Glioblastoma Multiforme: A Single Hospital Experience

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Abstract

Background & Aim: Glioblastoma multiforme (GBM), the highest grade glioma (grade IV), is the most malignant form of astrocytoma in adults. This study aimed at evaluating the relationship between demographic, clinical and medical factors with GBM outcome.

Methods & Materials/Patients: Through a cross-sectional design, 58 patients with newly diagnosed GBM were studied from 1999 to 2015 in Guilan province (North of Iran). Demographic, clinical and medical data including age, gender, score of Karnofsky Performance Scale (KPS), status at discharge, extent of resection (EOR) and administration of post-operative radio-chemotherapy were recorded in an individual questionnaire. The data were analyzed using chi-square and fisher exact tests.

Results: Of all patients, 35 (60.3%) cases were men and 23 (39.7%) were women. Age range (at the time of diagnosis of GBM) was 18-82 years (54.86±16.34). The most common side and location of tumor were left hemisphere and frontal lobe, respectively. 41 patients (70.7%) received total surgical resection. Half of patients were treated with simultaneous post-operative radiation therapy and chemotherapy.11 (19%) of all cases died. About 41 (70.6%) of patients demonstrated KPS 50-70.

Conclusion: GBM is a frequent malignant brain tumor with male predominance and high occurrence in age range of ≥50 years. The number of dead patients increases with decreased KPS. Total surgical resection followed by concomitant radiation therapy and chemotherapy were common standard therapeutic regimens.

Keywords: Glioblastoma Multiform; Extent of Resection; Radiotherapy; Chemotherapy

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Introduction

Tumors which arise from the glia are called "glioma". Astrocytoma is counted as a type of glioma, arising from the star shape astrocytes. Glioblastoma multiforme (GBM) is the most common malignant astrocytoma in adults that is classified as grade IV glioma. According to World Health Organization (WHO), GBM presents typical properties including high mitotic pleomorphic nuclei, necrotic foci, glomeruloid vascular structures and increased blood vessel in the margin of tumor zone. Grade IV tumor is rapidly growing along with other highly malignant tumors (1). GBM constitutes 30% of all primary brain tumors (2), 50% of all primary brain gliomas (3) and 60-75% of astrocytic tumors (4). About 51 million primary brain tumors are diagnosed in America each year, 36% of which are glioma; half of them being GBM, with approximately 3 in 100,000 individuals newly diagnosed each year (5). Also ten year's data of National Cancer Registry (NCR) in Iran has reported that primary malignant CNS tumors encompass 2.3% of all primary malignant tumors. Astrocytoma and glioblastoma together form 60.4% of the primary malignant registered brain tumors (6). The more the age, the more the incidence of GBM would be (7). Only 3 to 5 percent of patients survive for more than three years, and five years in very rare cases (8-9). Population-based data from the Central Brain Tumor Registry of the United States demonstrated a substantial, almost threefold decrease of one-year survival among patients above the age of 64 years compared with age groups 20–44 years and 45–64 years (10). Considering the exceptionally infiltrative nature of GBM and its proclivity to integrate into normal brain tissue, the treatment process would be hard (11). Preliminary standard therapy including surgical resection, combined radiation and chemotherapy and adjuvant chemotherapy can be considered for removing the remained glioma cells and increasing survival chance (12-13). Since patients with KPS≥70 indicated better prognosis than ones with

KPS<70, it should be noted that the level of functional outcome according to KPS plays an important role in determining the degree of prognosis which can guide the clinicians to decide for choosing the appropriate medical therapeutic regimens to remedy GBM sufferers (14-15). This study has two mainstays. First, accurate identifying the epidemiology and treatments which have a major role in outcome and survival. Second, a limited number of studies have been performed on GBM in Guilan province. Thus, this study sought to evaluate the relationship between demographic, clinical and medical factors with GBM outcome.

Methods and Materials/Patients

A cross-sectional design was adopted to study 58 (50.43%) patients with newly diagnosed GBM who were referred to neurosurgery department of Poursina Hospital in Rasht from 1999 to 2015. Patients with other types of malignant brain tumor, benign brain tumor, unknown diagnosis and out of this duration were excluded.

