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Original Article

Reirradiation with Cyberknife® fractionated stereotactic radiotherapy in adult recurrent low-grade gliomas

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Abstract

Aim: We aimed to present our clinical experience in patients with recurrent LGG who underwent the fractionated stereotactic radiotherapy (FSRT) with Cyberknife®.

Material and Methods: Ten patients with recurrent low grade glioma who had previously irradiated were treated with FSRT as a salvage treatment. At the initial diagnosis, the histology of the tumor was grade II astrocytoma or oligodendroglioma. Four of 10 patients underwent surgery as the primary treatment for recurrence.

Results: The median prescription dose was 24 Gy (range 21-25 Gy) with a median fractionation number of 4 (range, 3-5 fractions). No concurrent chemotherapy was administered except one with radiological tumor upgrading. The median interval between the first diagnosis and recurrence was 95 months (range, 45-191 months). From the time point of re-irradiation, median survival was 15 months (range, 1-30 months). CyberKnife® FSRT was well tolerated by all patients. No acute or late side effects were recorded. With a median follow-up of 17 months, 3 patients died. Seven patients were alive with local tumor control in 5 and tumor progression in 2 patients.

Conclusion: Fractionated stereotactic radiotherapy is a safe and effective salvage treatment for recurrent LGG. FSRT in adult recurrent LGGs showed encouraging short term results in this small number of cases. Prospective studies are necessitated as further evaluation.

Keywords: Cyberknife; radiosurgery; recurrent low grade glioma; re-irradiation; salvage treatment

INTRODUCTION

Low grade gliomas (LGGs) constitute 10-20% of primary CNS (Central Nervous System) tumors (1). The most common neuroepithelial grade 2 gliomas are diffuse astrocytomas (IDH mutant and wild type), oligodendrogliomas (IDH mutant and 1p / 19q co-deleted, NOS) and mixed oligoastrocytomas (NOS). LGGs have a low proliferation index but a malignant transformation over time (1,2).

The treatment alternative of patients with infiltrative LGG is still controversial. While the American and European literature (3,4) have advocated that the extent of resection in patients with LGG improves survival, prospective controlled studies failed to emphasize the importance of surgery in the treatment of LGG. Observation is acceptable in selected patients (5-7).

The prognosis and optimal treatment for patients with LGG vary according to many factors. These; Karnofsky Performance Scale score, presence of preoperative neurological deficit, tumor diameter, crossing the midline of the tumor, histological subtype, contrast enhancement lesion on MRI and expression of molecular markers (8-10).

Even the primary treatment of patients with LGG is arguable; there is no standard treatment in patients with recurrent LGG. In recurrent LGG, the prognosis is poor, and if left untreated survival may decrease to several months (11). Treatment options include re-surgery, chemotherapy, radiotherapy (RT) and supportive care. The main purpose of the re-surgery in patients with recurrent LGG is to eliminate the effect of compression and to determine the molecular-pathological features of tumors as shape the treatment (12).

Unfortunately, if RT is used in the adjuvant setting after the first surgery, its applicability to the recurrence decreases. However, promising results can be seen with the novel RT techniques. Stereotactic radiotherapy, which is a non-invasive method that can be applied to the lesion at ablation doses, can be promising in recurrent LGG treatments.

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There are the small series of retrospective studies related to this subject. In this study, we aimed to present our clinical experience in patients with recurrent LGG who underwent fractionated stereotactic radiotherapy (FSRT) with Cyberknife® in our clinic. The primary endpoint of this study was to determine the survival and oncologic outcomes in patients with recurrent LGG undergoing FSRT. The secondary endpoint was to evaluate the toxicity of FSRT in this patient group.

MATERIAL and METHODS

We retrospectively reviewed 10 patients with low grade glioma who had previously irradiated and underwent FSRT with Cyberknife® (Accuray In corporated, Sunnyvale, CA) salvage treatment at recurrence between April 2010 and July 2012 in our clinic. At the initial diagnosis, the histology of the tumor was grade II astrocytoma or oligodendroglioma. All patients previously received median 56 Gy (range, 50 -60 Gy) external radiotherapy. The patients and its characteristics are summarized in Table 1.

