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Clinicopathological features for High Grade Glioma Tumors in Rizgary Cancer Center: a Six Years' experience

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Original Article

Summary

High grade glioma is the most common type of primary malignant brain tumors, among it Glioblastoma Multiforme (GBM) , however, the overall the prognosis of this tumor is gloomy. This study aimed to study the clinicopathological features of high grade glioma according to histopathology, grade of glioma, age, sex, time frame between surgery and initiation of concurrent chemoradiotherapy for glioblastoma multiforme cases. We found that out of the 114 patients, 75 were males (65.8%) and 39 (34.2%) were females, the more frequently tumor location was frontal lobe , contributed for (32%) , Glioblastoma Multiforme histology was the most common histological type among all patients (80.7%), nearly half of patients were between 40-59 years. In conclusion, Glioblastoma multiforme is the most common type of registered high grade glioma, more common among male gender, age at diagnosis is at age group 40-59 years.

Keywords: *Glioma , high grade, epidemiology, histopathology, clinical feature, outcome*

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1. INTRODUCTION

High-grade gliomas are tumors of the glial cells, cells found in the brain and spinal cord. They are called “high-grade” because the tumors are fast-growing and they spread quickly through brain tissue, which makes them hard to treat, Glioblastoma multiforme (GBM) is one of the most malignant types of central nervous system tumors. Despite advances in treatment modalities it remains largely incurable (1). With an incidence rate of 3.19 per 100,000 persons in the United States and a median age at diagnosis of 64 years, it is uncommon in children. The incidence is 1.6 times higher in males compared to females and 2.0 times higher in Caucasians compared to Africans and Afro-Americans, with lower incidence in Asians and American Indians (2,3) High grade glioma account for about 85% of all malignant primary brain tumors, according to 2016 WHO classification of central nervous system tumors, Glioma were classified into four grades (WHO Grade I to Grade IV). WHO Grade I and Grade II gliomas are recognized as low grade glioma (LGG) while Grade III and IV are known as High grade glioma(HGG), in particular Glioblastoma multiforme (WHO grade IV) is the most common malignant primary tumor of the brain, keeping in mind that GBM has poor survival, the median survival time of GBM patient is approximately 15 months, even after receiving multimodality of treatment like: maximum safe surgical resection with preservation of neurological functions followed by concurrent chemoradiotherapy, after that at least half year of Temozolamide, with appropriate supportive care (2,4) Currently, safe optimal surgical resection followed by adjuvant radiotherapy and chemotherapy is considered as standard treatment approach for patients with GBM. However, despite advances in the last 3 decades, outcome remains poor and long-term survival is exceptional (4). The prognosis of GBM is poor and its survival is commonly less than two years. Radiation, head trauma, exposure of N-nitroso compounds, tobacco, alcohol were reported as risk factors [8-10]. Nevertheless an inverse relationship was reported between history of allergies, fruit and/or vegetables intake and brain tumors . Additionally, some studies reported that there was an increased incidence of brain cancer among white collar professionals, electrical, oil refinery and agriculture workers (5). Clinicopathological data showed that the mean age at diagnosis of patients was 50.06 years, the sex ratio was 11 F/23 M, and the median of Karnofsky performance score was 60. About 18 % of patients were initially treated by total tumor resection, 41 % by subtotal, and 38 %

by partial resection, but biopsy was performed for a single patient (3%). Twenty-five patients (74 %) received radiotherapy. In addition, the median survival of the all patients was 13 months following diagnosis (6)

2. PATIENTS and METHODS

A retrospective review of cases was conducted at Rizgary Cancer Center / Rizgary teaching Hospital, located in Erbil, Iraq, which is a major tertiary referral cancer. The study included patients with histopathology proven high grade glioma, registered in the mentioned center from Jan, 2015 to Dec 2020. Retrospective evaluation and assessment was carried out for 114 cases during the study period. The collected data included: gender of patients, tumor location in brain , ABO blood group , main presenting complain at time of diagnosis and time frame between surgical operation and starting concurrent chemoradiation for glioblastoma multiforme cases, time of death. The inclusion criteria were Glioblastoma multiforme, anaplastic astrocytoma IDH mutant GIII, anaplastic astrocytoma IDH non mutant GIII, anaplastic oligodendroglioma IDH mutant and 1p/19q codeletion GIII, anaplastic oligodendroglioma NOS GIII, all were high grade glioma III or Grade IV, and anaplastic Xanthoastrocytoma . Exclusion criteria were secondary brain tumors, low grade Glioma , diffuse astrocytoma GII, Oligodendroglioma GII, Oligoastrocytoma GII, gliosarcoma,, pituitary tumor and ependymoma (6)

Statistical analysis:

Data were entered managed and analyzed using the statistical package for social sciences version 23. Descriptive statistics presented as mean, standard deviation, range, frequencies and percentage. Appropriate statistical tests and procedures were applied according to the variable type at a level of significance of 0.05.

