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Simultaneous integrated boost by RapidArc therapy plus temozolomide for treatment of patients with glioblastoma multiform: A single institution experience

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Original Article

Abstract

Purpose: The aim of this study is to report the treatment outcomes, toxicities, and dosimetric feasibility of simultaneous integrated boost by RapidArc (RA-SIB) compared with 3dimentional-conformal radiation therapy (3D-CRT) for patients with glioblastoma. **Methods**: Eleven patients with unifocal glioblastoma (grade IV astrocytoma, WHO classification) were treated during the period from April 2011 until February 2013 with postoperative irradiation and concomitant temozolomide 75 mg/m^2 followed by 6-12 months of adjuvant temozolomide 200 mg/m^2 for 5 days/4weeks. One patient received temozolomide for 12 months, 5patients for 6 months, and 5patients did not receive adjuvant temozolomide. RA-SIB technique was used and patients received 46 Gy per fraction of 2 Gy in 23 sessions on the planning target volume (PTV1) (contrast enhancement + per-focal edema as seen in T2 MR + 2.3 cm) with concomitant daily superimposed boost (SIB) on PTV2 corresponding to the contrast enhancement + 2.3 cm. The treatment outcomes and toxicity were assessed. Dose Volume Histogram DVH analysis was performed between SIB-RA and 3D-CRT plans of each patient. For the PTV, the comparison parameters included, the mean dose, the standard deviation, maximum dose, conformity index (CI), and homogeneity index (HI). **Results**: The median progression free survival (PFS) and overall survival (OS) were 13 months (95% CI, 8.2-17.8), and 16 months (95% CI, 2.1-29.9) respectively. Four of six patients (67%) showed local progression (recurrence) after initial response, all recurrences occurred at the site of PTV2. Seven patients experienced acute grade 1-2 toxicities during the treatment. Late post radiation brain edema was reported in 3 patients. **Conclusion**: The SIB-RA did not prove the superiority in survival outcomes compared with the historical data using 3D-CRT. From the dosimetric standpoint, SIB-RA is a superior technique with respect to 3D-CRT when there are overlaps between organs at risk (OARs) and PTV.

Keywords: RapidArc; Glioblastoma Multiform; Radiation Therapy

Introduction

Glioblastomas are rapidly growing primary brain tumors associated with a high degree of morbidity and mortality. Current management is based on maximal cytoreduction with surgery followed by combined chemo-radiotherapy. Despite this multi-disciplinary approach to treatment, glioblastoma remains a life-threatening disease with median survival between 11 to 18 months.[1, 2] The current standard of care in newly diagnosed GBM patients consists of concomitant low dose temozolomide with radiation, followed by high dose adjuvant temozolomide for 6 to 12 months. Despite representing progress, this approach still does not offer cure to these patients, as long-term prognosis remains poor, suggesting that alternative therapeutic strategies are desperately needed.[1] Intensity modulated radiation therapy (IMRT) technique allows the planning and irradiation of different targets at different dose levels in a single treatment session, instead of successive treatment plans. These IMRT dose gradients are introduced in such a manner that normal tissues receive a much lower dose per fraction. Based on the linear-quadratic (LQ), for a similar total physical (nominal) dose, lowering the dose per fraction to below 2 Gy will reduce the biological effect, while increasing the dose per fraction to above 2 Gy will increase that effect.[3] The term "simultaneous integrated boost" (SIB) defines such treatment, delivering different doses per fraction in different target regions.[4] The SIB technique offers the biological advantage of shortened treatment duration, i.e. 70 Gy over 6 weeks, which has been shown to significantly increase the loco-regional control compared to the same dose delivered in 7 weeks.[5] Assuming a γ37 value of 2, such an increase in the biological dose of 7.5%

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could be translated into an increase in loco-regional control in the order of 15%.[6]

Irradiation with intensity-modulated dose application led to an improvement in target coverage compared with 3D-CRT in different tumor entities, like head and neck [7], lung [8], breast [9] or prostate [10, 11]. For radiotherapy of Glioblastomas the feasibility and efficacy of IMRT planning with a simultaneous boost was shown by Chan *et al.* [12] However, Narayana *et al.* found no improvement in target coverage using IMRT in high-grade gliomas in comparison with 3D-CRT. Nevertheless, the normal brain, which received a dose of ≥ 18 and ≥ 24 Gy as well as the mean dose to the brainstem, could be reduced with IMRT.[13] In contrast, MacDonald demonstrated in similar analysis improved target coverage and also confirmed reduced radiation dose to the brain, brainstem and optic chiasm.[14] Goswami *et al.* [15] demonstrated that the number of monitor units was 1.5 times lower for RapidArc and 2 times higher than 3D conformal technique.

