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ORIGINAL ARTICLE

Factors predicting recurrence in patients with grade III glial tumors: Impact of adjuvant temozolomide on recurrence

Ozge Gumusay[1], Bulent Cetin[2], Ahmet Ozet[1], Umut Demirci[3], Suleyman Buyukberber[1], Ugur Coskun[1], Efnan Algin[1], Aytug Uner[1], Ramazan Yildiz[1], Gokhan Kurt[4], Mustafa Benekli[1]

[1]Department of Internal Medicine, Division of Medical Oncology, Gazi University Faculty of Medicine, Ankara; [2]Department of Internal Medicine, Division of Medical Oncology, Van Education and Research Hospital, Van; [3]Department of Internal Medicine, Division of Medical Oncology, Dr. Abdurrahman Yurtaslan Training and Research Hospital, Ankara; [4]Department of Neurosurgery, Gazi University Faculty of Medicine, Ankara, Turkey

Summary

Purpose: *The purpose of this study was to evaluate the clinicopathological features of patients with grade III glial tumors associated with recurrence after treatment.*

Methods: *A retrospective analysis was carried out on 67 patients with grade III glial tumors between May 2007 and June 2013. Data were retrieved from patient electronic medical records and paper charts.*

Results: *The patient median age was 43 years (range 19-70). Of these, 50.7% (N=34) had anaplastic astrocytoma, 29.9% (N=20) anaplastic oligoastrocytoma and 19.4% (N=13) anaplastic oligodendroglioma. Among these 67 patients, 41 (61.2%) developed local recurrence. Fifty seven of them (80.6%) received radiotherapy (RT) with concomitant temozolomide. Of these patients, 14 (20.9%) received RT with concomitant temozolomide alone, and 43 (64.2%) were treated with concomitant chemoradiotherapy followed by adjuvant temozolomide. Time to recurrence (TTR) of patients who received adjuvant temozolomide after concomitant chemoradiation (TTR=14 months, 95% CI 9.3-22.7) as initial treatment for grade III glial tumors was not superior to RT with concomitant temozolomide alone (TTR=21 months, 95% CI 14.8-35.2; p=0.224) In multivariate analysis, histologic subtype (p=0.015), age (p=0.019) and presence of neurologic symptoms (p=0.021) were independent predictive factors of recurrence.*

Conclusion: *This analysis demonstrated that histologic subtype, age and presence of neurologic symptoms were significantly associated with recurrence in patients with grade III glial tumors. Adjuvant temozolomide was not significantly associated with recurrence in patients with grade III glial tumors. The identification of these predictors may be important for the patient follow-up and better treatment modifications*

Key words: *grade III glial tumors, predictive factors, recurrence, temozolomide*

Introduction

Grade III glial tumors and glioblastoma multiforme (GBM, grade IV astrocytoma), account for 7-10% and 54% of primary malignant brain tumors, respectively [1,2].

Treatment of GBM consists of maximal safe surgical resection, RT, and concomitant and adjuvant temozolomide [3]. However, in grade III glial tumors the effect of adjuvant temozolomide is unknown [4].

Chromosome 9p loss occurs in approximately 50% of anaplastic astrocytomas. Chromosome 13q loss occurs in one third to one half of high grade astrocytomas. Detection of CDKNA2 hoozygous deletion, CDK4 amplification of Rb deletion that influence Rb protein function is associated with poor prognosis of patients with anaplastic astrocytomas. Several studies suggested that hypermethylation of the O-6 methylguanine DNA-methyltransferase (MGMT) promoter and mutations of the isocitrate dehydrogenase1 (IDH1) gene and oligodendroglioma histology were associated with prolonged progression free survival [5,6].

Correspondence to: Ozge Gumusay, MD. Division of Medical Oncology, Department of Internal Medicine, Gazi University Faculty of Medicine, Besevler, Ankara 06500, Turkey. Tel: +90 312 2024238, Fax: +90 312 2025 825, E-mail: ozgebostankolu@gmail.com
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Grade III glial tumors include anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Treatment of grade III glial tumors is controversial. Patients with grade III glial tumors typically survive 2-3 years. Several prospective and retrospective studies have focused on prognostic factors associated with survival. Age, Karnofsky performance status (KPS), extent of surgery, total radiation dose, Ki-67 labeling index, the presence of convulsion, and sensitivity to chemotherapy determined by genetic tests have been reported as predictors of survival [7-10]. However, few studies have been reported to identify predictors of recurrence in patients with grade III glial tumors.

The aim of this study was to evaluate the clinicopathological features of patients associated with recurrence after treatment of grade III glial tumors.

