



Simultaneous integrated vs. sequential boost in VMAT radiotherapy of high-grade gliomas

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Abstract

Background In 20 patients with high-grade gliomas, we compared two methods of planning for volumetric-modulated arc therapy (VMAT): simultaneous integrated boost (SIB) vs. sequential boost (SEB). The investigation focused on the analysis of dose distributions in the target volumes and the organs at risk (OARs).

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Method After contouring the target volumes [planning target volumes (PTVs) and boost volumes (BVs)] and OARs, SIB planning and SEB planning were performed. The SEB method consisted of two plans: in the first plan the PTV received 50 Gy in 25 fractions with a 2-Gy dose per fraction. In the second plan the BV received 10 Gy in 5 fractions with a dose per fraction of 2 Gy. The doses of both plans were summed up to show the total doses delivered. In the SIB method the PTV received 54 Gy in 30 fractions with a dose per fraction of 1.8 Gy, while the BV received 60 Gy in the same fraction number but with a dose per fraction of 2 Gy.

Results All of the OARs showed higher doses (D_{max} and D_{mean}) in the SEB method when compared with the SIB technique. The differences between the two methods were statistically significant in almost all of the OARs. Analysing the total doses of the target volumes we found dose distributions with similar homogeneities and comparable total doses.

Conclusion Our analysis shows that the SIB method offers advantages over the SEB method in terms of sparing OARs.

Keywords Simultaneous integrated boost · Sequential boost · Volumetric-modulated arc therapy · High-grade glioma · Organs at risk

Vergleich zwischen simultan integriertem Boost und sequenziellem Boost für die VMAT-Strahlentherapie bei hochgradigen Gliomen

Zusammenfassung

Hintergrund Es wurden 2 Arten der Planung für die volumetrisch modulierte Rotationsbestrahlung (VMAT) bei 20 Patienten mit hochgradigen Gliomen verglichen: simultan integrierter Boost (SIB) und sequenzieller Boost (SEB).

Dazu wurde die Dosisverteilung in den Zielvolumina und den Risikoorganen analysiert.

Methoden Es wurden Planungsvolumina (PTV), Boostvolumina (BV) und Risikoorgane konturiert sowie SIB- und SEB-Pläne erstellt. Der SEB besteht aus 2 Plänen. Im ersten Plan erhält das PTV 50 Gy in 25 Fraktionen. Im zweiten Plan erhält das Boostvolumen 10 Gy in 5 Fraktionen (Einzeldosis jeweils 2 Gy). Die Dosis beider Pläne wurde summiert, um die gesamte verabreichte Dosis zu ermitteln. Beim SIB-Konzept erhält das PTV 54 Gy in 30 Fraktionen (Einzeldosis 1,8 Gy), während das Boostvolumen 60 Gy erhält (30 Fraktionen, Einzeldosis 2,0 Gy).

Ergebnisse Beim SEB erhielten die Risikoorgane höhere Dosen (D_{max} und D_{mean}) als bei der SIB-Technik. Die Dosisunterschiede zwischen den beiden Techniken waren für nahezu alle Risikoorgane statistisch signifikant. Die Analyse der Dosisverteilungen in den Zielvolumina ergab vergleichbare Gesamtdosen und Dosisinhomogenitäten.

Schlussfolgerung Unsere Analyse zeigt eine klare Tendenz, dass die SIB-Technik gegenüber der SEB-Technik einen Vorteil bezüglich der Schonung der Risikoorgane bietet.

Schlüsselwörter Simultan integrierter Boost · Sequenzieller Boost · Volumetrisch modulierte Rotationsbestrahlung · Hochgradiges Gliom · Risikoorgane

Introduction

The prognosis of high-grade gliomas is poor, despite the use of combined treatment modalities including surgery, radiotherapy, and chemotherapy. These tumours exhibit an infiltrative growth and it is necessary to control the peripheral infiltrating parts (microscopic tumour, not visible on imaging) as well as the local core tumour (macroscopically visible tumour on imaging). However, the required dose to control the core and the infiltrating volumes of the tumour may be different. At the same time, we must be careful about the tolerance doses of organs at risk (OARs) near the radiation treatment volumes including the optic apparatus and brainstem. Therefore, it seems logical to deliver different doses to a layered (core/periphery) target. In the era of three-dimensional conformal radiotherapy (3D-CRT), different strategies such as altered fractionation, interstitial brachytherapy boost, and stereotactic radiosurgery boost have been tested in several studies. These trials could not show significant survival benefits [1–6].

