Case Report
Middle East Journal of Cancer 2012; 3 (2 & 3): 79-83

Long-term Survival of Six Patients with Glioblastoma Multiforme: Case Series and Review of the Literature

Shapour Omidvari*, Hamid Nasrolahi*, Amir Abbas Kani, Niloofar Ahmadloo*, Ahmad Mosalaei***, Mohammad Mohammadianpanah*♦, Mansour Ansari***

*Shiraz University of Medical Sciences, Shiraz, Iran
**Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
***Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

The median overall survival in glioblastoma multiforme is usually less than one year. Long-term survival is rare and is seen in only 3%-6% of GBM patients. The present study reports the characteristics and treatment outcomes of six cases of glioblastoma multiforme with long-term survival. A literature review is also presented.

Between 1990 and 2008, 217 glioblastoma multiforme patients have been treated at our center of which six cases (four males) survived for three years or longer. The mean age of the six cases was 25.7 years. All patients received postoperative radiotherapy with a mean dose of 55 gray and four patients received nitrosourea-based chemotherapy. Patients' mean survival was 5.2 years. The results of this study and review of the literature have indicated that long-term (more than three years) survival is exceptional and mainly observed in younger patients with good performance status and following complete surgical tumor resection.

Keywords: Glioblastoma multiforme, Long-term survival, Young age, Complete resection, Radiotherapy, Chemotherapy

♦Corresponding Author:
Mohammad Mohammadianpanah, MD
Colorectal Reseach Center, Department of Radiation Oncology,
Namazi Hospital, Shiraz, Iran,
Postcode: 71936-13311
Tel/Fax: +98-711-6474320
Email: mohpanah@sums.ac.ir; mohpanah@gmail.com

Introduction

Glioblastoma multiforme (GBM) is a disease of the older population with a dismal prognosis. Median survival is about 12 months and the minority (less than 6%) of these patients have a prolonged (more than three years) survival.[1-6] Some prognostic factors such as age, performance status and extent of tumor resection have been proposed as predictors of survival, however it is not yet clear which patients achieve prolonged survival.[4] Herein, we describe long-term survival (LTS) in six patients with GBM and a review of the literature.

Case Report

This retrospective study was

Received: January 23, 2012; Accepted: March 1, 2012

Table 1. Characteristics, treatment and outcome of six patients with glioblastoma multiforme (GBM).

Patients	Sex	Age (yrs)	PS	Location	Side	Max tumor size (cm)	Surgery	RT	RT dose (Gy)	ChT	Last clinical status	Follow-up length (months)
1	M	15	0	Temporoparietal	Right	8	CR	WBRT	54	Not received	Lost FU	84
2	M	35	0	Temporoparietal	Left	9	NB	WBRT	54	Not received	Lost FU	37
3	M	16	0	Occipital	Left	6	IC	IFRT	54	Received	Alive	82
4	F	32	0	Temporoparietal	Right	5	CR	IFRT	60	Received	Alive	69
5	F	22	0	Parietal	Left	6	IC	IFRT	54	Received	Alive	66
6	M	34	1	Frontal	Right	9	IC	IFRT	54	Received	Lost FU	37
Mean		**25.7**				**7.2**			**55**			**62.5**

ChT = Chemotherapy; RT = Radiotherapy, PS = Performance status, Gy = Gray; Max = Maximum, M = Male, F = Female; WBRT = Whole brain radiotherapy; IFRT = Involved field radiotherapy; CR = Complete resection; NB = Needle biopsy; IC = Incomplete resection; FU = Follow-up.

performed in a tertiary academic hospital. Between 1990 and 2008, 217 patients with GBM were treated at our center. Patients' follow up ranged from one to 69 months (median 11 months). The median progression-free survival was six months. Median overall survival was 11 months. However, among this study population only six cases (2.8%) survived for three years or longer (Table 1). Three cases had regular follow up and were alive for more than five years with no evidence of disease recurrence. The remaining cases were lost to follow up 37, 37 and 84 months after initial diagnosis, but were disease-free at their last visit.