Methods

Patient population

The data of 72 consecutive patients with grade III glial tumors who were treated between May 2007 and June 2013 were retrieved from patient electronic medical records and paper charts. Sixty seven patients were analyzed after elimination of patients who had dropped out of follow up, and who had incomplete data for analysis. Data were collected retrospectively from patient electronic medical records, paper charts and by contacting patients as needed. For each patient, age, sex, stage, KPS, histologic subtype, extent of surgery, treatment modalities, radiation dosage, presence of headache, seizure and neurological symptoms at the time of diagnosis were recorded.

Statistics

Descriptive statistics were expressed with median values with range for baseline demographic and clinicopathologic characteristics. TTR was defined as the time from initial diagnosis to the evidence of disease recurrence on MRI scans. Survival was assessed with Kaplan-Meier method. Overall survival (OS) was defined as the time interval from date of histological diagnosis until death due to any reason. Log rank test was used to identify the features of patients with grade III glial tumors that were possibly predictive of recurrence. Employed was also the Cox proportional hazards model for uni- and multivariate analysis. Adjusted hazard ratio (HR), 95% confidence intervals (CI), and corresponding p values were evaluated. The variables that reached statistical significance ($p<0.05$) in this model were then deemed to be independent predictors of recurrence. All statistics were calculated using SPSS version 21 (SPSS Inc., Chicago, IL).

Results

Characteristics of patients

Patient demographics and baseline clinical characteristics are summarized in Table 1. Sixty seven patients were analyzed in this study. Their median age was 43 years (range 19-70) and most patients were male (61.2%). Of these, 50.7% (N=34) had anaplastic astrocytoma, 29.9% (N=20) anaplastic oligoastrocytoma, and 19.4% (N=13) anaplastic oligodendroglioma. Fifty eight patients (86.5%) had KPS ≥70 and 9 (13.5%) between 50 and 70. The extent of surgery included gross total resection in 48 patients (71.6%), and subtotal resection in 19 (28.4%). Of these patients, 41 (61.2%) developed recurrence. The median follow up time was 24 months (range 2-86). The median TTR was 21 months (range 14.7-27.2), and the median OS was 41 months (range 17.5-64.5). The median OS according to histologic subtypes was 28.1, 36.2 and 66 months for anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma, respectively. Patients received 2 Gy/d in 30 fractions (total dose 60Gy), with concomitant temozolomide (75 mg/m^2/d for 42 days); those treated with concomitant chemoradiotherapy plus adjuvant temozolomide received temozolomide 150-200 mg/m^2 once daily for days 1-5 of a 28-day cycle.

The role of adjuvant temozolomide for the treatment of grade III glial tumors

As shown in Table 1, 54 of the patients (80.6%) received RT with concomitant temozolomide. Of these patients, 14 (20.9%) received RT with concomitant temozolomide alone and 43 (64.2%) were treated with concomitant chemoradiotherapy followed by adjuvant temozolomide. The median number of temozolomide cycles administered was 4 (range 0-8). Among the patients who received adjuvant temozolomide 30 received 6 courses and 13 did not complete 6 courses. TTR of patients who received concomitant chemoradiotherapy plus adjuvant temozolomide (TTR=14 months, 95% CI 9.3-22.7) as initial treatment of grade III glial tumors was not superior to RT with concomitant temozolomide alone (TTR=21 months, 95% CI 14.8-35.2; p=0.224).

