The Helical Tomotherapy Experience on Radiotherapy of Glioblastoma Multiforme

Glioblastoma Multiforme Radyoterapisinde Helikal Tomoterapi Deneyimi

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ABSTRACT

Objective: The standard treatment of Glioblastome Multiforme (GBM) is surgical resection followed by chemoradiotherapy and adjuvant temozolamide. Intensity Modulated Radiotherapy (IMRT) offer an advantage in terms of reducing the dose to critical normal structures and a reduced dose to the normal brain. It also offers application of Simultaneous Integrated Boost (SIB).

Material and Methods: Among our 12 patients, 7 had a diagnosis of GBM whereas 3 of them were anaplastic oligoastrocytoma and 2 of them were diagnosed radiologically as high-grade glial tumor. In all patients, 60 Gy SIB-IMRT with concomitant Temozolomide was used.

Results: In post treatment Magnetic Resonance Imaging (MRI), 8 patients had no recurrence whereas 2 patients showed partial response and in 2 patients there was no response at all. After a median follow-up period of 12 months, 3 patients survived disease free, and 9 patients were expired. The overall survival was 14.8 months. Median progression free survival was 4.4 months. The mean dose received by the brain stem was 12.90 Gy and 12.72 Gy for the optic chiasm.

Conclusion: High doses can be given while protecting critical tissues with SIB-IMRT.

Key Words: Glioblastoma Multiforme, Tomotherapy, Radiotherapy

ÖZ

Amaç: Glioblastome Multiforme'de (GBM) standart tedavi cerrahi rezeksiyon sonrası eşzamanlı kemoradyoterapi ve adjuvant temozolamiddir. Intensity Modulated Radiotherapy (IMRT) normal dokuları koruyarak tümöre daha yüksek dozlar verebilme ve Simultaneous Integrated Boost (SIB) imkanı sunar.

Gereç ve Yöntemler: 12 beyin tümörlü hastanın yedisi glioblastome multiforme, üçü anaplastik oligoastrositom, ikisi radyolojik olarak yüksek gradlı glial tümördü. Hastalara toplam 60 Gy SIB-IMRT yapıldı. Tüm hastalara eşzamanlı temozolomid verildi.

Bulgular: Tedavi sonrası Manyetik Rezonans Görüntüleme (MRG) sonuçları tam rezeksiyon yapılan 8 hastada rekürrens olmadığını, 2 hastada parsiyel yanıt, 2 hastada da hiç yanıt alınmadığını gösterdi. Grad 3 hematolojik toksisite 1 hastada görüldü. 12 aylık ortanca takip süresi sonunda üç hasta hastalıksız yaşarken 9 hasta eksitus oldu. Toplam yaşam süresi 14,8 ay ve ortanca progresyonsuz sağkalım 4,4 ay idi. Beyin sapının aldığı ortalama doz 12,90 Gy iken optik kiazma için 12,72 Gy'dir.

Sonuç: Optik kiazma ve beyin sapı gibi kritik organlara verilen dozlar düşürülürken, hedef volüme verilen doz SIB-IMRT ile arttırılmıştır.

Anahtar Sözcükler: Glioblastoma Multiforme, Tomoterapi, Radyoterapi

INTRODUCTION

Glioblastoma multiforme (GBM) is the most commonly seen primary tumor of the brain. The standard treatment of GBM consists of surgical resection followed by concomitant chemoradiotherapy and adjuvant temozolamide (TMZ). Despite modern treatment

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modalities, it still has a poor prognosis (1). The median survival for patients with GBM has been reported as 11 months with surgical resection and radiotherapy alone. TMZ provided a survival advantage and increased the overall survival to 14.6 months with 26% survival at 2 years (2). Hegi et al. reported in a phase III trial that there was a 46% 2 years survival for those patients who had epigenetic silencing via methylation of the promoter of the gene that metabolizes TMZ (O-6-methylguanine-DNA-methyltransferase) (3). Although recent advances on targeted chemotherapies may provide a survival benefits on GBM, local treatment modalities need to be advanced keeping in mind that local tumor progression was the pattern of failure during GBM treatment, and the vast majority of recurrences are focal, at the initial site of neoplasm (4,5).