Of these six cases, four patients were male. All six patients were young with a median age of 27 (range: 15-35) years. The most frequent location of the tumors (in three patients) was the temporoparietal lobe. Frontal, parietal and occipital lobes were the locations of the tumors in the remainder of patients in the three remaining patiens. There were three lesions located on the right side and the remaining three were on the left side.

The mean maximum tumor diameter, according to pre-operative imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) was 7.2 cm (5-9 cm). All patients had pathologic diagnoses, but different operation techniques were used. One case underwent a stereotactic needle biopsy. Two cases had complete surgical resection. The other three cases underwent incomplete (subtotal) tumor resection. After surgery, all patients received radiotherapy (RT). Radiotherapy was performed by conventional techniques, with a Cobalt-60 or linear accelerator. The mean radiation dose was 55 (range: 54-60) gray (Gy). In two cases, irradiation began with whole brain RT and after 40 Gy the portals were reduced to the involved field which covered the preoperative contrast-enhancing volume that was associated with peritumoral edema and with a 3 cm margin.

After RT, chemotherapy was administered in four cases. No patients received temozolomide; however, all received six cycles of nitrosourea-based treatment. Two patients did not receive any adjuvant chemotherapy.

One patient who was a 22-year-old woman at the time of presentation had no evidence of GBM recurrence 66 months after treatment. However she developed simultaneous endometrial and rectal cancer, 61 and 62 months after the diagnosis of her brain tumor. Her endometrial cancer was an endometriod, stage IIIA tumor, whereas her rectal cancer was an adenocarcinoma stage T3N0M0. She is currently being treated for her second and third primary tumors.

Discussion

Glioblastoma multiforme is one of the most aggressive cancers in adults.[1] Glioblastoma multiforme is a disease of older adults with a male/female ratio of 1.3-1.45:1. On occasion, an astrocytoma of either a low or high grade following treatment can change into GBM. Secondary GBM occurs at a younger age.[1] In addition, GBM is sporadic with a minority of cases associated with Turcot or Li-Fraumeni syndromes. These two genetic disorders and ionizing radiation are known risk factors for GBM occurrence.[2]

Due to the poor prognosis for this disease, survival of more than three years (and in some studies five years) is considered prolonged

Table 2. Results of systematic electronic search for similar case series.

Database	Search strategy	Results
PubMed	(Long term [MeSH] AND survival [MeSH] AND glioblastoma [MeSH]); OR (Long term [MeSH] AND survivors [MeSH] AND glioblastoma [MeSH])	57
		20 Case reports
		29 Case series
		4 Original articles
		2 Commentaries
		2 Reviews
Scirus		74
		24 Case reports
		34 Case series
		12 Original articles
		4 Commentaries
Cochrane		1 Systematic review

survival. There have been reports from the early 20th century that 5% of GBM patients possibly survive for more than five years.[3,5,6] However, by careful review of pathology samples, this rate was less than previously reported.[3,7] In our cases, light microscopic pathology review confirmed the diagnosis of GBM.

Glioblastoma multiforme is a diffusely infiltrative tumor; therefore, for this neoplasm surgical curative treatment is rarely possible. The recommended treatment is optimal safe surgical resection followed by concurrent RT with chemotherapy and adjuvant chemotherapy with temozolomide. Adjuvant nitrosourea-based and temozolomide increase survival by a few months.[1,8]

Female gender, younger age, better performance status and more complete tumor removal are considered as prognostic factors for progression-free and overall survival.[4] The frontal lobe location is reported to carry a better chance for prolonged survival;[9] although, in our series, only one patient had a frontal lobe tumor. Mutations of tumor suppressor genes, particularly p53, and amplifications of oncogenes, especially the EGFR gene, play an important role in the pathogenesis and progression of GBM. These molecular genetic alterations are important targets for use in the early detection of these neoplasms. Consequently, molecular analysis and immunohistochemistry profiling would provide novel diagnostic and prognostic perceptions into the biology of GBM.[10] In our cases, there were no data regarding molecular markers as these markers are not routinely checked in our patients with GBM. Therefore, these potential genetic alterations may contribute to LTS of our cases despite the presence of large tumors, incomplete surgical resection and suboptimal adjuvant radiation doses.