With the arrival of intensity-modulated radiation treatment (IMRT), it was shown that this technique provided improved target conformity and better sparing of OARs [1, 7]. A special kind of rotational IMRT is volumetric-modulated arc therapy (VMAT) [8]. During rotation of the gantry, the dose rate and

shape of the multileaf collimator are dynamically modulated. Compared with “conventional” IMRT, VMAT achieves equal or better coverage of target volumes and improved OAR sparing while using fewer monitor units and requiring less time to treat high-grade gliomas [9, 10]. The faster dose delivery of the VMAT technique can decrease the treatment time at the linac machine and limit the potential for intra-fraction organ and patient motion. The motions can cause unwanted deviations in the dose distribution. However, VMAT may involve more time for plan optimization [11, 12].

One of the advantages of IMRT and VMAT when compared with traditional 3D radiation treatment is that these newer techniques are suitable for the application of the simultaneous integrated boost (SIB) method. SIB offers the possibility to apply a dose to the larger volume, the so-called planning target volume (PTV), and at the same time deliver an escalated dose to the core tumour mass, the so-called gross tumour volume (GTV) [1, 13, 14]. According to ICRU-83 [15], the GTV represents the palpable or visible (on imaging) tumour, whereas the so-called clinical target volume (CTV) is an additional volume with a certain probability of microscopic (subclinical) malignant disease. The irradiated PTV is a geometrical concept. It comprises the CTV plus a safety margin. This safety margin compensates for the effects of organ and patient movement during the radiation fraction and for inaccuracies in patient set-up. Of course, in brain tumours, organ movement is of minor importance.

This study was done performed on the hypothesis that the SIB method is superior to sequential boost (SEB) technique for treating patients with brain tumours. In order to deliver different doses to a layered target, we carried out treatment planning using the SEB and the SIB methods, both by VMAT. The aim of the study was to compare these two methods in terms of coverage of the target volumes and also of the sparing of OARs. To the best of our knowledge, this is the first study comparing SIB vs. SEB in a larger population of patients with brain tumour.

Patients and methods

Our study included 20 patients with pathology-proven high-grade gliomas. All patients underwent surgical resection of their tumour (seven total and 13 subtotal resections) between 2010 and 2013. They received radiation treatment based on the decision of the interdisciplinary board for brain tumours. However, in this planning study we exclusively focused on comparing the dose distributions in the isodose plans of the SIB and SEB techniques.

Patient characteristics are listed in Table 1. Ten patients were men and the other 10 were women; their age range was 23–68 years (median, 51.5 years; average, 49.2 years). According to the World Health Organization (WHO) grad-

Table 1 Patient characteristics

Characteristics		
Age		
Median	51.5 years	
Average	49.2 years	
Range	23–68 years	
Sex		
Male	<i>n</i> =10	(50%)
Female	<i>n</i> =10	(50%)
WHO grade		
III	6	(30%)
IV	14	(70%)
Surgery		
Total resection	7	(35%)
Subtotal resection	13	(65%)
Tumour location		
Left temporal lobe	4	(20%)
Right temporal lobe	3	(15%)
Right frontal lobe	2	(10%)
Right parietal lobe	2	(10%)
Left frontal lobe	2	(10%)
Pons	1	(5%)
Left cerebellopontine angle	1	(5%)
Left occipital lobe	1	(5%)
Left insula	1	(5%)
Right parieto-temporal lobes	1	(5%)
Right parieto-occipital lobes	1	(5%)
Left fronto-temporal lobes	1	(5%)

ing criteria, six patients presented with grade III (anaplastic astrocytoma) and 14 patients with grade IV (glioblastoma) tumours.

We used the iPlan planning system (BrainLab AG, Feldkirchen, Germany) for delineating the target volumes and contouring the OARs. The Eclipse 10 planning system (Varian Medical Systems, Palo Alto, Calif.) was applied for treatment planning and dose distribution calculations.