Studies of the past decade have concentrated on new treatment regimens for GBM, various radiation therapy dose schemas and delivery techniques. Several studies have reported employing intensity modulated radiotherapy (IMRT) techniques that offered an advantage in terms of reducing the dose to critical normal structures and a reduced dose to the normal brain (6,7). Although these dosimetric advantages have not been translated into an improvement in reported survival in many studies, Aherne et al in their study with 31 patients reported that the combination of IMRT at standard radiation doses with TMZ can lead to an increase in median overall survival (8).

In this study we evaluated the radiotherapy plans of 12 GBM patients who received simultaneous integrated boost (SIB) radiotherapy with Helical Tomotherapy (HT) which uses image guided intensity modulated radiotherapy (IG-IMRT) and presented the survival and acute and late side effects. This study also presents the brain V18, V36 and V50 received by healthy brain tissue.

MATERIAL and METHOD

The patients' characteristics are given in Table I. Preoperative and postoperative MRIs were performed in all patients in a 1.5 tesla MRI scanner with a standard head coil and the images were integrated in the planning process. The MRI protocol included enhanced T1-weighted, a T2-weighted and a FLAIR (fluid attenuation inversion recovery) sequence. All patients were immobilized using a commercially available head and neck thermoplastic mask system and underwent computed tomography (CT) simulation. CT images were reconstructed with 3 mm slice thickness. CT scans were transferred to the Tomocon Workstation for definition of target volumes. CT simulation and postoperative MRI image fusion was performed for contouring. Gross tumor volume (GTV) was defined as the operative cavity with any residual contrast-enhancing tissue on T1-weighted magnetic resonance imaging or as unresected enhancing tumor. The clinical target volume 1 (CTV1) was defined as the edema visible volume in T2-weighted images. The planning target volume (PTV1) was defined as the extension of CTV1 by 3 mm. CTV2 was defined as the volume produced with 2 cm expansion of GTV. PTV2 was defined as CTV2 + 3 mm volume, which is also defined as SIB volume. Outlined target volumes, non target tissue and organs at risk (OAR) structures including the brainstem, optic chiasm, lens and total brain were transferred to the TOMO planning system. Tomotherapy plans were completed in the Hi-Art II planning system (TomoTherapy Inc, Madison, WI, USA). In tomotherapy planning systems, 3 major factors are defined: the field width, the pitch and the modulation factor. The longitudinal field width is described as the fan beam width. The pitch is the ratio of the field width for every gantry rotation and table movement. The modulation factor is described as the ratio of the mean intensity of all bundles to the intensity of the most intense bundle.

All patients received external radiotherapy at a dose of 60 Gy in 200 cGy fractions.

Dose prescription for the SIB was 60 Gy, initial target volume received typically 45 Gy, in daily 150 cGy fractions.

Table I: Patients' characteristics.

	n= 12 (%)
Age (years)	
Median	52
Range	19-76
ECOG	
1	6 (50)
2	4 (33)
3	2 (17)
Surgery	
Complete resection	8 (66)
Biopsy	2 (17)
Radiologic diagnosis	2 (17)
Pathology	
Unknown	2 (17)
GBM	7 (58)
Anaplastic Oligoastrocytoma	3 (25)
Localization	
Frontal lobe	4 (33)
Temporal lobe	5 (42)
Parietal lobe	2 (17)
Occipital lobe	1 (8)
Temozolomide	
With	9 (75)
Without	3 (25)

TMZ in dose of 75 mg/m² was given concomitantly with radiotherapy. After completion of radiotherapy, the chemotherapy with TMZ was continued at a dose of 150 or 200 mg/m² for five days every 28 days, 6 cycles in total. Toxicity was prospectively assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. All patients were followed for hematological side effects of TMZ. The patients had baseline toxicity assessment prior to initiation of chemoradiotherapy and were seen weekly with weekly toxicity assessment during chemoradiotherapy treatment. All patients were under follow-up every 28 days until chemotherapy was completed and every 3 months thereafter. MRI scans were undertaken three monthly to assess for radiological progression. Perfusion MRI images were used to differentiate disease progression and radiation necrosis. In patients with disease progression, reoperation or retreatment with TMZ or reirradiation was planned according to the patient's condition.