Among genetic factors, O6-methylguanine methyltransferase (MGMT) promoter hypermethylation was found to be correlated with higher progression-free and overall survival.[2,4] Lower mitotic activity, combination of loss of heterozygosity (LOH) 1p and 19q have also been suggested as good prognostic factor in patients with GBM.[11] Genetic alterations in some genes such as P53, P16, and P27 have been noticed; however, no tumor marker is available for this neoplasm.[11]

In this study, we have performed a literature review of PubMed, Scirus, and Cochrane databases using the search terms "long term survival and glioblastoma" or "long term survivors and glioblastoma" to find all reports regarding the LTS in patients with GBM (Table 2). However, for selecting the eligible articles for discussing the present study, we have considered the following exclusion criteria: all case reports that included less than five cases, articles that were not written in English or with an unavailable full text, and all

Table 3. Major reports on long-term survival (LTS) of glioblastoma multiforme (GBM).

Author (referece number)	Patient numbers with LTS (total no. of GBM)	Mean age (years)	M/F	LTS definition	Age range (years)	Mean RT dose (Gy) (years)	Mean survival	Time period
Krex (2)	55 (-)	51	28/27	>3years	21-72	-	4.6	-
McLendon (3)	17 (766)	40.2	11/6	>5 years	12-70	62.6	-	1976-1996
Sonoda (4)	18 (123)	48	12/6	>3 years	22-64	-	4	1996-2004
Chandler (6)	22 (499)	39.2	10/12	>5 years	15-63	-	9.4	1969-1985
Scott (7)	12 (689)	43	-	>3 years	-	-	-	1975-1991
Ganigi (10)	12 (521)	-	-	>7 years	-	-	-	1954-1987
Deb (11)	6 (1296)	27	-	>5 years	8-45	-	9	1989-1999
Shinojima (13)	6 (113)	44.2	0/6	>5 years	31-60	-	-	1987-1998
Martinez (14)	9 (195)	47	-	>3 years	36-58	58	-	1993-2002
Das (15)	7 (-)	43.5	5/2	>3 years	35-56	60	3.9	-
Salvati (16)	11 (-)	39	5/6	>5years	24-55	55	9	1980-1989
Burton (17)	39 (-)	38	-	>3years	0.25-75	-	-	-
Present study	6 (217)	25.7	4/2	>3 years	15-35	55	5.2	1990-2008
Total	220	44	75/67	>3 years	8-70	58.68	6.08	-

LTS = Long-term survival; M = Male; F = Female; RT = Radiotherapy; Gy = Gray.

reports with the definition of less than three years for LTS. Therefore in all, we found 12 series that included 214 glioblastoma long-term survivors which constituted 2.5% of 4419 cases with GBM.

By analyzing the data of the reported series and our cases, the mean age of 208 patients was 40.5 (mean range: 25.7-51; age range: 3 months to 75 years) years and the male/female ratio of 142 patients was 1:1. The mean RT dose of 50 patients was 58 Gy. In addition, the mean survival of 125 patients was 6 years (Table 3).[3,4,6,7,11-17]

Compared to these reports, our cases had similar good performance status and compatible mean survival. However, the mean age of our cases was significantly lower (25.7 versus 42 years) than the average value of other reported series in the literature.[3,4,6,7,11-17]

Conclusion

Herein, we report the characteristics and treatment outcomes of six cases of GBM with LTS. Our cases were of a young age and had good performance status. Most cases had LTS despite the presence of large tumors, incomplete surgical resection and suboptimal adjuvant radiation doses. Further investigation using molecular analysis and immunohistochemical profiling is suggested for providing novel diagnostic and prognostic information regarding the biology of patients with GBM.

