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Clinical outcome of patients with glioblastoma multiforme: Single center experience

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and fatal brain tumor in adults. Prognosis remains dismal and median overall survival rarely exceeds 12 months. In this study, we evaluated the demographic and clinical features of Turkish glioblastoma patients from single institute to identify the important prognostic factors which might be related with patient outcomes in this population, retrospectively. Demographic data, clinicopathological data and treatment parameters (i.e. extent of surgical resection, radiotherapy and use of chemotherapy) were obtained from medical records. SPSS version 22 was used for all statistical analyses. The median progression-free survival and overall survival was 9,9 and 13,7 months; respectively. The group of patients with the highest mean overall survival had a tumor at the fronto-temporal region, followed by frontal localization. In univariate analysis, age, concurrent chemoradiotherapy and adjuvant temozolomide use were all predictors for both PFS and OS. However, in multivariate analysis, age and concurrent radiotherapy were significant predictors of survival. Patients receiving cyberknife after recurrence had longer OS. We retrospectively evaluated glioblastoma patients from single institute, the results supported previously reported factors that influence survival time in glioblastoma.

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1. Introduction

Glioblastoma multiforme (GBM) is the most common malignant brain tumor in adults. Prognosis is dismal and the median overall survival is around 12 months despite advances in treatment modalities.[1] The standard therapy is a combined modality approach which consists of maximal safe surgical resection of primary tumor, and subsequently radiotherapy with concomitant and adjuvant temozolomide.[2–4] Advances in surgery and radiotherapy techniques and the addition of chemotherapy to treatment resulted in better local control, and also prolongation of survival in recent years. However; the disease almost always recur and long-term survival rarely occurs. Treatment options are limited after disease recurrence. New approaches include antiangiogenic therapy, immunotherapy, targeted molecular therapy, gene therapy, and radiation-enhancement therapies and under investigation in various clinical trials.[5]

Clinical factors such as age at presentation, tumor location, Karnofsky performance status, the extent of surgery and histopathological factors are important prognostic factors for GBM.[6] In this study, we retrospectively analysed the clinical and demographic features of Turkish glioblastoma patients from single institute to identify the important prognostic factors which might be related with patient outcomes in this population.

2. Methods

This retrospective, single-center study was achieved in the radiation oncology and medical oncology departments at Samsun Training Hospital. Patients who were diagnosed between January 2012 to December 2016 were enrolled the study. Local Ethics Committee approved the study.

Demographic data, clinicopathological data and treatment parameters (i.e. extent of surgical resection, radiotherapy and use of chemotherapy) were obtained from medical records. Data on patient death was obtained from the National Registry of Death System, Turkey.

2.1. Statistical analysis

Progression-free survival (PFS) was determined as the duration between initial surgery and progressive disease or death. Overall

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survival (OS) was described as the time from the diagnosis date to death, or to the last follow-up for surviving patients. Statistical evaluations was performed using Statistical Package for Social Sciences for Windows version 23 [SPSS Inc; Chicago, IL, USA] software package. Kaplan-Meier curves were used to calculate the overall survival OS and PFS. Log-rank test was used for univariate analyses. Multivariate linear regression analyse was made to evaluate independent variables for overall survival. A p value less than 0.05 was considered statistically significant.

3. Results

A total of 99 patients diagnosed with GBM are included in the present study: 50 (50.5%) males and 49 (49.5%) females. Median age of patients were 57 and median tumor diameter was 40 mm. Tumor and treatment characteristics are described in Table 1.

Most of the patients had received concurrent chemoradiotherapy after operation. The majority of patients (n = 70/99) received subsequent temozolomide, and 70% of patients completed their chemotherapy regimen (see Table 2).

Patients received first, second and third line treatment after recurrence, 45,5%, 18,2%, 8,1%; respectively. Cyberknife stereotactic radiotherapy was the most preferred first-line treatment regimen after disease progression. Patients mostly received irinotecan and bevacizumab chemotherapy in second line setting. Only a few patients could able to take a third line treatment as a result of patient's overall clinical worse condition.