Beside planning CT, every patient (*n*=20) underwent magnetic resonance imaging (MRI; T1 and T2 FLAIR with contrast using 1-mm slice thickness) within a few days before starting the contouring of OARs and delineation of target volumes. MRI was performed because it provides better visualization of the resection cavity, residual tumour, and oedema. We first contoured the OARs, which included the brainstem, chiasm, and the following (always bilateral): optic nerves, retinas, lenses, eyeballs, and lachrymal glands. Contouring was performed on the planning CT scans (application of contrast medium and 2-mm slice thickness).

In the following step, the PTVs and the boost volumes (BVs) were delineated on the planning CTs and MRIs, based on our institutional protocol. Figures 1a and 1b show the workflow and the details of the delineating process of the target volumes. For delineation of the PTV, first the CTV1 and CTV2 were fused together. Then, parts of this volume that surpassed the bony skeletal borders were deleted.

Delineation of the BVs was based on shrinking the PTV. We mainly excluded those parts of OARs that were located within the PTVs in order to reduce the risk of side effects. In eight patients, ten OARs were invaded by the tumour. These ten OARs were partially located inside the BV. Owing to the anatomical sites and the extension of the tumours, in all the patients (*n*=20) at least one of the OARs was included either completely or partially inside the PTV but outside of the BV (Table 2).

All the contoured volumes were transferred from the iPlan to the Eclipse system using DICOM. Treatment planning and calculation of the dose distributions for both methods (SIB and SEB) were carried out for all 20 patients in the Eclipse planning system. In all patients the delineated target volumes (PTV and BV) were the same for the SEB and the SIB methods alike. Figure 2 presents an example of one of the patients showing the delineated target volumes and contoured OARs and also the dose distributions in the SIB and the SEB methods.

Treatment planning for both methods was performed with a two-arc/VMAT technique. The SEB method consisted of two plans. In the first plan the PTV received 50 Gy in 25 fractions with a dose per fraction of 2 Gy. In the second plan the BV received 10 Gy in 5 fractions with a dose per fraction of 2 Gy. Both dose plans were summed up to show the total doses delivered during treatment. In SIB planning, the PTV received 54 Gy in 30 fractions with a dose per fraction of 1.8 Gy, while the BV received 60 Gy in the same number of 30 fractions but with a dose per fraction of 2 Gy. All plans (SEB and SIB) were normalized to a mean dose of 100% of the prescription dose to the target volume.

The upper dose constraints for the OARs corresponded to their tolerance doses: 56 Gy for the brainstem; 54 Gy for the optic nerves, chiasm, retinas, and eyeballs; 40 Gy for the lachrymal glands; and 5 Gy for the lenses. In order to achieve better plans in terms of coverage of target volumes and sparing of OARs, planning for both methods was repeated several times. After plan optimization was finished we determined the delivered doses to the target volumes (PTV and BV) and OARs for both methods. In addition we assessed doses to the difference volumes, PTV–BV, which are those parts of PTVs containing some OARs partially or totally. These data included the maximum dose (D_{\max}) and the mean dose (D_{mean}). The dose distributions in the SIB and SEB plans were then compared.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous measures as means and standard deviations or medians and ranges. We used Bland–Altman plots to show the similarity of the doses received by the target volumes in the two planning methods. The exact Wil-

Fig. 1 a Workflow of patient selection and the sequential steps of treatment planning.

b Workflow of definition of the target volumes. *OAR* organ at risk, *CT* computed tomography, *MRI* magnetic resonance imaging, *GTV* gross tumour volume, *CTV* clinical target volume, *PTV* planning target volume, *SEB* sequential boost, *SIB* simultaneous integrated boost