3. RESULTS

Table 1 shows that among 114 patients, nearly half (48.2%) of respondents aged 40-59 years and 28.1% of participants were ≥ 60 years, males were dominant with a male to female ratio of 1.92 to one (**Figure 1**). Around two thirds (65.8%) of the patients were males, the tumor was located in the frontal lobe in 31.6% of participants, while the tumor was located in the parietal and temporal lobe in 21.9% of patients. The majority (80.7%) of

participants had GBM while only 9.6% of respondents had anaplastic oligodendroglioma. The majority (89.5%) of patients received CCRT, while only 9.6% of them received cytotoxics. Less than one third (28%) of the patients were alive, 33.4% of respondents died after 1 - 2 years of diagnosis, and 28.9% of them died after less than one year, in total , 82 patients died and 32 survived (**Figure 2**).Findings of table 2 reveals that there was a significant statistical association between outcome and histopathology. The majority (78.3%) of patients who had GBM died, compared with 36.4% of patients with anaplastic oligodendroglioma, and all anaplastic pleomorphic xanthoastrocytoma cases were alive (p = 0.004). There was a significant association between outcome and grade, the majority (78.3%) of patients with grade IV died, followed by 45.5% of patients of grade III (p = 0.004). There was a significant association between outcome and level of surgery, The least death rate (60%) was observed when the safe surgical resection was feasible, while it was 90.9% when only biopsy was taken (p = 0.041). The results of table 3 show that there was a non-significant association between outcome and treatment modalities. All (100%) DXT cases died, the vast majority (90.9%) of participants who received cytotoxics were dead (p = 0.330). There was a non-significant association between outcome and time frame, the majority (78.8%) of patients with 4-8 weeks died, followed by most (72.7%) of patients during >8 weeks died (p = 0.066). There was a non-significant association between outcome and symptoms, the majority (87.5%) of patients who had paresis were dead, the majority (78.9%) of participants who had repeated nausea and vomiting died, (67.9%) of them got headache were dead (p = 0.489). There was a no significant association between outcome and age (p = 0.230) but the least death rate (59.3%) was observed among patients aged less than 40 years. There was a non-significant association between outcome and blood groups (p = 0.750), All these findings are shown in (**Tables 1, 2 and 3**).

Table 1. General characteristics of participants.

Variables	Categories	Frequency	Percent
Age (years)	< 40	27	23.7
	40- 59	55	48.2
	≥ 60	32	28.1
Gender	Male	75	65.8
	Female	39	34.2
Tumor location	Frontal lobe	36	31.6
	Parietal	25	21.9
	Frontoparietal	7	6.1
	Corpus callosum	4	3.5
	Temporal	25	21.9
	Occipital	7	6.1
	Parietoccipital	5	4.4
	Parietotemporal	5	4.4
Histopathology	GBM	92	80.7
	Anaplastic astrocytoma	10	8.8
	Anaplastic oligodendroglioma	11	9.6
	Anaplastic pleomorphic xanthoastrocytoma	1	0.9
Treatment modalities	DXT	1	0.9
	Cytotoxics	11	9.6
	CCRT	102	89.5
Time to death	Alive	32	28
	< 1 year	33	28.9
	1- 2 years	38	33.4
	> 3 years	11	9.7
Total		114	100