Factors predictive of recurrence

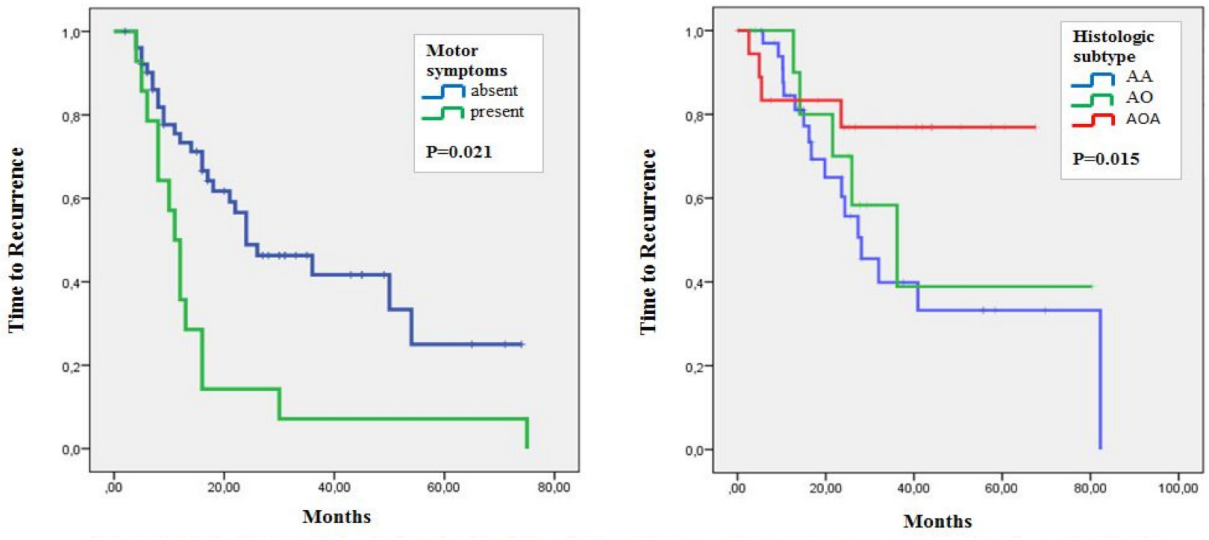

Figure 1. Kaplan-Meier analysis showing that histologic subtype and presence of motor symptoms were significantly associated with recurrence in patients with grade III glial tumors. AA: anaplastic astrocytoma, AO: anaplastic oligodendroglioma, AOA: anaplastic oligoastrocytoma.

In univariate analysis, KPS (p=0.003), older age (p=0.001), male gender (p=0.013), histologic subtypes without grade III anaplastic oligoastrocytoma (p=0.011), and presence of neurologic symptoms (p=0.003) had a significant influence on TTR. Adjuvant temozolomide therapy, extent of surgery, presence of headache and seizures at the time of diagnosis were not significantly associated with recurrence in patients with grade III glial tumors (Table 2). In multivariate analysis histologic subtype (p=0.015), age (p=0.019), and presence of neurologic symptoms (p=0.021) remained significant predictors of recurrence (Table 3; Figure 1).

Table 1. Patient, disease and treatment characteristics

Variables	*N=67*
	N (%)
Age, years	
Median (range)	43 (19-70)
Sex	
Male	41 (61.2)
Female	26 (38.8)
Histologic subtype	
Anaplastic astrocytoma	34 (50.7)
Anaplastic oligoastrocytoma	20 (29.9)
Anaplastic oligodendroglioma	13 (19.4)
Extent of surgery	
Gross total resection	48 (71.6)
Subtotal resection	19 (28.4)
Treatment	
CRT+adjuvant temozolomide	43 (64.2)
CRT only	14 (20.9)
RT alone	8 (11.9)
Surgery alone	2 (2.9)
Median survival	
Months (95% CI)	41 (17.5-64.5)
Time to recurrence	
Months (95% CI)	21 (14.7-27.2)

RT: radiotherapy, 95% CI: 95% confidence interval, CRT: radiotherapy with concomitant temozolomide

Discussion

WHO grade is an important prognostic and predictive factor in high grade glial tumors. Other factors to predict response to therapy and outcome reported in previous studies were age of the patient, neurological status, tumor location, radiologically contrast enhancement, extent of surgical resection, proliferation indices, and genetic alterations [7,10-13].

Several studies about predictors of survival in patients with grade III glial tumors have been reported. Age, KPS, extent of surgical resection, use of adjuvant RT, KI-67 immunohistochemical staining, genetic mutations were associated with survival [3,6,7,12]. Little is known, however, about factors associated with recurrence in grade III glial tumors. We have shown that histologic subtype, age and presence of neurologic symptoms were associated with recurrence after treatment of grade III glial tumors. The risk of recurrence was lower in young patients, in patients without neurologic symptoms at the time of diagnosis, and in patients with diagnosis of grade III glial tumors. This study reported a median time TTR of

Table 2. Univariate analysis of clinicopathologic variables associated with time to local recurrence

Variable	*N=67* *N (%)*	*Time to recurrence* *(months, median)*	*Log rank, p*
Age, years			
≤45	41 (61.2)	24	0.001
>45	26 (38.8)	16	
Sex			
Male	41 (61.2)	16	0.013
Female	26 (38.8)	36	
KPS			
>70	64 (95.5)	22	0.003
≤70	3 (4.5)	6	
Histologic subtype			
Anaplastic astrocytoma	34 (50.7)	16	0.011
Anaplastic oligoastrocytoma	20 (29.9)	not reached	
Anaplastic oligodendroglioma	13 (19.4)	16	
Neurologic symptoms			
Present	14 (20.9)	11	0.003
Absent	53 (79.1)	24	
Extent of surgery			
Gross total resection	48 (71.6)	22	0.696
Subtotal resection	19 (28.4)	16	
Adjuvant temozolomide			
CRT+Adjuvant temozolomide	43 (64.2)	14	0.224
CRT	14 (20.9)	21	