The median follow up time was 12 months (3–55 months). The median progression free survival (PFS) was 9,9 months (Fig. 1). PFS was not statistically different according to gender, localization and operation type. Concurrent chemoradiotherapy resulted with a longer PFS compared with radiotherapy alone. Patients who received adjuvant temozolamide had longer PFS than patients who did not take temozolamide (11,9 vs 8,3 months).

Overall survival was 13,7 in the whole study population; 12,3 months in women and 15,1 months in men (p; 0.4)(Fig. 2). Patients with secondary tumors (progression from low-grade diffuse astrocytoma or anaplastic astrocytoma) lived longer than primary glioblastomas but the difference was not statistically significant

Table 1
Tumor and treatment characteristics.

Tumor site	Temporal	28 (28.3%)
	Parietal	16 (16.2%)
	Frontal	15 (15.2%)
	Frontoparietal	12 (12.1%)
	Parietooccipital	10 (10.1%)
	Frontotemporal	7 (7.1%)
	Occipital	4 (4%)
	Other	7 (7%)
Primary/secondary	Primary	92 (92.9%)
	Secondary	5 (5.1%)
	Unknown	2 (2%)
Hemisphere	Right	41 (41.4%)
	Left	53 (53.5%)
	Midline	4 (4.1%)
	Unknown	1 (1%)
Operation type	Total	53 (53.5%)
	Subtotal	35 (35.4%)
	Biopsy	7 (7.1%)
	Unknown	4 (4%)
Adjuvant treatment	Chemoradiotherapy	88 (88.9%)
	Radiotherapy	5 (5.1%)
	No treatment	4 (4%)
	Unknown	2 (2%)
Temozolamide	Yes	70 (70.7%)
	No	14 (14.1%)
	Unknown	15 (15.2%)

Table 2
Treatments in recurrence.

First line		45
	Cyberknife	22 (48,9%)
	Operation	16 (35,6%)
	Irinotecan + bevacizumab	5 (11,1%)
	Temozolomide	2 (4,4%)
Second line		18
	Irinotecan+bevacizumab	10 (55.6%)
	Cyberknife	4 (22.2%)
	Temozolomide	3 (16.7%)
	Chemoradiotherapy	1 (5.6%)
Third line		8
	Cyberknife	4 (50%)
	Irinotecan + bevacizumab	2 (25%)
	Temozolomide	2 (25%)

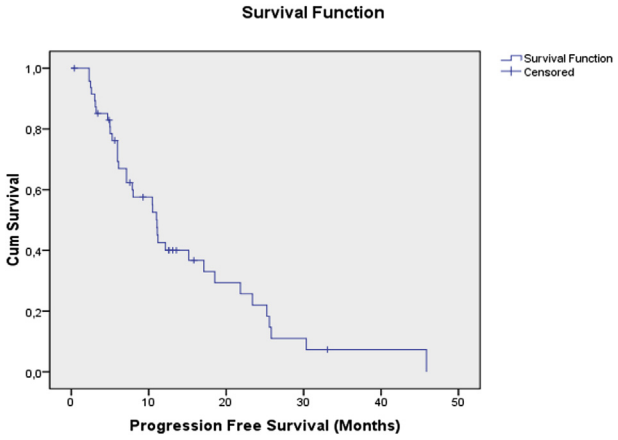

Fig. 1. Progression free survival for study population.

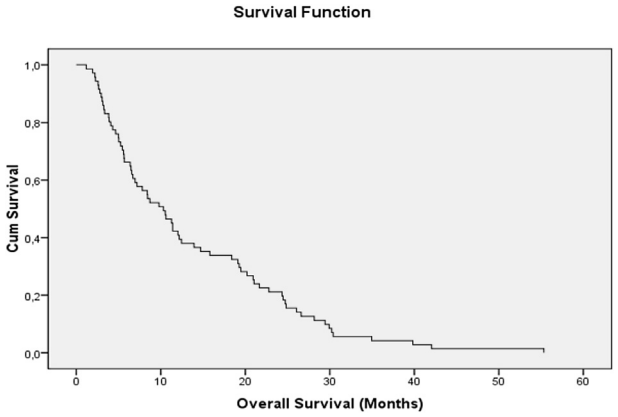

Fig. 2. Overall survival for study population.