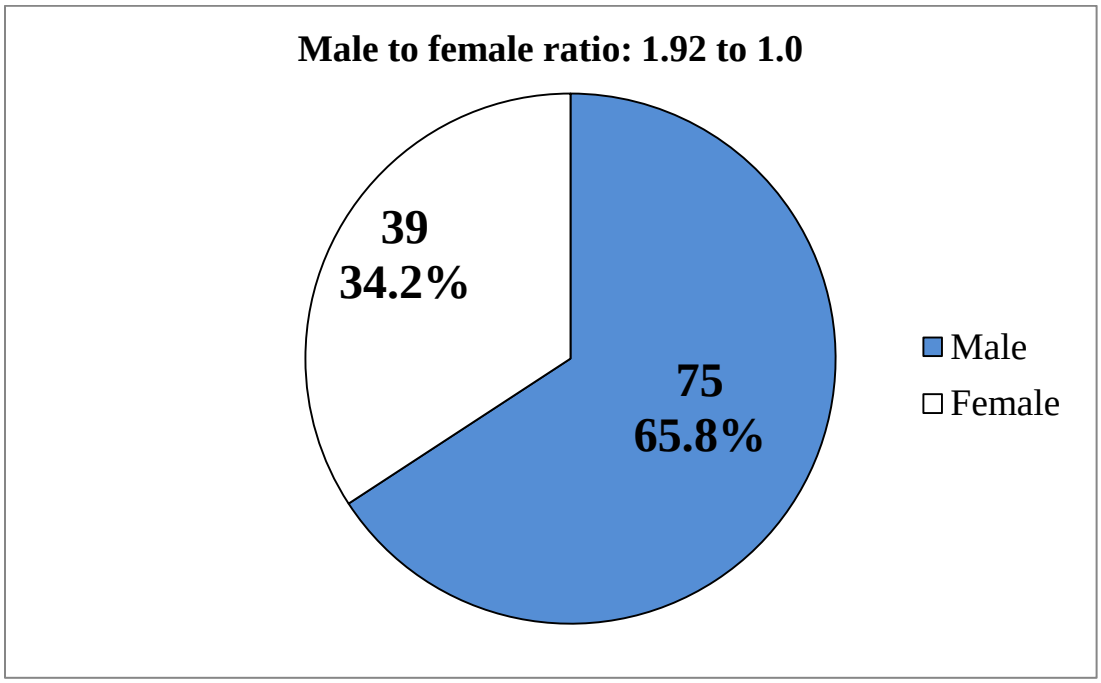

Figure 1. Gender distribution of the studied group (N=114)

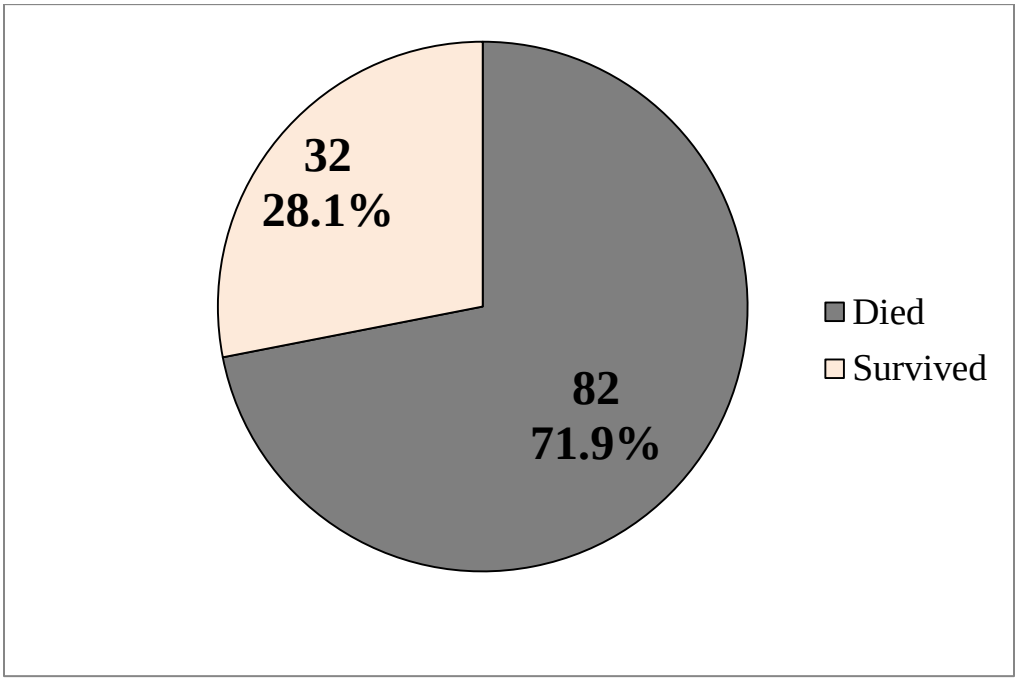

Figure 1. Mortality and survival rates of the studied group (N=114)

***Table 2. Association between outcome and histopathology, grade and level of surgery*.**

Variable	Categories	Outcome		p-value
		Alive	Dead	
Histopathology	GBM	20 (21.7%)	72 (78.3%)	**0.004**
	Anaplastic astrocytoma	4 (40%)	6 (60%)	
	Anaplastic oligodendroglioma	7 (63.6%)	4 (36.4%)	
	Anaplastic p. xanthoastrocytoma	1 (100%)	0 (0%)	
Grade	III	12(54.5%)	10(45.5%)	**0.004**
	IV	20(21.7%)	72(78.3%)	
Level of surgery	Safe surgical resection, feasible	12(40%)	18(60%)	**0.041**
	Safe surgical resection, non-feasible	18(29%)	44(71%)	
	Biopsy only	2(9.1%)	20(90.9%)	
Total		32 (28.1%)	82 (71.9%)	

Table 3: Association between outcome and treatment modalities, time frame, symptoms and age groups.