Table 1. Clinicopathological characteristics of patients with recurrent low grade glioma

Clinicopathological characteristic	At diagnosis	At recurrence
Number of patients	10	10
Sex, n		
Male	8	8
Female	2	2
Age, years		
Median	36	47
Range	18-52	23-64
≤ 40 years, n	7	3
Tumor size, cm		
Median	-	3,2
Range	-	2.1-5.5
Tumor location, n		
Frontopariatel	3	3
Frontal	2	2
Temporal	1	1
Central cerebrum	2	2
Unknown	2	2
Surgery received, n		
Yes	10	4
No	0	6
Tumor subtype, n		
Astrocytoma	4	
Oligodendroglioma	5	2
Unknown	1	2
EBRT and FSRT doses, Gy		
Median	56	24
Range	50-60	21-25
Chemotherapy received, n		
Yes	0	1
No	10	9

Abbreviations: EBRT: External Beam Radiotherapy, FSRT: Fractionated Stereotactic Radiotherapy

Tumor progression was detected clinically and radiologically during regular follow-up by contrast enhanced and perfusion magnetic resonance imaging (MRI). When the recurrence pattern was examined, all recurrences were within the radiotherapy field or localized at the field border. Four of 10 patients underwent surgery as the primary treatment for recurrence. No high grade transformation was observed radiologically or pathologically except one patient. In that patient high grade histology was demonstrated radiologically by metabolic evolution with perfusion MRI.

Statistical Analysis

Statistical analysis was performed using SPSS version 18. continuous (quantitative) variables are presented as the minimum-maximum and median. The Categorical variables are presented as number (n) and ratio (%). Nonparametric tests were used. Categorical demographic characteristics of the patients were calculated by Chi-square and Fisher's exact test. Kaplan-Meier survival analysis was utilized to predict overall survival (OS) and the log rank test was employed for comparison. $P<0.05$ was regarded as statistically significant.

RESULTS

In the present study, ten patients with recurrent LGG underwent CyberKnife® FSRT with skull-base tracking method as a reirradiation between April 2010 and July 2012 in Ankara Oncology Hospital, Turkey. The median age of the patients were 47 years (range, 23-64 years) at the time of recurrence.

Table 2. Details of Treatment of Stereotactic Radiotherapy

Median PD in Gy (range)	24 (21-25)
Median maximal dose in Gy (range)	26 (23-29)
Median isodose in % (range)	91 (80-94)
Fraction number (range)	4 (3-5)
PTV volume in cc (range)	30 (7-813)

Abbreviations: PD: Prescribed Dose, PTV: Planned Target Volume

The median prescription dose was 24 Gy (range 21-25 Gy) with a median fractionation number of 4 (range, 3-5 fractions) (Table 2). The median prescription isodose was 91% (range, 80-94 %). The median value for PTV, V95 (volume receiving 95% of the prescribed dose) and V107 (volume receiving 107% of the prescribed dose) was 100% and 38%, respectively. The median brainstem and optic pathway maximum doses were 5 (range, 2-27 Gy) and 2 (range, 1-13 Gy), respectively. No concurrent

chemotherapy was administered except one with high grade tumor with the radiological assessment.

The median OS from the initial diagnosis to the time of analyses was 117 months (range, 47-213 months). The median interval between the first diagnosis and recurrence was 95 months (range, 45-191 months). From the time point of re-irradiation, median survival was 15 months (range, 1-30 months). CyberKnife® FSRT was well tolerated by all patients. No acute or late side effects were recorded. Three of 10 patients died owing to comorbidities (n=1) and tumor progression (n=2). With a median follow-up of 17 months (from re-irradiation) in patients who were alive, tumor progression is detected in 2. Five of 10 patients were alive with local tumor control and improvement in performance status. The characteristics of the patients who have progressive disease are listed in Table 3.

Table 3. Characteristics of patients with progressive disease after FSRT

Patient number	Age	Sex	Pathology type	Tumor diameter (cm)	Surgery in reccurrence	Time from diagnosis to recurrence (months)	Initial EBRT doses (Gy)	FSRT doses in recurrence (Gy)
1	38	Male	Astrocytoma	-	Yes	60	54	24
2	37	Male	Oligodendroglioma	4	No	45	54	23.5
3	48	Female	Astrocytoma	2.1	No	83	56	22
4	54	Male	Oligodendroglioma	3.5	No	163	60	24.5

Abbreviations: EBRT: External Beam Radiotherapy, FSRT: Fractionated Stereotactic Radiotherapy

DISCUSSION

In our study, we aimed to present the results of re-irradiation with CyberKnife® FSRT in patients who had previously received RT in patients with recurrent LGG so that there is no standard treatment approach in this group of diseases. The median survival after re-irradiation was 15 months. FSRT was applied to the residue / cavity in 4 patients who underwent surgery as the treatment of recurrence. CyberKnife® FSRT was well tolerated by all patients. No acute or late side effects were recorded. With a median follow-up of 17 months, 3 patients died. Seven patients were alive with local tumor control in 5 and tumor progression in 2 patients.