(13,3 vs 23,9 months; p:0,25).

Overall survival was different according to tumor localization. The group of patients with the highest mean overall survival had a tumor at frontotemporal region (20,3 months), followed by frontal localization (17,4 months). Left sided and right sided tumors had similar overall survival (p; 0,19). Univariate and multivariate analysis showed that patients receiving cyberknife after recurrence had longer OS.

In univariate analysis, age, concurrent chemoradiotherapy and adjuvant temozolomide use were all predictors for both PFS and OS. However, in multivariate analysis, age and concurrent radiotherapy were significant predictive factors for survival (Table 3 and Table 4).

Table 3
Univariate and multivariate analysis for progression-free survival.

Characteristic		Univariate			Multivariate		
		OR	CI	P-value	OR	CI	P-value
Age	<65 >65	2.2	1.3–3.6	0.002	2.1	1.2–3.6	0.006
Gender	Women Men	1.3	0.8–2.1	0.313	0.9	0.5–1.5	0.613
Surgery	Biopsy Subtotal Total	1.1	0.8–1.4	0.642	1.1	0.8–1.4	0.741
Radiotherapy	Concurrent Alone	4.5	1.5–13.2	0.006	4.1	1.2–14.0	0.023
Temozolomide	Yes No	1.9	1.4–2.6	0.0001	1.8	1.3–2.6	0.001
Side	Right Left	1.1	0.7–1.8	0.638	0.9	0.5–1.5	0.756

Table 4
Univariate and multivariate analysis for overall survival.

Characteristic		Univariate			Multivariate		
		OR	Cl	P value	OR	Cl	P value
Age	<65 >65	1.8	1.0–2.8	0.044	1.5	0.9–2.6	0.112
Gender	Women Men	1.2	0.7–2.0	0.489	1.0	0.6–1.6	0.866
Surgery	Biopsy Subtotal Total	1.1	0.7–1.3	0.656	1.0	0.8–1.4	0.842
Radiotherapy	Concurrent Alone	10.7	3.4–33.1	0.0001	29.8	6.5–137.2	0.0001
Temozolomide	Yes No	1.2	0.9–1.6	0.208	1.2	0.9–1.6	0.342
Side	Right Left	1.2	0.7–1.9	0.556	0.9	0.6–1.5	0.740
Cyberknife	Yes No	2.5	1.5–4.3	0.001	2.4	1.4–4.2	0.003
İrino+bev	Yes No	0.5	0.3–1.0	0.052	0.6	0.3–1.2	0.130

4. Discussion

In this study, we evaluated clinical features of glioblastoma patients from a single center institution. Tumor localization, age, concurrent radiotherapy, adjuvant use of temozolomide and cyberknife for recurrence therapy, were the clinicopathologic factors which were associated with clinical outcome.

In our study population, median PFS and median OS was 9,9 months and 13,7 months respectively. The results are consistent with previous reports. Patients who received combined modality treatment had better PFS, consistent with recent studies showing that addition of concomitant chemotherapy resulted with better outcomes.[7] Stupp et al. reported 14.6 months OS in glioblastoma patients with median age of 56 years treated with radiotherapy plus concomitant and adjuvant temozolomide.[2] In this study, the median ages was 57 years and OS was 16.9 months compatible with Stupp's study.