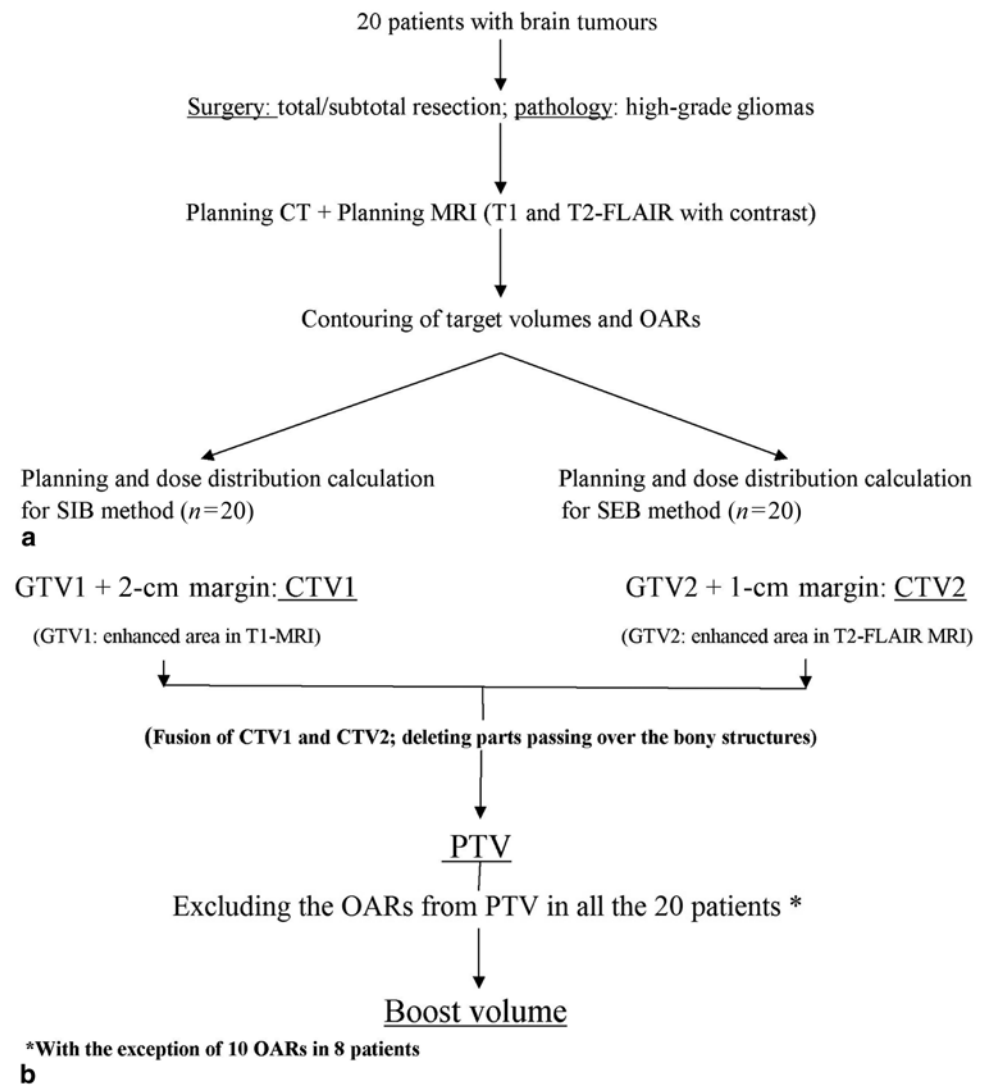


Table 2 Involvement of organs at risk within the boost volume or the planning target volume

	Boost volume		Planning target volume	
	Patients (n=20)	%	Patients (n=20)	%
Right optic nerve	1	5	6	30
Left optic nerve	0	0	8	40
Chiasm	2	10	13	65
Brainstem	7	35	13	65
Right retina	0	0	2	10
Left retina	0	0	2	10
Right lachrymal gland	0	0	2	10
Left lachrymal gland	0	0	2	10
Right lens	0	0	0	0
Left lens	0	0	0	0
Right eyeball	0	0	2	10
Left eyeball	0	0	3	15

coxon signed-rank test was used to compare the doses of the OARs between the two methods. All *p* values reported are two-tailed, with a *p* value of 0.05 indicating statistical significance. Analysis was performed using R software version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The first important point was to compare the dose inside the target volumes between the two methods. Bland–Altman plots (Fig. 3) show the mean dose against the dose difference between the two methods for each patient. In the plots “ D_{\max} to BV” and “ D_{\max} to PTV” the mean difference is 0.3 Gy (to the benefit of the SIB method). In the plot “ D_{mean} to BV”, again the mean difference is 0.3 Gy, but to the ben-