We found that the irradiation time of RapidArc fields was 3 times faster than that of IMRT and 1.5 times faster than that of 3D conformal technique. RapidArc was even about 5 times faster than IMRT because of additional time that is necessary to move the gantry between different IMRT fields. The aim of this study is to report the treatment outcomes, toxicities, and dosimetric feasibility of simultaneous integrated boost by Rapid Arc (RA-SIB) compared with 3-DCRT.

Methods and Materials

Local institutional research ethics board approval was obtained to select eleven patients after diagnosis as Glioblastoma Multiform (WHO grade IV) during the period from April 2011 until February 2013.

Patients' criteria and tumor locations are listed in **Tables 1 and 2**. All Patients had unifocal glioblastoma (grade IV astrocytoma, WHO classification), Aged ≥ 18 years with resectable GBM and the patient has received curative surgery, or unresectable and the diagnosis was confirmed by a biopsy of tumor tissue. Surgery or biopsy had occurred ≤ 45 days before the start of radiotherapy, Zubrod performance status ≤ 2. Hematologic, renal, and hepatic status were documented before entry into the study and negative serum pregnancy test performed before starting treatment for females in child bearing potential.

CT Simulation

Patients were immobilized supine using an individualized thermoplastic mask. Planning CT and magnetic resonance imaging scans, both with a 3 mm slice thickness, were fused to aid tumor delineation.

TABLE 1: Patient characteristics.

Characteristic	No. of patients	% of total no. of patients
Age (years)		
Mean	56 (28-72)	
Gender		
Male	7	64
Female	4	46
Duration of symptoms (months)		
<4	5	45.4
≥4	6	54.6
Presenting symptoms/sings		
Headache	6	54.6
Convulsions	5	45.4
Hemiplegia/Hemiparesis	4	36.3
Amnesia	1	9.1
Dysartheria	1	9.1
Zubrod PS		
0	2	18.2
1	5	45.4
2	4	36.4
Initial tumor size		
<5	3	27.4
≥5	8	72.6
Initial Tumor location		
Frontal	1	9.1
Fronto-parital	4	36.3
Temporal	2	18.2
Tempro-parital	2	18.2
Tempro-frontal	2	18.2
Laterality		
Right sided	8	72.6
Left sided	3	27.4
Extent of surgery		
Biopsy	5	45.4
Subtotal excision	4	36.3
Near total excision	2	18.2
Adjuvant temozolomide		
Yes	6	54.6
No	5	45.4

TABLE 2: Tumor location and PTVs.

Location	PTV1 (Cm^3)	PTV2 (Cm^3)
Rt. Fronto-parital	301.1	211.0
Rt. Temporal	428.5	244.6
Rt. Tempro-parital	352.2	242.6
Rt. Fronto-tempro-parital	542.6	187.3
Lt. Frontal	357.5	182.6
Rt. Temporal	643.3	337.6
Lt. Fronto-parital	209.6	95.7
Rt. Fronto-temporal	650.3	343.3
Rt. Tempro-parital	465.5	279.7
Rt. Fronto-parital	247.2	157.1
Rt. Fronto-parital	330.7	211.4

Treatment planning and Target volume definition

Target volumes were based upon postoperative-enhanced MRI. Preoperative imaging was used for correlation and improved identification. Two planning target volumes (PTV) were defined, the initial gross tumor volume (GTV1) was

defined by either the T2 or the FLAIR abnormality (perifocal edema) on the post-operative MRI scan, MRI enhancements, and the surgical cavity. The initial clinical target volume (CTV1) was the (GTV1) plus a margin of 2 cm. The boost gross tumor volume (GTV2) was defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan and the surgical cavity margins. The boost clinical target volume (CTV2) was the GTV2 plus a margin of 2.0 cm. The CTV margin was reduced to 0.5 cm around natural barriers such as the skull, ventricles, and falx, and also to allow sparing of the optic nerve/chiasm, if necessary. The planning target volume (PTV) is an additional margin of 3 mm. Reducing PTV margins to modify organ at risk (OAR) dose(s) was not generally permissible. However, OAR was defined, along with a planning risk volume (PRV) for each OAR. Each PRV was its OAR plus 3 mm. In the event that an OAR was in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTV overlap), defined as the overlap between the PTV and the particular PRV of concern, was created and dose to PRV did not exceed OAR dose limits.