Using Hospital Information System (HIS), the collected data were recorded in a pre-designed specific form including demographic (age, gender), clinical (KPS, side and location of tumor, discharge status) and medical (EOR and administration of post-operative radio-chemotherapy). Post-medical treatment KPS scores were categorized as able to work (80-100), unable to work (50-70) and unable to care for self (40 or less) (16).

It is noticeable that quality of tumor resection was accurately assessed by a proficient neurosurgeon via early post-operative CT scan within 24 h after surgery.

All obtained data were analyzed by SPSS 18 software using chi-square and fisher exact tests. Quality and quantity variables are tabulated as number (%) and mean ± SD, successively.

Results

Of total patients suffering newly diagnosed GBM, 35 (60.3%) and 23 (39.7%) were men and women, respectively. Age range (at the time of diagnosis of GBM) was 18-82 years (54.86±16.34). The most common side and location of tumor were left hemisphere and frontal lobe, respectively.

Other affected locations included the frontotemporal, frontoparietal, tempoparietal and parietooccipital lobes with a frequency less than 10 cases for each of them.

In terms of treatment protocols, 41 patients (70.7%) received total surgical resection. Half of patients were treated with simultaneous post-operative radiation therapy and chemotherapy. No patient received single radiotherapy or single chemotherapy. Functional outcome of patients is based on KPS. Most of patients belonged to alleged category of unable to work (70.6%) and 11 (19%) of cases died. Duration of hospitalization in both alive and dead groups were 21.16 (15.94) and 21.13 (20.63), respectively. The patient's characteristics are shown in Table 1.

In the next step, we compared the post-medical treatment KPS score with studied variables. Results indicated that only functional outcome had a significant relationship with KPS score (Table 2).

Our results showed that 11 (19%) of cases died. Only in the KPS variable, a statistically significant difference was observed between alive and dead groups (P=0.01).

Table 1. Demographic, Clinical and Medical Characteristics in GBM Patients

Variables		Frequency	Percent
Age	≥50	39	67.2
	<50	19	32.8
Gender	Male	35	60.3
	Female	23	39.7
Side of tumor	Right	23	39.7
	Left	25	43.1
	Midline or Bilatral	2	5.2
	Unknown	7	12
Location of tumor	Frontal lobe	10	17.2
	Temporal lobe	6	10.3
	Parietal lobe	9	15.5
	Occipital lobe	3	5.2
	Other	21	36.1
	Unknown	9	15.7
Extent of resection	Total	41	70.7
	Partial	5	8.6
	Unknown	12	20.7
Radiation therapy	Yes	29	50
	No	28	48.3
	Unknown	1	1.7
Chemotherapy	Yes	29	50
	No	28	48.3
	Unknown	1	1.7
Combine Chemo-Radio-therapy	Alive	22	46.8
	Dead	7	63.6
Functional Outcome	Alive	47	81
	Dead	11	19
Post-medical treatment KPS	Able to work (80-100)	3	5.2
	Unable to work (50-70)	41	70.6
	Unable to care for self (0-40)	14	24.2

Discussion

This study showed a higher number of male than female patients. Most of the patients belonged to subcategory≥50 age range. Patients' characteristics of this study based on age and sex were incompatible with other studies (13,17-18).

In our study, it was found that in the group that were unable to care for self (KPS=0-40), the number of patients ≥50 years of age was more than that of patients <50 years. Age has been reported as a strong predictor in treatment of patients suffering GBM. Also, age≥50 years has been introduced as a significant prognostic factor in categorization of GBM, in the RPA of EORTC (European Organization for Research and Treatment of Cancer recursive partitioning analysis) (19). There are several hypotheses to explain the poor clinical outcome of elderly patients. These include increased pre and post-operative

Table 2. Comparison of Post-medical Treatment Karnofsky Performance Scale Score with Studied Variables