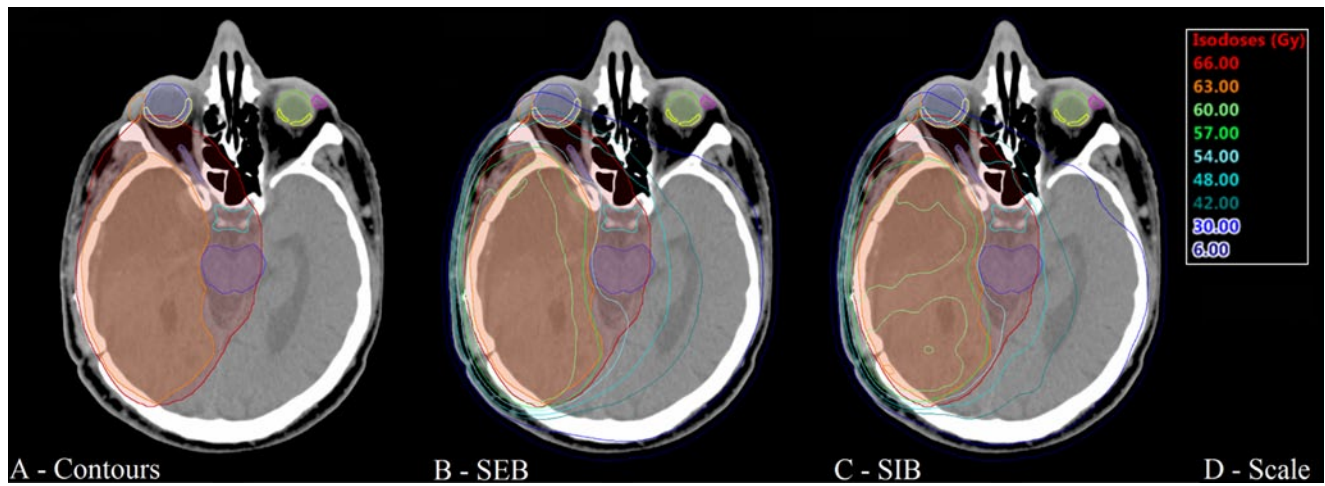
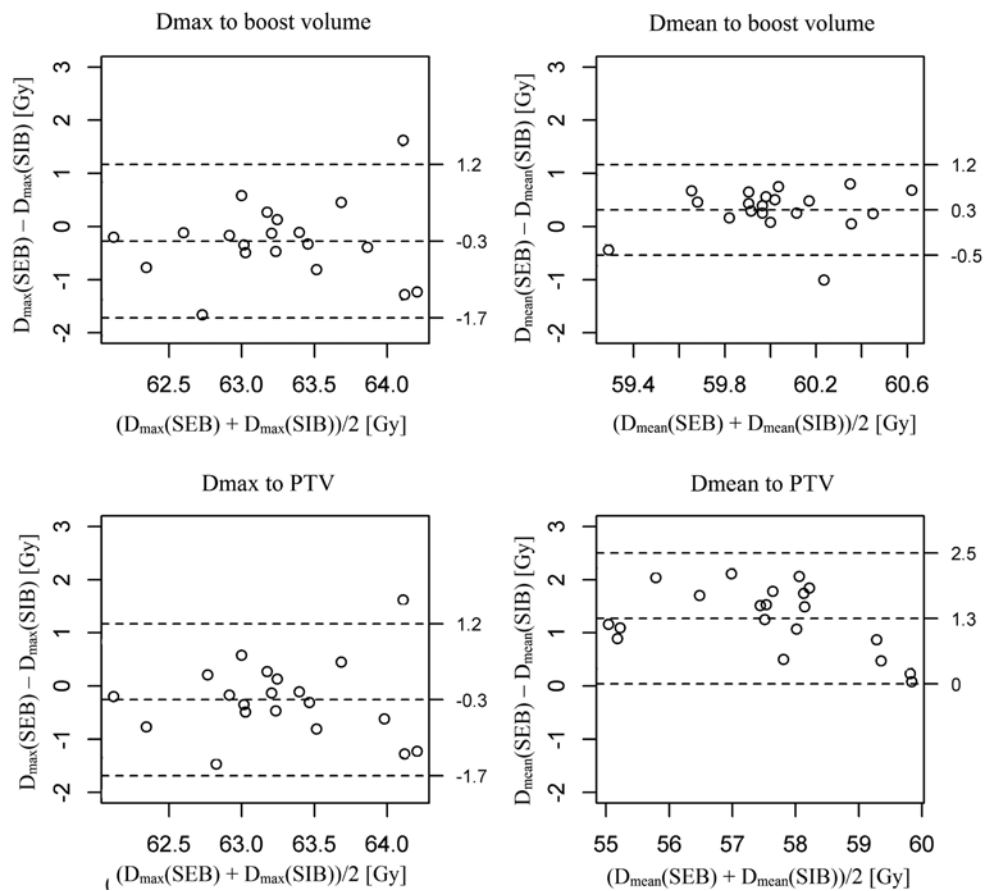