Treatment planning and dose constrain

The plans for RA and 3D were performed by two different planners each had excellent experience in treatment planning. All plans were reviewed by the supervising physicist. All 3D and RA plans were generated using 6-MV photon beams commissioned for a Varian CL21EX linear accelerator and Millennium 120-leaf Multileaf collimator (MLC) (5-mm width leaves over target extent). A dose calculation grid of 2.5 mm was used for both plans. Final dose calculation was performed using the anisotropic analytical algorithm (AAA), including heterogeneity management. The DVH calculations were also performed in Eclipse.

The 3D-CRT planning was performed by forward planning designed based on the standard RTOG regimen [16] for treatment of GBM giving a total dose of 60 Gy in two phases: phase one plane to the PTV1 aiming at 46 Gy/23 fractions given over a period of 31 days (5 fractions/week), followed by phase 2 plan aiming at 14 Gy/7 fractions to PTV2 over a period of 9 days (5 fractions/week). Multiple fields either coplanar or non-coplanar, automatic wedges were used and field shaping was done through MLCs. The RA-SIB plans were generated using an in-house inverse planning approach, in which MLC-shaped fields were progressively added throughout a single 360° arc during optimization applying Otto's VMAT technique in which direct optimization of leaf positions and the weights of field samples were done simultaneously along the arc, so eliminating the leaf sequencing step.[17] Patients received 46 Gy per fraction of 2 Gy in 23 sessions on the PTV1 (contrast enhancement + per-focal edema as seen in T2 MR + 2.3 cm) with concomitant daily superimposed boost (SIB) on PTV2 corresponding to the contrast enhancement + 2.3 cm. In order to calculate the RTOG equivalent dose scheme we used the linear quadratic model with ∞/β of 10 giving PTV2 daily fraction of 2.5 for a total dose of 57.5 Gy. The PTV2 received a daily dose of 2.5 Gy for a cumulative dose of 57.5 Gy over a period of 31days. The planning goal was as follows: the 95% of prescription dose encompassed at least 95% of the PTVs; no more than 20% of the PTVs received more than 110% of prescribed dose; no more than 5% of the target received less than 95% of the prescribed dose; and no more than 2% of the tissue outside the PTV received more than 110% of the prescribed dose. For OARs, the tolerance dose was as follows: 54 Gy to the brain stem and 60 Gy point dose as second criteria, 54 Gy to optic nerve, 54 Gy to optic chiasm, 45 Gy to the spinal cord, 35 Gy mean dose to the eye, and 6 Gy to the lens.

Chemotherapy

During Radiation therapy temozolomide 75 mg/m^2/day was given daily by oral route followed by 6-12 cycles of temozolomide 200 mg/m^2 for 5 days/4week.

Dose volume histogram analysis

Quantitative evaluation of plans was performed by means of standard dose-volume histogram (DVH) and dosimetric parameters were calculated and compared for the PTV and OARs. For the PTV, the comparison parameters included, the mean dose, the standard deviation, maximum dose, conformity index (CI), and homogeneity index. The CI of the PTV was defined as:

$$CI = \frac{V_{95\%}}{V_{PTV}}$$

where, $V_{95\%}$ was volume within the 95% isodose and V_{PTV} was volume of the PTV. Consequently, CI will be larger than one, and will increase with decreasing plan conformity. The homogeneity index (HI) of the PTV described the uniformity of the dose within the planning target volume was defined as the ratio of maximum point dose in the PTV divided by the covering isodose (95%):

$$HI = \frac{\text{PTV Max Dose in \%}}{95}$$

The lower values of HI represented a more homogenous PTV dose distribution.

