	D_{mean}	28.35±7.04	26.11±7.13	2.23±1.10	**0.000**
Left optic nerve	D_{max}	44.84±8.70	42.59±8.62	2.24±0.96	**0.000**
	D_{mean}	31.25±5.76	28.45±5.43	2.80±1.07	**0.000**
Left eye	D_{max}	38.15±9.25	36.36±9.11	1.79±0.83	**0.000**
	D_{mean}	22.26±7.93	21.16±8.13	1.10±0.58	**0.000**
Right optic nerve	D_{max}	16.68±4.73	15.73±4.77	0.94±0.48	**0.000**
	D_{mean}	12.38±4.69	10.83±3.32	1.54±1.62	**0.000**
Right eye	D_{max}	15.17±4.15	14.37±3.66	0.80±0.82	**0.013**
	D_{mean}	6.22±2.85	5.32±2.56	0.89±0.44	**0.000**

*p<0.005.

SD: Standard deviation, OAR: Organ at risk, IMRT: Intensity-modulated radiation therapy, SIB: Simultaneous integrated boost

Onal et al.[17] compared sequential boost (SEB) technique and SIB techniques dosimetrically in volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT). In their study, they stated that the SIB technique protects the heart better than the SEB technique in HT plans. In our study, it was observed that critical organs were better protected with the SIB technique.

Farzin et al.[18] compared the SIB and SEB method for VMAT in 20 patients with high-grade gliomas. In their study, in the SIB method, PTV received 54 Gy in 30 fractions with a dose of 1.8 Gy per fraction, while the tumor bed received 60 Gy from 2 Gy per fraction. According to their results, they found that both techniques were similar in terms of target coverage, but the SIB technique was significantly superior in protecting critical organs. The results obtained from this study were found to be similar to our study.

Nageeti et al.[19] compared the dosimetric coverage of PTV and OAR with SIB and SEB method in VMAT technique for 7 patients with a diagnosis of high-grade glioma. They stated in their study that although the protection of critical organs was similar for all plans, the use of SIB with fewer fractions of the total dose might be the best option for the treatment of patients with short survival without increasing toxicity. Contrary to this study, in our study, it was shown that the SIB-IMRT technique was more advantageous than IMRT plans because it protects critical structures at risk, and it provides a dosimetric advantage over IMRT plans because it protects healthy tissues.

In their study, Çelen and Kızılkaya[20] aimed to dosimetrically compare PTV and OAR with sequential IMRT and SIB-IMRT techniques to the entire breast and boost area in patients who underwent breast-conserving surgery. In their study, they gave 50 Gy/25 fractions to the whole breast and 10 Gy/5 fractions to the boost area to the patients who underwent sequential IMRT, and they gave a total of 50.4 Gy/28 fractions to the whole breast for patients who were applied SIB IMRT while, at the same time, they gave an additional dose of 60 Gy/28 fractions to the boost volume. In their study, in the administration of the SIB-IMRT technique and the sequential IMRT technique to the same side lung; the comparison of the mean doses of V5 value for 10 patients revealed no statistically significant results, while the comparison of the mean dose values for V_{20} value in 10 patients revealed a statistical significance. They demonstrated that with the SIB-IMRT technique, treatment could be performed with a lower dose at V20 in the ipsilateral lung. They stated that the SIB-IMRT technique might be suitable for standard use in breast-conserving RT to reduce irradiated excess normal tissue volumes and to reduce the dose in organs at risk. Similar results were obtained in our study, and it has been shown that the SIB technique can be used to reduce the dose of organs at risk.

Study Limitations

There are several limitations in our study. This is a dosimetric study and does not include vital aspects necessary for clinical use. The number of patients used for comparison was limited to 10, which can be expanded in the next study to obtain a better sample.

CONCLUSION

It is known that IMRT therapy has many advantages over conventional RT. IMRT therapy is capable of delivering a highly compatible dose of irradiation to the target while preserving surrounding tissues. In the SIB-IMRT technique, on the other hand, all target volumes can become conformal by using different fraction sizes simultaneously. The SIB-IMRT technique can also be an easier, more effective and error-free IMRT planning and implementation method, because the same plan is used throughout the entire treatment. Studies have shown that the use of SIB-IMRT provides dosimetric advantages due to shorter treatment time, potential radiobiological gains, and preservation of normal tissues.

Ethics

Ethics Committee Approval: Permission for this study was obtained from the Ethics Committee of Selçuk University Faculty of Medicine, with the decision dated 07 April 2021 and numbered 2021/198.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.B., G.İ., O.V.G., Design: H.B., G.İ., O.V.G., Data Collection or Processing: H.B., G.İ., O.V.G., Analysis or Interpretation: H.B., G.İ., O.V.G., Literature Search: H.B., G.İ., O.V.G., Writing: H.B., G.İ., O.V.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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