Collected data regarding planning, treatment and survival parameters were analyzed using the SPSS 16.0 statistical software. Kaplan-Meier survival analysis was performed using survival data.

RESULTS

In general, the patients tolerated the treatment well. We observed no neutropenia, neither acute nor late form. Only one patient had acute grade 3 thrombocytopenia and was unable to complete the TMZ treatment. The same patient developed local recurrence in 9 months and required reoperation. Complete resection was impossible and the patient received reirradiation and survived 10 more months. In the follow-up period of the last 10 months, he developed cognitive disturbance that was classified as grade 3 late toxicity. We have not observed any other late toxicity. We have observed grade 2 nausea/vomiting only in one patient as an acute toxicity.

Post treatment MRI revealed that 8 (66%) patients who had complete resection had no recurrence whereas 2 (17%) patients showed partial response and in 2 (17%) patients no response at all. Progression free survival was 75% in 3 months, 50% in 6 months and 16.7% in 12 months. Median progression free survival was 4.4 months. None of the patients has developed radiotherapy related necrosis or pseudo-progression. After a median follow-up period of 12 months, 3 (25%) patients survived disease free, and 9 (75%) patients have expired. The overall survival was 14.8 months. All recurrences were within 2 cm of the operative bed.

The mean V18 value was 58.27%, V36 value was 30.90% and V50 value was 18%. The mean dose received by the brain stem was 12.90 Gy and the optic chiasm had received a mean dose of 12.72 Gy.

Table II: Target coverage and normal tissue sparing.

Mean volume (cm³)	
PTV45	252.75
PTV60	92.37
V95% (%)	
PTV45	99.82
PTV60	99.74
Brain (%)	
V18	57
V36	30
V50	17
Optic chiasm (Gy)	
Dmean	12
Dmax	28
Brainstem (Gy)	
Dmean	12
Dmax	40

The target coverage was 99.74% of the prescribed dose for PTV60 Gy V95% (percentage of the volume of PTV60 that receives at least 95% of the prescribed dose) and 99.82% for PTV45 V95% (Figure 1). Median volumes of PTV60 and PTV45 were 92.37 cm³ (range: 45.92-156.27 cm³) and 252.75 cm³ (range: 153.00-329.73 cm³) respectively (Table II).

DISCUSSION

IMRT has made it possible to deliver a radiation dose to tumor with a highly conformal dose distribution especially for tumors with irregular shapes, enabling delivery of the intended dose accurately. The capability to produce dose plans with variable dose allows for graduated dose plans and SIB. This is possible using rotational IMRT (9).

IMRT is less forgiving for set up inaccuracies. Thus, the full benefit of IMRT can only be obtained with the use of accurate targeting using image-guided radiotherapy (IGRT). All of the central nervous system (CNS) cases were considered to have benefitted substantially from integrated IG-IMRT (10). The use of IGRT can reduce the margin with the achievement in imaging techniques and it provides greater biological dose to the tumors like GBM that have a tendency to spread through normal brain tissue. IGRT may lead to a reduced integral dose as well (11). It is a clinical concern to keep normal tissue receiving as low a dose as possible. In clinical studies with high-grade glial tumors, IMRT actually reduces the integral dose compared with conformal radiotherapy, by up to 7-10% (12). Additionally, IG-IMRT did offer an advantage in terms of reducing the dose to critical normal structures and reduced the dose to the normal brain (7).