Endpoint and follow-up

The primary endpoint in this study was assessment of dosimetric potentials and treatment capabilities of SIB-RA versus 3D-CRT. Secondary endpoints included the treatment toxicity, failure patterns (local or distant), Progression-free survival (PFS), and overall survival (OS) times. All the patients were evaluated at least once per week during radiotherapy. The patients were followed every 1–2 months for the first 6 months, and every 3 months thereafter. MRI with contrast enhancement was usually evaluated every 3 months. Radia-

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tion therapy oncology group (RTOG) neurotoxicity scores were used to evaluate acute and late toxicities.

SPSS software Package version 21.0 was used for statistical analysis. Events for the calculation of survival were defined as death from any cause for overall survival (OS) and as disease progression or death from any cause for progression-free survival (PFS). These survival rates were calculated from the date of the start of treatment to the date of the documented event by using the Kaplan-Meier method. Variables were described using mean, median, minimum and maximum values. The Wilcoxon's matched-pair signed-rank test for non-parametrically distributed data was used to compare the means between 3D-CRT and RA-SIB. Values will be expressed as mean ±standard deviation or as mean value and the range of the values according to data distribution. All p-values reported are two-sided and $p < 0.05$ is considered significant.

Results

Treatment outcome

With a median follow up period of 13 months (rang, 4-37 months), the median progression free survival (PFS) and overall survival (OS) were 13 months (95% CI, 8.2-17.8), and 16 months (95% CI, 2.1-29.9), respectively (**Figures 1** and **2**). At time of analysis only three patients were still alive, one of them showed evidence of progression and the other two patients were free of progression (**Table 3**). Four of six patients (67%) showed local progression (recurrence) after initial response, all recurrences occurred at the site PTV2 (57.5 Gy dose volume).

Toxicity

Radiation treatment was interrupted for 2 weeks in one patient after 8 fractions due to loss of consciousness and development of uncontrolled seizures. Patient was hospitalized and kept on corticosteroid, intravenous anti-epileptics and oxygen till his condition stabilized. A causal relationship between this adverse event and the radiotherapy was unclear. The other ten patients completed the scheduled radiotherapy without interruption. Seven patients experienced acute grade 2-3 toxicities during the treatment, including grade 2-3 headache in 4 patients, headache and vomiting (grade 2) in 3 patients and seizures in one patient. All acute toxicities were controllable with corticosteroids, anti-emetics and anti-epileptic drugs; all patients were given prophylactic anti-epileptic drugs after surgery. Late post radiation brain edema was reported in 3 patients and was associated with worsening of the neurological symptoms. In one patient it was associated with increase in the enhancement area on follow up MRI with no response to medical treatment indicating tumor recurrence. Radiation-induced necrosis was observed in one patient 10 months post radiation and diagnosed during follow up MRI. None of the patients who progressed after radiation had second surgical intervention.

TABLE 3: Dosimetric comparison between RA –SIB plan and 3D-CRT.

Variables	RA-SIB	3D-CRT	
	Mean (range)	Mean (range)	*P*-value
Mean dose to PTV1/Gy	47.7 (45.7-49.9)	46.9 (46.1-47.7)	0.04
SD of PTV1/ Gy	2.2 (1.3-3.9)	1.4 (0.9-1.8)	0.02
V≤95% PTV1 / %	2.5 (0.1-5.5)	2.1 (0.3-4.2)	0.63
V≥107% PTV1 / %	10.1 (0.0-17.3)	3.1 (0.0-8.5)	0.01
Mean dose to PTV2/Gy	57.6 (56.3-58.6)	61.2 (60.1-62.2)	0.003
SD of PTV2	1.4 (0.7-2.3)	1.7 (1.1-2.1)	0.05
V≤95% PTV2 / %	2.6 (0.0-4.5)	2.2 (0.0-5.6)	0.6
V≥107% PTV2 / %	0.1 (0.0-4)	1.9 (0.0-7.3)	0.01

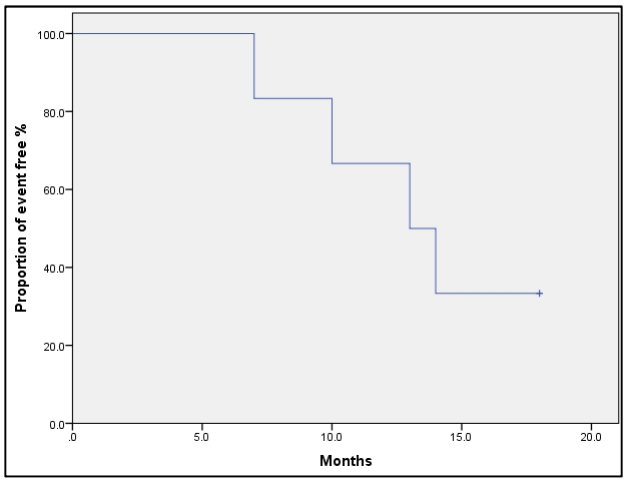

FIG. 1: Progression free survival for all patients.