In the study population, frontotemporal and frontal located tumors had highest overall survival. In three consecutive clinical trials of Radiation Therapy Oncology Group (RTOG) evaluating the influence of location on clinical outcome, showed that patients with frontal lobe tumors had longer survival than those with parietal or temporal lobe tumors (11.4 months, 9.1 months, and 9.6 months, respectively) consistent with our results.[8]

Salvage re-irradiation has long been proposed as a treatment modality for recurrent tumors. Although there is not a consensus for favorable effect of cyberknife for recurrent glioblastoma treatment, retrospective data suggest that there is an improvement in tumor control.[9] Recent studies have evaluated radiosurgery and fractionated stereotactic radiosurgery as a treatment option for recurrent glioblastoma patients. Retrospective single institution trials have shown stereotactic radiosurgery was well tolerated, and efficacy results appeared to be promising. Retrospective studies showed one-year OS rates ranging from 15 to 45% for recurrent GBM treated with SRS/fSRT. Larson et al. and Greenspoon et al. showed median OS s of 9.5 and 9 months in two prospective studies, respectively.[10,11] Our patients received their primary treatment in radiation oncology clinic and mostly they were on follow up by both medical and radiation oncologists. Patients mostly admitted to radiation oncology at first recurrence and radiation oncologists mostly preferred to give cyberknife treatment on first recurrence. Patients generally admitted to medical oncology department after primary recurrence treatment. As a result; they mostly received cyberknife treatment in first recurrence and chemotherapy in second recurrence. In our study, patients who received cyberknife for recurrent tumor, had longer overall survival compared with those who did not take this treatment.

There are certain limitations of this study. Some data was missing as a result of the retrospective nature of the study, Although we tried to check possible confounders by multivariate analyses, a randomized controlled trial would control the factors

which may influence the outcome. Treatment modalities after recurrence were heterogeneous as a result of personal choices and experience. Furthermore the common response criteria were uncertain, and evaluation of pseudoprogression was not systematic.

Although this is a retrospective study of patients in a single institute, the results supported previously reported factors that influence survival time in glioblastoma. We would support prospective studies evaluating the role of cyberknife in the management of glioblastoma.

References

1. Behin A, Hoang-Xuan K, Carpentier AF, Delattre JY. Primary brain tumours in adults. *Lancet*. 2003;361:323–331.
2. Stupp R, Mason WP, van den Bent MJ, et al, European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987.
3. Athanassiou H, Synodinou M, Maragoudakis E, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol*. 2005;23(10):2372.
4. Kole AJ, Park HS, Yeboa DN, et al. Concurrent chemoradiotherapy versus radiotherapy alone for "biopsy-only" glioblastoma multiforme. *Cancer*. 2016 Aug;122(15):2364–2370.
5. Kanu OO, Mehta A, Di C, et al. Glioblastoma multiforme: a review of therapeutic targets. *Expert Opin Ther Targets*. 2009;13:701–718.
6. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol*. 2004;6(3):227.
7. Gutenberg A, Bock HC, Reifenberger G, Brück W, Giese A. Toxicity and survival in primary glioblastoma patients treated with concomitant plus adjuvant temozolomide versus adjuvant temozolomide:Results of a single-institution, retrospective, matched-pair analysis. *Acta Neurochir (Wien)*. 2013;155:429–435.
8. Simpson JR et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive radiation therapy oncology group (RTOG) clinical trials. International Journal of Radiation Oncology Biology Physics. Volume 26, Issue 2, 239–244.
9. Hasan S, Chen E, Lanciano R, et al. Salvage fractionated stereotactic radiotherapy with or without chemotherapy and immunotherapy for recurrent glioblastoma multiforme: a single institution experience. *Front Oncol*. 2015;5:106.
10. Greenspoon JN, Sharieff W, Hirte H, et al. Fractionated stereotactic radiosurgery with concurrent temozolomide chemotherapy for locally recurrent glioblastoma multiforme: a prospective cohort study. *OncoTargets Ther*. 2014;7:485–490.
11. Larson DA, Flickinger JC, Loeffler JS. Radiobiology of radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993;25:557–561.