Osman et al. (13) examined the survival benefit of re-irradiation with the conformal radiotherapy technique and sequential temozolomide in the study of 20 patients with recurrent G2 brain glioma. In 8 of 20 patients (2 complete responses - 6 partial responses) objective response was obtained. The median survival was reported as 15.5 months (13). Similarly, the median survival was 15 months in the present study. Apart from, unlike our study, 4-5 cycles of temozolomide were implemented prior to RT, and re-irradiation was administered in moderate doses (30 Gy - 40 Gy) with the conformal technique. We applied temozolomide only to one patient with high grade transformation and higher biological effective doses were achieved because we employed the stereotactic radiosurgery (SRS) technique.

Fukuya et al. (14) investigated the recurrence pattern of 81 patients with recurrent astrocytoma and oligodendroglioma. They reported that survival was significantly lower in rapid radiological progressive disease and early recurrence (within two years of initial surgery) and non-local recurrences (14). In our study, all relapses were within or at the border of the RT field and the earliest relapse occurred 45 months after surgery, so it was the late recurrence.

Sadık et al. (15) reported the survival outcomes of 94 patients with recurrent low and high grade glioma (HGG) who underwent Gammaknife radiosurgery. Radiosurgery was administered as a median dose of 18 Gy in single fraction. Improvement in survival has been shown with Gammaknife radiosurgery, especially in high grade glioma. The median survival was 86.6 months for LGG and 12.8 months for HGG. No serious side effects were reported after radiosurgery (15).

As in the treatment of all glial tumors, surgery is the standard treatment in the initial diagnosis of LGG. But should it be standard and safe to perform recurrent surgeries in recurrent LGG. The role of surgery in the treatment of the recurrent LGG is uncertain. Uppstrom et al. (16) in a review published, they were reported that maximal extent of resection improved progression-free survival (PFS) and overall survival (OS) in recurrent LGG. The authors argued that recurrent surgery should be the standard if gross or near total resection is possible (16). However, it is also common for these group of patients to be unsuitable for recurrent surgery. RT may be beneficial in cases where patients are unsuitable for maximal safe resection or refuse surgery. Adjuvant RT improves PFS if subtotal resection has been carried out in the primary treatment of LGG. However, if total resection was performed, there was no difference between early RT and delayed RT in terms

of OS and PFS (17). Although the role of early adjuvant RT or deferred RT is confirmed, the role of re-irradiation in recurrent LGG is not clear. In the decision of re-irradiation, it is crucial that do not exceed the tolerance doses of the critical organs (especially serial organs) in the initial RT plans. In re-irradiation, the optic pathway and brainstem should be protected to the maximum and irradiation should be conducted with precise accuracy. Therefore, re-irradiation should be implemented with high conformal techniques (e.g. stereotactic radiotherapy technique). The series of re-irradiation in recurrent LGG are small and retrospective (13, 18).

Because the expected survival is relatively long in patients with recurrent LGGs, healthy brain tissue (especially the hippocampus) must be well protected from radiation for possible neurocognitive dysfunction. So the toxicities and side effects should be considered in re-irradiation (19). Although there are larger series of FSRT as re-irradiation in malignant gliomas, the side effect is less due to lower survival. Although, in malignant gliomas, larger series with FSRT as re-irradiation have been submitted in the literature, fewer side effects have been reported due to low survival (20, 21). Hence, re-irradiation-related toxicities become more important due to the long follow-up time. In this study, no acute or late toxicity was observed in any patient at a median follow-up of 17 months.

LIMITATIONS

Limitations of this study were its single-center retrospective and a small number of patients.

CONCLUSION

Fractionated stereotactic radiation therapy is a safe and effective salvage treatment for recurrent LGG. FSRT in adult recurrent LGGs showed encouraging short term results in this retrospective analysis of limited number of cases. Prospective studies are necessitated as further evaluation.

Competing interests: The authors declare that they have no competing interest.

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