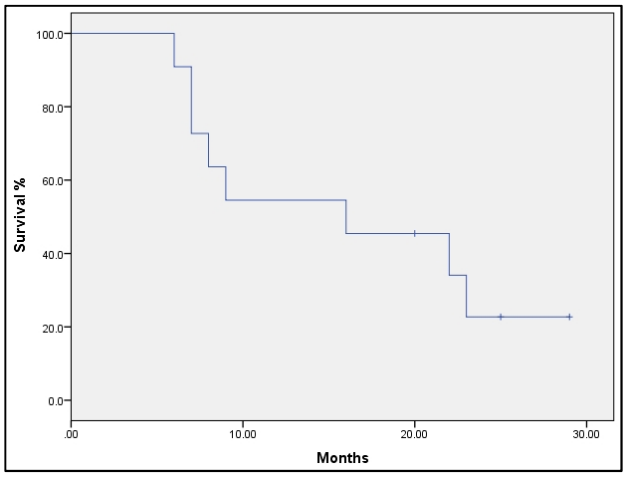

FIG. 2: Overall survival for all patients.

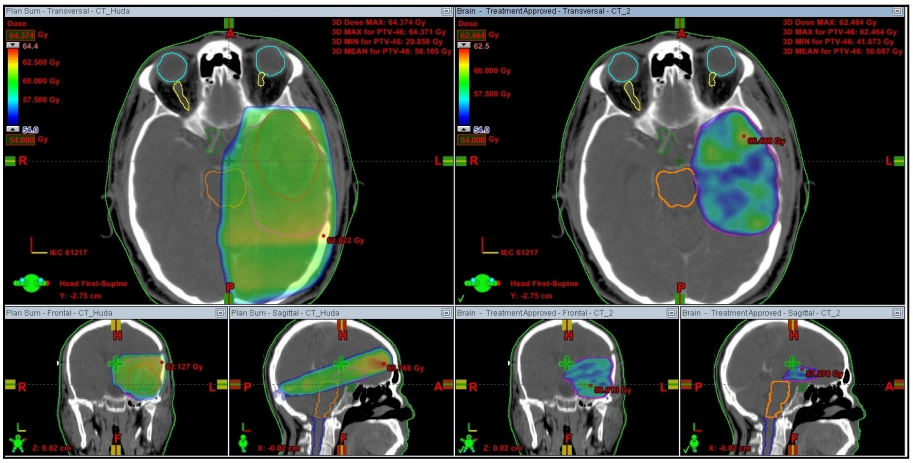

FIG. 3: Color wash distribution for isodose 54 Gy level. On the left, 3D-CRT plan part of the brainstem and healthy brain tissue were included in the dose region. On the right side, SIB-RA plan, the PTV is covered nicely with the dose level while sparing the brainstem and healthy brain tissue.

DVH analysis

Isodose distribution of RA-SIB and 3D-CRT plans of one patient is illustrated in **Figure 3**. The sizes of PTV1 and PTV2 were illustrated in **Table 2**. Both plans achieved 95% isodose coverage to at least 95% of the PTVs. The dose coverage, Conformality and homogeneity were equivalent in both RA-SIB and 3D-CRT (**Table 3** and **4**). Both the mean dose and volume of PTV1 receiving dose ≥ 107% is significantly higher in the RA plan than 3D plan due to the overlapped dose region between both PTV1 and PTV2 in RA-SIB. On the other hand, the dose ≥ 107% for PTV2 is significantly higher in 3D plan than RA plan due to the effect of plan sum. Comparing the maximum dose to the ipsilateral optic nerve and eye, there was statistically significant lower doses to these neurological structures in the RA plan compared with 3D plan by 8.5 Gy (23.5%) and 11.5 Gy (35.2%) respectively (**Table 5**).