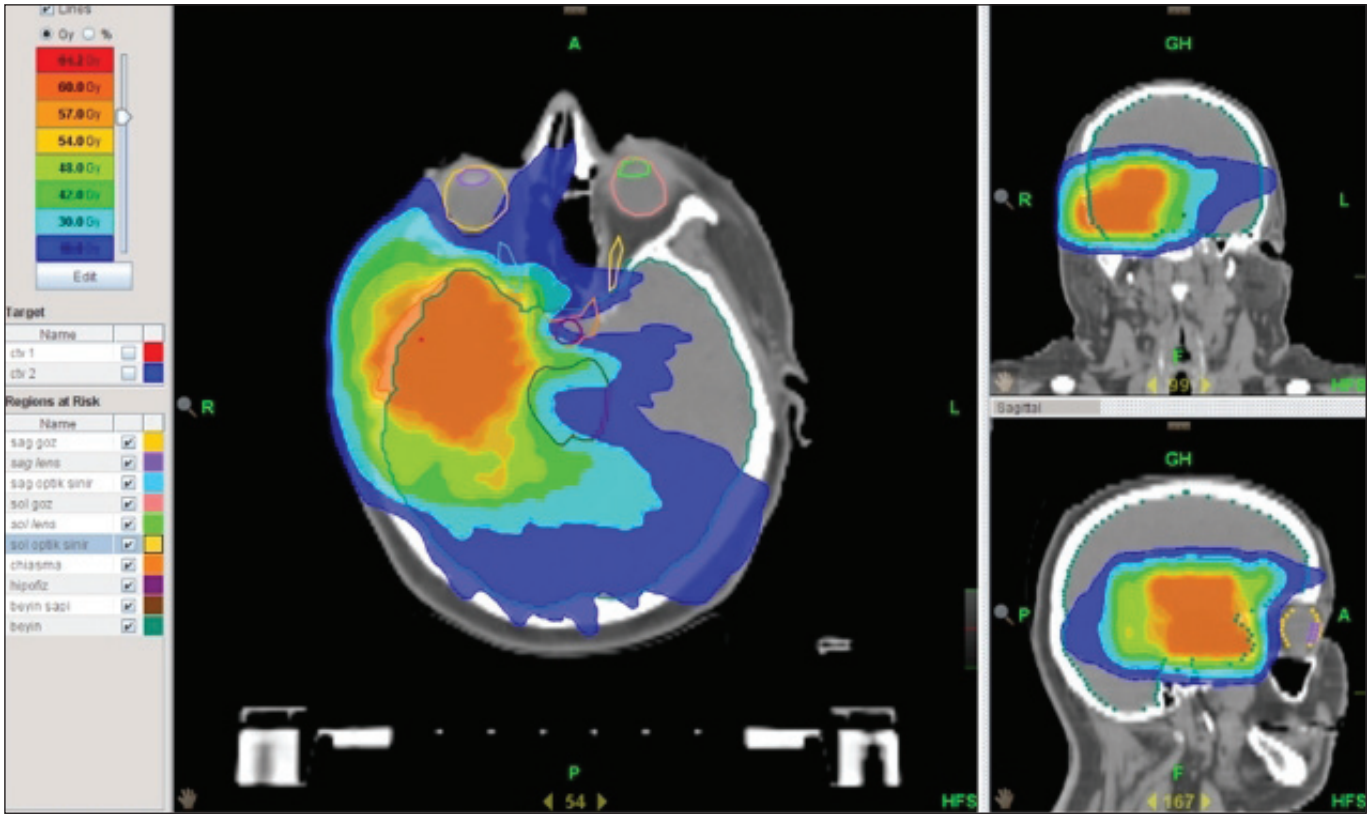

Figure 1: Target coverage and normal tissue sparing.

More than 90% of failures occur within the irradiated volumes during GBM treatment (13). For this reason, it is necessary to study further the alternative fraction protocols in patients with GBM. The results of dose escalation have been reported in small, single institution, phase I-II studies (14,15). In these studies, the overall survival has been reported as 20.1 months in patients treated with hypofractioned IMRT. The long-term survival at 4 and 5 years was similar to conventional treatment (16). Despite the survival advantage, there was no increase in acute side effects. Despite the increase of radiation induced necrosis incidence, the authors concluded that the treatment was safe and the outcomes comparable with standard practice (2). In several studies the incidence of late toxicity was greater with hypofractioned treatment regimen, specifically a 20% incidence of cerebral necrosis (17). In brachytherapy studies that pioneered hypofractioned treatment models, survival benefits have been reported but a greater incidence of radiation necrosis has been observed (18).