Variable	Categories	Outcome		p-value
		Alive	Dead	
Treatment modalities	DXT	0 (0%)	1 (100%)	0.330
	Cytotoxics	1 (9.1%)	10 (90.9%)	
	CCRT	31 (30.4%)	71 (69.6%)	
Time frame	< 4 weeks	12 (48%)	13 (52%)	0.066
	4 - 8 weeks	7 (21.2%)	26 (78.8%)	
	> 8 weeks	12 (27.3%)	32 (72.7%)	
Symptoms	Headache	18 (32.1%)	38 (67.9%)	0.489
	Repeated nausea and vomiting	4 (21.1%)	15 (78.9%)	
	Paresis	2 (12.5%)	14 (87.5%)	
	Convulsion	6 (37.5%)	10 (62.5%)	
	Cranial nerve palsy	2 (28.6%)	5 (71.4%)	
Age (years)	< 40	11 (40.7%)	16 (59.3%)	0.230
	40- 59	14 (25.5%)	41 (74.5%)	
	≥ 60	7 (21.9%)	25 (78.1%)	
Blood groups	A+	9 (36%)	16 (64%)	0.750
	O+	11 (28.9%)	27 (71.1%)	
	AB+	4 (25%)	12 (75%)	
	B+	4 (19%)	17 (81%)	
	A-	1 (20%)	4 (80%)	
	B-	1 (20%)	4 (80%)	
	O-	1 (33.3%)	2 (66.7%)	
	AB-	1 (100%)	0 (0%)	
Total		32 (28.1%)	82 (71.9%)	

4. DISCUSSION

Incidence of CNS tumors is varied worldwide, available data revealed that age-standardized rates varied globally. In different nations the incidence ranges between zero to 12.7 per 100000 population in general, lower rates reported in Africa while the highest rate in Northern Europe. However, comparison of data according to countries is limited due to variation in the diagnosis, registration and reporting in different countries (7,8). Ethnic variation in the incidence of nervous system and intracranial tumors attributed to the fact that heterogeneous classification systems into broad groups like white, Asian, Black , etc. However, the incidence of meningioma is much higher among blacks in comparison to others (9). That variation in gliomas incidence by ethnicity cannot be explained by environmental factors and may be partially attributed to gene polymorphism among different ethnic groups (10,11)

Little is known about the etiology of brain neoplasms which are usually highly incurable. No underlying carcinogenetic causes can be identified. To date exposure to high dose ionizing radiation is the only confirmed risk factor (1), In our study, about two thirds (65.8%) of the patients were males, as GBM has more tendency to male gender and also more darker outcome come in male gender in comparing to female gender , also in a study done showed tumors would tend to indicate that there is a hormonal influence on the growth of the heterotransplanted tumours. These results provide further evidence for an influence of sex-steroid hormones on the growth of glioblastomas (12) , as its obvious from our data that(65.8%) of our patients were males and (34.2%) were females giving a male to female ratio of almost 1.9 to one. In a study performed at Kiel, Germany, Stark et al. (13) showed that male to female ratio was 1,26: 1, and the median patient age was 62 years (range: 22–93 years). Moreover, recent two studies conducted by Yang et al. and Carrano et al., documented a male to female ratio of 1.6 to one (14,15),

Prominent findings of this study, as they have been in others, were the inverse non-significant relation between the age of the patient and the duration of survival, the inverse relation between age and the duration of preoperative symptoms, and the positive relation between the age and the degree of histologic malignancy. The relationship between increasing age and decreasing survival could be due to diminishing resistance of

the host, accelerating malignancy of the neoplasm, or both. Such relationship with age also documented in previous studies (16,17)

Differences in treatment would appear not to be a factor since within a given treatment arm, all patients were treated identically. Relationships between age and histologic variables were therefore sought in the patients with the anaplastic astrocytoma to explain the detrimental prognostic effect of advancing age. However, even when patients with either or both of these variables were excluded, there was still a significant relationship between older age and shorter survival. We anticipated that other variables, such as cellularity, might also be related to age and help explain the shorter survival in the older patients. There were tendencies for small cell anaplastic lesions to occur in older patients, and gernistocytic lesions to arise in younger individuals, however these relationships were not statistically significant (18,19)..