The maximum dose to the brainstem in the 3D plan exceeded 60 Gy in one 3D plan (second criteria for BS tolerance), also, the mean dose to BS was significantly higher in 3D plan than in RA plan by 10Gy (43%). The mean dose to the whole brain was significantly higher in RA plan than 3D-CRT plan by 11.2 Gy (43.5%) as we did not consider the brain as risk organ in our plan optimization.

TABLE 4: Homogeneity and conformity indices for PTV1 & 2 in RA-SIB and 3D-CRT.

	Homogeneity index			Conformity index		
	RA-SIB	3D-CRT	P-value	RA-SIB	3D-CRT	P-value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
PTV1	0.83 ± 0.04	0.87 ± 0.2	0.01	1.03 ± 0.04	1.01 ± 0.01	0.41
PTV2	0.89 ± 0.01	0.87 ± 0.02	0.01	1.02 ± 0.1	1.02 ± 0.2	0.67

TABLE 5: Dosimetric comparison between RA-SIB and 3D-CRT for organs at risk.

Variable	Dose	RA-SIB (Gy)		3D-CRT (Gy)		P-value
		Mean	(range)	Mean	(range)	
Normal Brain	Maximum	60.7	(55.8-62.5)	60.5	(49.7-66.8)	0.78
	Mean	25.8	(1.1-40.2)	14.6	(2.8-37.5)	0.03
Optic chaisma	Maximum	36.6	(3.6-51.6)	37.9	(2.7-54.6)	0.28
	Mean	30.1	(1.1-45.8)	31.1	(2.1-48.8)	0.47
Ipsilateral Optic nerve	Maximum	27.8	(3.0-47.8)	36.3	(2.2-54.1)	0.01
	Mean	14.51	(2.6-27.6)	18.68	(0.5-38.9)	0.11
Ipsilateral eye	Maximum	21.4	(8.5-40.1)	33	(12.1-51.9)	0.03
	Mean	8.7	(2.1-16.1)	7.7	(2.0-17.9)	0.5
Brainstem	Maximum	46.1	(6.1-56.1)	50.5	(6.8-60.9)	0.6
	Mean	14.4	(2.2-36.9)	24.5	(2.7-39.1)	0.05

Discussion

In our study dosimetric comparison between SIB-RA and 3D-CRT plans, showed that sparing of the eye, optic tract and brain steam was better in the SIB-CRT plan. However, the coverage of both PTVs was equivalent in both plans. The randomized phase III EORTC/NCIC trial for GBM quality assurance demonstrated that achieving adequate target coverage while sparing OARs is a real concern in GBM irradiation.[18] In this analysis, more than 50% of patients had tumors in close proximity of optical pathways and/or brainstem. In 19% of the cases field size was reduced to decrease the dose to adjacent critical structures and 39% of the participating centers registered PTV under-dosage. From this point of view, the use of more advanced techniques such as IMRT and VMAT could be beneficial. According to previous reports [14, 15] IMRT contributes to a moderate decrease in the dose delivered to critical structures in the brain compared to 3D-CRT while maintaining target coverage without significant variations. Chen *et al.* [19] reported that IMRT seemed to allow better sparing of organs at risk than 3D-CRT did (P = 0.055). However, there was no significant difference for toxicities of irradiation between the IMRT group and the 3D-CRT group. Also, Chan *et al.* [13] demonstrated that SIB-IMRT could deliver a higher dose to the GTV compared to 3D-CRT without elevating the dose delivered to organs at risk. At the same time, in their comparative dosimetric study Wagner *et al.* [20] and Thilmann *et al.* [21] pointed out that IMRT achieved better target coverage with respect to 3D-CRT, scoring a V95% improvement of 13.5 and 13.1%, respectively. This advantage was much more significant when PTV was in proximity of OARs (20). Lorentini *et al.* [22] reported that IMRT always provides better target coverage than 3D-CRT, regardless the clinical-dosimetric scenario. Moreover, the higher the number of PTV-OARs overlaps, the better the target coverage provided by IMRT with respect to 3D-CRT.