Since dose escalation studies have a limited number of patients and present some controversial results, we decided to use SIB-IMRT with standard dose schedules. Our decision was based on the fact that the SIB-IMRT strategy not only produces superior dose distribution but is also an easier, more efficient and perhaps less error-prone way of planning and delivering IMRT because it involves the use of the same plan for the entire course of treatment (19). The protection of normal brain tissue is of particular importance for tolerance to dose increases. It is crucial to prevent radiation necrosis and neurocognitive deficits and reduce the dose received by critical structures (chiasm, brainstem) (20). This method allows secondary irradiation in such a disease with high recurrence rate and the recurrences are more frequent within 1 to 2 years of initial diagnosis. In vivo radiobiological data suggest that after an initial course of RT, brain tissue may repair the radiation related damage depending on the primary total dose and fractionation as well as the time lapse between treatments (21). The cumulative tolerance dose of normal brain tissue delivered in 2 Gy per fraction approximates 100 Gy (22). In our study, one patient had reirradiation and secondary surgery after development of local recurrence. The patient survived 10 more months but developed grade 3 cognitive disturbances after reirradiation. The brain V18, V36 and V50 values of the same patient were 55%, 27% and 13% respectively during the initial radiotherapy. The patient developed recurrence 9 months after initial diagnosis and had no cognitive disturbance in neurological examination at the time of recurrence. We found 5 to 10% higher values in brain V18, V36 and V50 compared to other SIB-IMRT studies. Ken et al. reported that brain V18, V36 and V50 values showed minute increments when the dose rose to 72 Gy. (20)

In our study, we have limited the number of patients. These patients had a high percentage of cold dose area in 3 dimensional conformal radiotherapy plans. When we tried to correct these cold dose areas, we recognized that the doses of the critical organs had unacceptably increased and we need to use SIB-IMRT. Although it was a small group, we presented the results since we think that these results may pioneer further prospective studies. When the patients were treated with the standard dose of 45 Gy, the dose was administered in 150 cGy fractions. When the recurrences are concerned, there were recurrences that developed outside the 150 cGy fraction treated area. Additionally, three patients with anaplastic oligoastrocytoma were treated with the same protocol and did not develop recurrence. The overall survival rates were in accordance with the literature. Chang et al. reported in their study that there is no obvious relationship between peritumoral edema and recurrence pattern. Target delineation with 2 cm initial margin and 1 cm boost margin without including edema seems not to alter the typical GBM pattern of failure (23). In our study, recurrences were not in the 150 cGy region, which supports this study. The gross tumor seems to be more important concerning the recurrence pattern of gliomas.

During radiotherapy for GBM it is a difficult compromise between preventing radiation necrosis and neurocognitive impairment and the tumor control that has to be achieved. In our study group, we have not observed any radiation necrosis since we did not use dose escalations and used SIB-IMRT in HT. The critical organs such as the optic chiasm and brainstem received quite low doses. In our study, although normal brain tissue received 5-10% higher radiation doses compared to other IMRT plans, it is possible to reduce this doses with TomoDirect plans (24). Since healthy tissues can be protected well, phase III dose escalation studies can be designed with Tomotherapy. While designing such studies, previous low patient size studies should be considered.

We used conventional MRI for the treatment planning stage. Recently, new methods have been developed that enable elucidation of the biologic pathways of tumors, yielding additional information about the metabolism of the tumor tissue. Functional imaging studies, such as PET-CT and MRI spectroscopy have demonstrated increased metabolic activity of glioma cells compared to normal brain tissue (20, 25). We used PET-CT, MRI spectroscopy to differentiate recurrences from necrosis. When these methods are integrated with planning systems, the dose escalations in the regions with a high relapse risk would provide better results.

CONCLUSION

We presented our findings of SIB-IMRT with HT in this study. Although the number of patients in our study group was limited, our study may guide further SIB-IMRT dose escalation studies. We presented survival rates that were similar to the literature but with lower acute and late side effect rates. Our findings are comparable with the findings in the literature.

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