Variable	Post-medical Treatment Karnofsky Performance Scale Frequency (%)			p-value
	0-40	50-70	80-100	
Age				
<50	4 (28.6)	15 (36.6)	0	0.4
≥50	10 (71.4)	26 (63.4)	3 (100)	
Sex				
Male	8 (57.1)	24 (58.5)	3 (100)	0.4
Female	6 (42.9)	17 (41.5)	0	
Side of Tumor				
Right	4 (28.6)	19 (48.7)	0	0.07
Left	7 (50)	16 (41)	2 (66.7)	
Two-sided	0	3 (7.7)	0	
Unknown	3 (21.4)	1 (1.8)	1 (33.3)	
Location of Tumor				
Frontal	1 (7.1)	8 (19.5)	1 (33.3)	0.6
Temporal	0	6 (14.6)	0	
Parietal	3 (21.4)	6 (14.6)	0	
Unknown	3 (21.4)	5 (12.2)	1 (33.3)	
Others	7 (50)	16 (39)	1 (1.7)	
Extent of Resection				
Total	9 (100)	32 (88.9)	0	0.1
Sub-total	0	4 (11.1)	1 (100)	
Radiation Therapy				
Yes	9 (64.3)	19 (47.5)	1 (33.3)	0.5
No	5 (35.7)	21 (52.5)	2 (66.7)	
Chemotherapy				
Yes	9 (64.3)	19 (47.5)	1 (33.3)	0.5
No	5 (35.7)	21 (52.5)	2 (66.7)	
Functional Outcome				
Alive	3 (21.4)	41 (100)	3 (100)	0.01
Dead	11 (78.6)	0	0	

Table 3. Reporting Mortality according to Age, Gender, Side, Location, Therapeutic Regimens and KPs Score of the Tumor

Variable	Alive	Dead	p-value
Age	55.4 (16.7) N=47	52.55 (15.22) N=11	0.6
Sex			
Male	27 (57.4)	8 (72.7)	0.3
Female	20 (42.6)	3 (27.3)	
Side of Tumor			
Right	20 (87)	3 (13)	0.3
Left	19 (76)	6 (24)	
Two-sided	2 (100)	0	
Unknown	3 (60)	2 (40)	
Location of Tumor			
Frontal	9 (90)	1 (10)	0.6
Temporal	6 (100)	0	
Parietal	7 (77.8)	2 (22.2)	
Unknown	7 (77.8)	2 (22.2)	
Others	18 (75)	6 (25)	
Chemotherapy			
Yes	22 (47.8)	7 (63.6)	0.3
No	24 (52.2)	4 (36.4)	
Radiotherapy			
Yes	22 (47.8)	7 (63.6)	0.3
No	24 (52.2)	4 (36.4)	
Extent of Resection			
Total	33 (86.8)	8 (100)	0.2
Sub-total	5 (13.2)	0	
Post-medical Treatment KPS Score			
Able to Work (80-100)	3 (6.4)	0	0.01
Unable to Work (50-70)	41 (87.2)	0	

morbidity and mortality and reduced tolerance in therapeutic procedures. In addition, neurodegeneration, resistance to radiotherapy and chemotherapy, different histology, and genetic mutations are also possible reasons for reduced survival (20).

Regarding the side and location of the tumor, left hemisphere and frontal lobe were mostly observed in studied GBM population. Matsuda et al. (2011) investigated 67 newly diagnosed GBM. They found that tumors of left side and frontal lobe possessed a high frequency (19).

Post medical treatment KPS score ranged from 50 to 70 pertaining to the category of unable to work was the most prevalent category of KPS in all patients. Furthermore, all dead patients were in the range of 0-40 (Unable to care for self). In addition to age, level of performance is the most important variable for predicting outcome and survival in GBM patients (21-22). Curran et al. (1993) reported that median survival was 18 months in patients with GBM who were <50 years of age and had KPS of 90-100, so that it was only five months in patients with aged ≥ 50 years with low KPS(23). Lacroix et al. (2001) portrayed the same findings (24). KPS is the most widely used method of quantifying the functional statues of cancer patients (25-26). Mor and colleagues (1984) stated that this tool, when used by trained personnel, can be really valuable for research (27).

Today, maximum possible microsurgical resection followed by concomitant radiation therapy and chemotherapy are common standard multimodal therapy for GBM (28), which was considered in the present study.