Fig. 2 Patient example. **a** Delineated target volumes—boost volume (BV) and planning target volume (PTV)—and contoured organs at risk. BV: orange; PTV: red; brainstem: blue; chiasm: azure; right optic nerve: purple; right and left retina: yellow; right eyeball: dark blue; left eyeball: green; right lachrymal gland: orange; left lachrymal gland: pink. **b** Dose distribution for the same patient with the sequen-

tial boost (SEB) method. **c** Dose distribution for the same patient with the simultaneous integrated boost (SIB) method. **d** Scale of dose distribution. SIB has the advantage that the high-dose region is more distant from the relevant OARs when compared with SEB. This is especially shown for the left eyeball, left retina, and left lachrymal gland in this case

Fig. 3 Bland–Altman plots for maximum dose (D_{max}) and mean dose (D_{mean}) to boost volume and planning target volume (PTV) show the mean dose against the difference in dose of both methods for each patient. The mean difference between the sequential boost (SEB) and simultaneous integrated boost (SIB) methods and the 95% confidence interval (± 2 SD) are depicted as dashed lines



efit of the SEB method. Except for one patient, all values are within the 95% confidence interval. In the plot “ D_{mean} to PTV” there is a mean dose difference of 1.3 Gy between the SEB and SIB methods. This indicates that the mean dose

to the PTV in the SEB method is higher than in the SIB method, while “ D_{mean} to BV” in both methods is similar. The higher dose in the PTV in the SEB method can be attributed to those parts of the PTV that are not inside the BV (PTV–

Table 3 Difference between the doses received by the total volume of organs at risk and the difference volume “PTV–BV” in the two methods

	Median of D_{\max} (Gy)		Range of D_{\max} (Gy)		p of D_{\max}	Median of D_{mean} (Gy)		Range of D_{mean} (Gy)		p of D_{mean}
	SEB	SIB	SEB	SIB		SEB	SIB	SEB	SIB	
Right optic nerve	37.75	34.65	2.89–54.08	2.94–54.1	0.001	25.7	23.97	2.18–50.97	2.2–50.57	0.004
Left optic nerve	46.52	42.59	2.82–53.84	2.86–53.56	<0.001	31.44	29.17	2.01–50.38	2.02–50.17	0.005
Chiasm	52.73	51.11	28.84–54.03	31.18–54.09	0.004	48.6	45.28	17.15–52.56	18.42–52.11	0.002
Brainstem	55.37	53.98	53.43–60.52	51.06–62.22	0.003	39.73	38.37	25.97–56.85	24.48–55.45	0.015
Right retina	21.85	19.9	1.85–53.72	1.85–54.29	0.209	15.67	13.7	1.31–42.58	1.29–41.03	0.002
Left retina	22.14	21.32	1.55–59.36	1.55–56.62	0.013	16.77	14.34	1.15–47.95	1.14–47.18	<0.001
Right lachrymal gland	21.47	19.87	1.72–60.12	1.72–59.84	0.001	14.55	12.25	1.2–39.28	1.19–37.8	<0.001
Left lachrymal gland	22.4	22.08	1.4–54.72	1.4–53.18	0.086	14.64	13.62	1.03–44.91	1.02–44.03	0.006
Right lens	5.64	5.06	1–22.95	0.99–20.47	<0.001	4.94	4.46	0.93–19.64	0.92–18.12	<0.001
Left lens	6.06	5.15	0.89–40.83	0.88–38.86	<0.001	5.3	4.62	0.83–28.11	0.82–27.13	<0.001
Right eyeball	21.85	19.79	1.84–53.06	1.84–52.74	0.054	11.15	9.5	1.18–35.15	1.17–32.72	<0.001
Left eyeball	22.31	21.07	1.54–28.52	1.54–58.04	0.009	11.51	10.06	1.03–41.16	1.02–40.05	<0.001
PTV–BV	62.35	61.80	58.52–63.33	57.95–64.29	0.0922	56.19	53.97	53.62–57.88	53.42–54.29	<0.001