KPS: Karnofsky Performance Status, CRT: radiotherapy with concomitant temozolomide

Table 3. Multivariate analysis of clinicopathologic variables of grade III glial tumors associated with recurrence

Factors	*HR*	*95% CI*	*Log rank, p*
Age	1.036	1.006-1.067	0.019
Histologic subtype	0.0325	0.0131-0.807	0.015
Grade III anaplastic oligoastroctoma vs others			
Motor symptoms	2.286	1.134-4.608	0.021
Present vs absent			

HR: hazard ratio, 95% CI: 95% confidence interval

21 months (range 14.7-27.2), and a median OS of 41 months (range 17.5-64.5).

Tortosa et al. reported a study in patients with anaplastic gliomas to investigate clinical, neuroradiologic, pathologic and molecular parameters with prognostic significance for survival. Ninety-five patients with a histologic diagnosis of anaplastic astrocytoma (73%), anaplastic oligoastrocytoma (16.6%) or anaplastic oligodendroglioma (10.4%) were analyzed. Median OS was 29 months. Age of 49 years or younger (p<0.03), postoperative KPS score of 80 or higher (p<0.007), absence of ring enhancement (p=0.03), and a proliferation index of 5.1% or lower (p=0.044) were independently associated with longer survival [7].

Retrospective analyses have revealed that gross total resection has important role in prolonging survival in patients with grade III glial tumors [15-18]. RT is used routinely with or without chemotherapy. The benefit of chemotherapy remains controversial. Most phase 3 trials have

demonstrated that chemotherapy had no benefit compared with radiation alone. Single agent carmustine and PCV were used with minimal improvement in survival [19]. A large randomized trial by the Medical Research Council reported no difference between adjuvant PCV and RT alone [20]. Temozolomide and nitrosurea-based regimens are effective for the treatment of recurrent anaplastic astrocytomas [21]. A phase 3 trial (RTOG-9813) was launched to compare RT with BCNU and RT with temozolomide in recurrent anaplastic astrocytoma and the results are awaited.

The clinical features of anaplastic oligodendroglioma are different from other grade III glial tumors with a relatively favorable prognosis. In our study co-deletions of 1p/19q were not examined and all patients received similar treatments. Most patients received adjuvant temozolomide (64.2%). TTR of patients who received adjuvant temozolomide (TTR=14 months, 95% CI 9.3-22.7) as initial treatment of grade III glial tumor was not superior to RT with concomitant chemoradiotherapy with temozolomide (TTR=21 months, 95% CI 14.8-35.2; p=0.224). OS was not different between patients who received adjuvant temozolomide and patients who didn't (p=0.180).

Anaplastic oligodendroglioma and oligoastrocytoma showed better prognosis than anaplastic astrocytomas. Anaplastic oligoastrocytoma is a heterogeneous group with differences in survival [22]. Nuno et al. reported a study including 1766 patients with anaplastic astrocytoma, and 570 patients with anaplastic oligodendroglioma diagnosed between 1990 and 2008. The median OS of anaplastic oligodendroglioma patients (42 months) was significantly longer than that for anaplastic astrocytoma patients (15 months) [14]. Park et al. reported that the median survival of anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma were 29, 37 and 79 months, respectively [23].

Our study, showing worst prognosis in patients with anaplastic astrocytoma, is consistent with other studies. The median OS was 28.1, 36.2 and 66 months for anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma, respectively. However, there were some inconsistencies with other studies. First, OS of anaplastic oligoastrocytoma was longer than OS of anaplastic oligodendroglioma. A possible explanation for this result is that 1p/19q deletion status was not evaluated. The combined 1p/19q loss predicts response to chemotherapy and a favorable prognosis in anaplastic oligodendroglioma [12,24,25]. Second, all of the patients were treated similarly, and none of them received PCV (procarbazine, lomustine, vincristine).

The first limitation of this study is that genetic abnormalities and molecular parameters were not evaluated. Other limitations include its retrospective nature and low patient number.

Conclusion

Our retrospective analysis demonstrated that histologic subtype, older age and presence of neurologic symptoms were associated with recurrence in patients with grade III glial tumors. Identification of these predictors may be important for the follow-up and the treatment management. TTR of patients who received adjuvant temozolomide after concomitant chemoradiotherapy as initial treatment of grade III glial tumor was not superior to RT with concomitant temozolomide alone in our study. Further prospective studies with larger sample size are needed to evaluate the impact of adjuvant temozolomide on the recurrence of patients with grade III glial tumors.

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