In this study we used a daily fraction of 2.5 Gy for total dose of 57.5 Gy with SIB-RA which is equivalent to 60 Gy/30 fractions. Similar daily fractionation was used in other studies using SIB-IMRT.[23-24] The progression free survival and overall survival were 13 and 16 months respectively. Our results are similar to Raymond *et al.* [25] who reported the results of SIB-IMRT with TMZ in 35 patients with GBM. Doses of 60 Gy and 40 Gy were delivered in 20 fractions to the GTV and the PTV (GTV plus a 15 mm margin), respectively. Median OS was 14.4 months with median PFS of 7.7 months. Cho *et al.* [23] reported the results of 40 patients (WHO grade III, 14 patients; grade IV, 26 patients) treated with SIB-IMRT, a dose of 2.0 Gy was delivered to the planning target volume with a SIB of 0.4 Gy to the gross tumor volume with a total dose of 60 Gy to the gross tumor volume and 50 Gy to the planning target volume in 25 fractions during 5 weeks and 20 patients received concurrent TMZ. At a median follow-up of 13.4 months (range, 3.7–55.9 months), median survival was 14.8 months. One and 2-year survival rates were 78% and 65%, respectively, for patients with grade III tumors and 56% and 31%, respectively, for patients with grade IV tumors. Inferior results were recorded in other studies; Sultanem *et al.*[26] evaluated the efficacy of SIB-IMRT in 25 patients with GBM. A dose of 60 Gy in 20 fractions of 3 Gy was given to the GTV, whereas the PTV (GTV plus a 15 mm margin) received a minimum of 40 Gy in 20 fractions of 2 Gy. Median survival was 9.5 months, with disease progression observed in 21 patients (84%). Recent retrospective analysis of 54 patients with GBM by Chen *et al.* [18] assessed whether IMRT improved clinical outcomes compared with 3D-CRT. The median follow-up was 13 months. Of the 54 patients, 50 (92.6%) completed the combined modality treatment (patients underwent postoperative IMRT or 3D-CRT with concurrent and adjuvant temozolomide). The 1-year overall survival rate (OS) was 79.6%. The pattern of failure was predominantly local. A comparative analysis revealed that no statistical difference was observed between the IMRT group (n = 21) and the 3D-CRT group (n = 33) for 1-year OS (89.6% vs. 75.8%, P = 0.795), or 1-year progression-free survival (PFS) (61.0% vs. 45.5%, P = 0.867). The authors concluded that preliminary results suggest that delivering standard radiation doses by IMRT is unlikely to improve local control or overall survival for GBM compared with 3D-CRT.

In all the previous studies the total dose, dose per fraction and the PTV delineation are different from one study to another in addition these studies were retrospective analysis and some studies include both high grade gliomas and GBM.[24, 25] In our study, we used the RTOG recommendation for delineation of both the PTV1 and PTV2, So, our PTV margins are generous than previous studies. In the previous studies they considered alpha/beta (α/β) ratio of 10 like our study and BED ranged from 66.1 Gy [23], 72.5 Gy [25, 26] up to 126.9 Gy [24] and our BED was 60 Gy to PTV2 which is the standard radiation dose for GBM. All our patients received concurrent TMZ followed by adjuvant TMZ in 6 patients. The local failure was 67% in our patients and was the only pattern of failure with no distant failures reported in our patients. Previous studies reported equivalent local failure rates of more than 60%.[24-26] Iuchi *et al.* reported lower rate of local failure (24%) and he explained this improved local control by the high BED of 126.9 given to the GTV. On the other hand, he reported 32% leptomeningeal dissemination which was the commonest cause of death (70%).

The limitation of our study includes a small number of patients, and there is no direct clinical comparison with patients treated by the 3D-CRT technique. For dose calculations, Acuros XB – the most advanced dose calculation algorithm available in Eclipse treatment planning system [27]– was not used in this study. Treatment plans were calculated using AAA, which has its limitation in dose predicting accuracy in the inhomogeneity media. Several studies [27-29] have recommended to calculate treatment plans using Acuros XB, which

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is a more accurate dose calculation algorithm compared to AAA.

Conclusion

SIB-RA is feasible and safe, with acceptable acute and late toxicities, despite the large fractional doses that were delivered to the GTV. The shortening of overall treatment time by using the SIB-RA technique could have better patient`s convenience, as far as it is safe and provides a similar survival outcome. From the dosimetric standpoint, SIB-RA is a superior technique with respect to 3D-CRT when there are overlaps between OARs and PTV. In these situations, SIB-RA allows for a better target coverage by maintaining at the same time an equivalent OARs sparing.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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