BV boost volume, *SEB* sequential boost, *SIB* simultaneous integrated boost.

BV, Table 3). As previously mentioned, PTV–BV consists mainly of OARs that were located in the PTV and were excluded in the process of defining the BV.

Table 2 shows the involvement of any of the OARs inside the target volumes. For example, in seven patients the brainstem was involved in the BV and in 13 patients in the PTV (not in the BV). The retinas were not involved in the BVs but were involved in the PTVs of two patients. Table 2 also shows that ten OARs (brainstem, chiasm, and right optic nerve) were inside the BV. The details concerning the doses in these ten OARs are shown in supplementary material 1.

Only in very few cases did the D_{\max} and D_{mean} exceed the tolerance doses of the OARs in any of the methods. The only exceptions were the lenses. In both methods, the D_{\max} and D_{mean} values exceeded the tolerance dose of the lenses in a considerable number of treatment plans. The reason for this exception is due to the low tolerance dose of the lenses, which is only 5 Gy (supplementary material 2).

Table 3 shows the difference between the doses received by OARs and the PTV–BV volumes in the two methods. All OARs received more doses (D_{\max} and D_{mean}) in the SEB method than in the SIB procedure. These differences between the two methods are significant both for D_{\max} and D_{mean} in all OARs, except for D_{\max} in three OARs (right retina, left lachrymal gland, and right eyeball). Higher D_{\max} and D_{mean} values were also found in the SEB method for PTV–BV.

Discussion

IMRT is an innovative technique in radiation oncology [1, 7, 16]. During the last decade it was increasingly applied in clinical radiation treatment of tumours. For a number of

entities, such as prostate cancer, head and neck tumours, and brain tumours, it could be shown that IMRT is advantageous owing to its better dose distribution and better sparing of normal tissues when compared with traditional 3D radiation treatment [17–20].

The aim of our study was to find out whether in high-grade gliomas treated with the IMRT technique, different modes of radiation application to the BV (SEB vs. SIB) offer the potential of further improvements. We tested this question by using VMAT (see introductory section). The most important result of our study is that the SIB method within the VMAT technique can achieve high conformity in dose delivery to the irradiated target volumes (PTV and BV) and in addition the SIB method is obviously linked to an improved chance of sparing the OARs. This latter very important advantage of SIB has been shown in several other cancers such as prostate cancer, head and neck malignancies, lung cancer, etc. [21–25].

As mentioned, very few comparative SIB/SEB studies in brain tumours have been conducted [26–28]. These studies have shown better sparing of normal brain tissues and OARs and also equal or better coverage of target volumes. However, it is important to mention that these studies were done on hypothetical lesions [26] or on a small number of patients [27] or on phantoms [28]. In contrast to these three investigations, our study has focused only on patients (not phantom) and on real tumours. In addition, our study was performed with a comparatively larger sample volume (Table 4). Our study was of patients with high-grade gliomas, but the potential benefit of better sparing of OARs can be expected for other brain tumours too.