Results showed a significant association between histopathology and grade of tumors, as GBM is Grade IV carry worse outcome, while other lower grade , GIII , like anaplastic astrocytoma (AAC), anaplastic oligodendriogioma (AOD) and anaplastic Xanthoastrocytoma have better outcome in comparison to GBM. Different studies documented Histopathological correlates with survival in reoperated glioblastomas in addition to other clinical , pathological and genotyping (20–23)

*Presenting features included seizure, loss of consciousness, headache, speech or visual disturbance, weakness and confusion, as were tumour sites within the brain (24).

To our knowledge, glioblastomas presenting with ischemic stroke are rare, and such patients should be considered to be at high surgical risk (25).

Regarding main presenting complain or symptom which triggered diagnosis of HGG, around half of the patients (49.1%) presented with headache, in a study eighty five patients with brain tumors, found that 60% of them had headache, Eighty-five brain tumor patients were examined for further characteristics of brain tumour-associated headache. The overall prevalence of headache in this population was 60% (25).

Regarding the relationship between ABO blood group distribution and incidence of glioblastoma or other brain tumors, previous studies showed such relationship, for instance, Allouh et al. from Jordan, found that people with blood group A are at higher risk to have develop glioblastoma while individual with group O were at lower risk , authors from

Jordan concluded that distribution of ABO blood group antigens is associated with a risk of brain tumors and could play a significant role in the pathogenesis of and development of these tumors, almost similar findings documented in other studies (5,26) .

The impact of timing of RT initiation on survival after surgical resection remains controversial among different studies . From a biological point of view, there are arguments to support an early as well as a late initiation of RT, on the one hand, an early start of RT could have a negative impact on survival due to reduced radiosensitivity secondary to postoperative hypoxia or due to the "second-impact" effect leading to a further deterioration of the clinical condition of an already compromised patient. On the other hand, a similar case can be made for a delayed initiation of RT: some GBM exhibit increased growth rates and a delayed RT fails to take advantage of this increased radio-sensitivity (27)(28) However, the optimal time to start RT still under debate and depend on the clinical practice and judgment of managing surgeon and oncologist (29). In our study there was a non-significant association between outcome and time frame , as the majority (78.8%) of patients with time frame 4-8 weeks were dead, followed by most (72,2%) for time frame more than 8 weeks, while around half (52%) were dead for those time frame less than 4 weeks

Regarding surgical intervention, as GBM is a fast growing tumor and occupying large portion of the brain parenchyma, feasible safe surgical resection is highly recommended, but as the brain tissue is very sensitive, hence it is not always applicable to do such resection, as the brain tissue should be dealt with it precisely during the operation. There is a growing body of evidence supporting improved overall survival, improved progression-free survival, and superior quality of life with greater extent of resection (30).

In our study, safe surgical resection was not feasible and applicable in more than half (54.4%) of the patients, while safe surgical resection was feasible in about quarter of our cases (26.3%). In around one fifth (19.3%) of the patients, biopsy was the only surgical intervention performed mostly due to one or more than one of the following causes: large tumor size, occupying very crucial part of the brain tissue, most of the tumors were non superficial, severe comorbidities, and the bad general condition of patient.

Regarding grade and histopathology as GBM grade IV was making around (80.7%) of all patients in study, at the same time has main share in mortality among other histology like

Anaplastic astrocytoma , anaplastic oligodendroglioma(ODG) , and anaplastic xanthoastrocytoma . while at the same time (63.6%) of patient with anaplastic ODG were a live

Over the past 25 years, malignant primary brain tumor has increased at an annual rate of 2%, higher rate among middle age and old age groups (2,4), while in our study cases of HGG in 2016 were 21 cases, also on 2020 were 20 cases.

Glioblastoma continues to have a poor prognosis. Advanced age, poor performance status, and incomplete extent of resection are all well-established negative prognostic factors.10, 11 In elderly patients, the median survival is <4 months with best supportive care alone.12 Molecular features, however, such as isocitrate dehydrogenase 1 (IDH-1) and IDH-2 mutation and MGMT methylation, confer a favorable prognosis (2)

Treatment options in the relapsed or recurrent setting are less well defined, with no established standard of care and little evidence for any interventions that prolong OS. Indeed, a significant proportion of patients may not even be eligible for second-line therapy.37, 38 Options include further surgical resection, reirradiation, systemic therapies such as lomustine or bevacizumab, combined approaches, or supportive care alone (2). Overall survival in GBM is usually less than 12 months and long-term survival is rare (4,21,23,24).

5. CONCLUSIONS

Glioblastoma multiforme is the most common type of registered high grade glioma, more common among male gender, age at diagnosis is mainly at 40-59 years.

Ethical Clearance: Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches involving humans, informed consent obtained from all patients. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

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