References

1. Filippini G, Falcone C, Boiardi A, Broggi G, Bruzzone MG, Caldiroli D, et al. Prognostic factors for survival in 676 consecutive patients with newly diagnosed primary glioblastoma. *NeuroOncol* 2008;10(1):79-87.
2. Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, et al. Long-term survival with glioblastoma multiforme. *Brain* 2007;130(Pt 10):2596-606.
3. McLendon RE, Halperin EC. Is the long-term survival of patients with intracranial glioblastoma multiforme overstated? *Cancer* 2003;98(8):1745-8.
4. Sonoda Y, Kumabe T, Watanabe M, Nakazato Y, Inoue T, Kanamori M, et al. Long-term survivors of glioblastoma: Clinical features and molecular analysis. *Acta Neurochir* (Wien) 2009;151(11):1349-58.
5. Scott JN, Rewcastle NB, Brasher PM, Fulton D, MacKinnon JA, Hamilton M, et al. Which glioblastoma multiforme patient will become a long-term survivor? A population-based study. *Ann Neurol* 1999;46(2):183-8.
6. Chandler KL, Prados MD, Malec M,Wilson CB. Long-term survival in patients with glioblastoma multiforme. *Neurosurgery* 1993;32(5):716-20.
7. Scott JN, Rewcastle NB, Brasher PM, Fulton D, Hagen NA, MacKinnon JA, et al. Long-term glioblastoma multiforme survivors: A population-based study. *Can J Neurol Sci* 1998;25(3):197-201.
8. Nieder C, Astner ST, Molls M, Grosu AL. Analysis of long-term survivors of glioblastoma multiforme in a single institution with aggressive local retreatment protocol. *Anticancer Res* 2007;27(4C):2993-6.
9. Phuphanich S, Ferrall S, Greenberg H. Long-term survival in malignant glioma. Prognostic factors. *J Fla Med Assoc* 1993;80(3):181-4.
10. Ganigi PM, Santosh V, Anandh B, Chandramouli BA, Sastry Kolluri VR. Expression of p53, EGFR, pRb and

bcl-2 proteins in pediatric glioblastoma multiforme: A study of 54 patients. *Pediatr Neurosurg* 2005;41:292-9.
11. Deb P, Sharma MC, Mahapatra AK,Agarwal D, Sarkar C. Glioblastoma multiforme with long term survival. *NeurolIndia* 2005;53(3):329-32.
12. Salford LG, Brun A, Nirfalk S. Ten-year survival among patients with supratentorial astrocytomas grade III and IV. *J Neurosurg* 1988;69(4):506-9.
13. Shinojima N, Kochi M, Hamada J, Nakamura H, Yano S, Makino K, et al. The influence of sex and the presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme. *J Neurosurg* 2004; 101(2):219-26.
14. Martinez R, Schackert G, Yaya-Tur R, Rojas-Marcos I, Herman JG, Esteller M. Frequent hypermethylation of the DNA repair gene MGMT in long-term survivors of glioblastoma multiforme. *J Neurooncol* 2007; 83(1):91-3.
15. Das P, Puri T, Jha P, Pathak P, Joshi N, Suri V, et al. A clinicopathological and molecular analysis of glioblastoma multiforme with long-term survival. *J Clin Neurosci* 2011;18(1):66-70.
16. Salvati M, Cervoni L, Artico M,Caruso R, Gagliardi FM. Long-term survival in patients with supratentorialglioblastoma. *J Neurooncol* 1998;36(1):61-4.
17. Burton EC, Lamborn KR, Feuerstein BG, Prados M, Scott J, Forsyth P, et al. Genetic aberrations defined by comparative genomic hybridization distinguish long-term from typical survivors of glioblastoma. *Cancer Res* 2002;62(21):6205-10.