When comparing both methods, it is important to note that the comparatively higher D_{mean} to PTV in SEB (D_{mean} to BV is similar in SEB and SIB) is related to the delivered

Table 4 Results of previous studies comparing SIB and SEB in brain tumours

Study	Material	Techniques	Dose	Results
Baisden et al. [26]	42 hypothetical lesions and 3 glioblastoma patients	HT-SIB and HT-SEB	50 Gy to PTV 60 Gy to boost volume	Significant sparing of normal brain parenchyma in HT-SIB. OARs not evaluated separately
Prokic et al. [27]	10 patients with multiple brain metastases	VMAT-SIB and VMAT-SEB	SIB: 30 Gy/12 fractions WBRT and 51 Gy/12 fractions boost to metastases SEB: 30 Gy/12 fractions WBRT and 18 Gy/2 fractions as sequential boost to metastases	Similar coverage of target volumes in both methods and better sparing of hippocampus and other OARs in VMAT-SIB
Yang et al. [28]	Phantom and 5 patients with brain tumours	VMAT-SIB, VMAT-SEB and HT	30 Gy to PTV 35–90 Gy to boost volume	Superior plans in VMAT-SIB over the VMAT-SEB and HT. OARs were not evaluated
Our study	20 patients with high-grade gliomas	VMAT-SIB and VMAT-SEB	SIB: 54 Gy/30 fractions to PTV and 60 Gy/30 fractions to boost volume SEB: 50 Gy/25 fractions to PTV and 10 Gy/5 fractions to boost volume	Similar coverage of target volumes and significantly better sparing of OARs with SIB

VMAT volumetric-modulated arc therapy, SIB simultaneous integrated boost, SEB sequential boost, HT helical tomotherapy, PTV planning target volume, OAR organ at risk, WBRT whole-brain radiation treatment.

doses to PTV–BV. These volumes consist mainly of parts of OARs that were inside the PTV and were deleted in the process of defining and contouring the BV. Thus, in our study, while the SIB seems to be able to spare OARs more efficiently, some parts of the PTV that consist of OARs receive lower doses.

One point that should be taken into consideration is that the SEB method was mostly used before the arrival of IMRT, within the 3D conformal irradiation technique [1]. However, in our study we used VMAT not only for the SIB method but also for the SEB method. Therefore, it could be expected that the homogeneity and conformity of doses to the target volumes would be similar in the two methods. However, concerning the OARs, this study shows that the SIB method is significantly superior to the SEB procedure. The superiority is true for almost all of the OARs (right and left optic nerves, chiasm, brainstem, left retina, right lachrymal gland, right and left lenses, and left eyeball) that we investigated.

Finally, we would like to mention a radiobiological aspect that might be of interest in patients with brain tumours with longer life expectancies. It is a well-known fact that higher single doses are potentially more dangerous regarding the development of late radiation side effects such as necrosis of central nervous system tissues and other injuries [29–31]. In our study with the SIB method, the single dose per fraction to the PTV (not BV) was lower when compared with the SEB. This is of advantage when considering that in the PTV there is a comparatively high probability of irradiation of sub-volumes of relatively sensitive OARs. Thus, in addition to “physical sparing”, the SIB method can also offer the possibility of a “biological sparing”. The biological effective doses (BED) to the OARS also proved to be superior in the SIB method compared with the SEB method (supplementary material 3), but the true significance of this “theoretical” advantage of SIB should be evaluated in clinical trials.

Conclusion

Our results from 20 patients with high-grade gliomas suggest a greater potential of sparing of OARs when using the SIB technique. Dose coverage of the BV with the SIB method is similar to that with the SEB method, while the delivered dose to the PTV is higher in the SEB method. This difference is related to the higher delivered dose to the PTV–BV. This volume mainly contains sub-volumes of OARs that were located in the PTV but not in the BV. Because to date it is unclear whether SIB offers a better outcome of patients (including radiation-treated brain tumour patients with a longer survival) more large-scale studies are needed. On the basis of our planning study observations, we believe the clinical advantages and disadvantages of these two methods in clinical radiation treatment should be investigated in more detail.

Compliance with ethical guidelines

Conflict of interest M. Farzin, M. Molls, S. Astner, I-C. Rondak, and M. Oechsner state that there are no conflicts of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 (in its most recently amended version).

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