In our investigation, most of patients had total surgical resection. In recent decade, abundant evidence has approved that the extent of resection is associated with better outcomes in patients with GBM (29). Sanai et al. (2011) showed that more favorable recovery was obviously achieved in high EOR (30). Margusian also put that survival rate in patients with total

resection was better than those with subtotal resection or only biopsy (31). Along with these researches, findings of Lacroix et al. (2001) revealed that full resection caused the major effectiveness. First efforts to precisely determine the benefits of survival following microsurgical resection were done by a neurosurgery team in MD Anderson Cancer Center in 2001. According to their study, removing 98% or most of a tumor significantly increased survival chance (24). The maximum extent of resection depends on the tumor size, shape and location of blood vessels and arteries and sensitive areas of the brain (32).

Our results showed that half of patients received radiotherapy. It is a strong predictive factor in post-operative period. Mineo and colleagues proposed that radiotherapy is a highly notable independent predictor of outcome. Therefore, the average of overall survival rate in the patients undergoing radiotherapy was 16 months versus 13.5 months for those without radiotherapy (33). Other studies have reported analogues results (34-35). Latest studies suggested that diversity of GBM molecular pathology affected the treatment sensitivity. Yount et al. found that ionizing radiation resulted in less cell apoptosis in GBMs with non-functional P53 (36). While GBMs containing wild type gene of P53 were willingly suppressed through apoptotic death by radiation (37). However, p53 gene mutation is common among young GBM patients. This indicates the presence of a correlation between other molecular defects and radiation reaction assessed radiographically in GBM (38). GBM in older patients tends to display the deletion of the tenth chromosome, and it is probable that the genes that are important in terms of radiosensitivity in gliomas are located on this chromosome (39). Some studies have reported ray reactions evaluated optically in malignant glioma patients who manifested favorable performance and underwent total resections (40). These conclusions indicate that radiation therapy has prognostic value in malignant glioma during the post-operative period, confirming the previous findings (34–35).

In the present study, half of patients had chemotherapy in addition to radiation therapy in the post-operation period. First time in an assay it was described that simultaneous TMZ (temozolomide) and radiotherapy increased median survival rates up to 26.5% within 24 months, a vast improvement over the 10.4% with radiotherapy alone (41).

Ekici et al. (2013) showed that combined chemotherapy and radiotherapy offered good prognosis with a treatment value (15). In this line, Barker et al. asserted that there was a good outcome in old patients, when TMZ was accompanied to radiotherapy (42).

Present study had some limitations including incomplete available data on some variables, such as side and location of tumor. The small sample size was also another problem which limited out analysis.

Conclusion

It is generally accepted that GBM is the most common primary brain tumor in adults and the most invasive human tumor. The present study determined that GBM is a frequent malignant brain tumor with male predominance with high occurrence in ages ≥50 years. Mortality rate increases with increased age and decreased KPS. Total surgical resection followed by concomitant radiation therapy and chemotherapy were commonly considered as standard therapeutic regimens.

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Conflicts of Interest

The authors report no conflict of interest.

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Comments

"Study results of 58 patients hospitalized from 1999 to 2015 in Poursina University Hospital, Rasht, Iran" is the title I choose for the study of my colleagues in Poursina. However, they did not mention even the name of their hospital. They mentioned cross-sectional design for their retrospective study of 16 years duration. They wrote about survival of the patients with Glioblastoma multiforme (GBM) in the literature while there is no evidence of their follow-up of patients after three-week hospitalization period. I believe the association of Karnofsky Performance Scale (KPS) and GBM outcome is better understood if we wrote the above-mentioned title. They wrote about many factors such as microscopic evaluation of the GBM tumor, and P75 gene without mentioning of any related results in their own patients. Therefore, we do not see any correlation between their methods, results and discussion. In introduction, they wrote: "About 51 million primary brain tumors are diagnosed in America each year". However, this is one-thousand times more than the real data (1). The overall incidence rate for primary brain tumors in USA is 18.1 per 100 000 person-years which equals 58,241 patients with GBM based on the US population of 321,773,000 for 2015.

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