

Hemorrhagic Glioblastoma Multiform: Prevalence, Predisposing Factors and Prognosis Among Adult KFMC Patients

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Abstract

Gliomas is a collection of tumors arising from glial cells or their precursors within the central nervous system. Histopathologically, gliomas are divided into four grades; the most aggressive of these grades is grade 4 or Glioblastoma Multiform (GBM), which is considered the most common primary intracranial neoplasm of the central nervous system. It has a prevalence of 15% to 20% of all primary central nervous system tumors. These GBM tumors can be presented in different forms. Intracranial hemorrhage (ICH) is one of these forms, which can happen to different degrees and extension with variation in the degree of prognosis. The general prognosis for GBM associated with ICH worsens with increasing age in elderly patients. (1,2). The rationale behind this study is to determine the effect of hemorrhage on the diseases prognosis, know the prevalence and predisposing factors which could help to get good prognosis for patients and could prevent the complication development.

We have documented 530 brain tumor patients at the national neuroscience institute database. Both male and female patients who are ≥ 18 years old with pathological diagnosis of glioblastoma multi form were included. The exclusion criterion was patients who have any hemolytic disease. A retrospective medical record review was performed for patients diagnosed between 2008 through 2013. We reviewed how many patients presenting with ICH among GBM, data of the predisposing factors that is common between ICH GBM and compare it with non hemorrhagic GBM patients. In addition, the study reviewed the prognosis of ICH GBM patients, and then compared them with non hemorrhagic GBM patients.

We found the prevalence of hemorrhagic GBM in the study population 29.2%, where the non-hemorrhagic GBM accounted for 70.8%. The prevalence of hemorrhagic GBM in relation to the gender was almost the same between males and females (29 %). Hemorrhagic GBM patients' mean survival time was (1.8 years), and they had worse prognosis (less survival time) than non-hemorrhagic GBM patients did. The predisposing factor, which increased the risk of the development ICH in GBM patients, was increasing age of the patient. Frontal lobe location was the least prognostic factor to develop ICH in GBM patients comparable to other lobes locations.

Keywords: *Glioblastoma multiform, intracranial hemorrhage, Primary brain tumor, intracerebral hemorrhage.*

Introduction

Gliomas is a collection of tumors arising from glia or their precursors within the central nervous system. Histopathologically, gliomas are divided into four grades; the most aggressive of these

grades is 4 or GBM.(1) GBM is the most common primary intracranial neoplasm of the central nervous system. It has a prevalence for 15% to 20% of all primary central nervous tumors. These GBM tumors can be presented in different forms. Intracranial hemorrhage (ICH) is one of these forms, which can happen to different degrees and extension with variation in degree of prognosis. It has been reported that GBMs can masquerade as traumatic ICH, or intraventricular hemorrhage (IVH). The imaging characteristics of GBMs are different and variable. However, almost all Glioblastoma Multiform lesions have a unique and pronounced mass effect with heterogeneous enhancement and centrally necrotic regions on computerized tomography (CT).(2)

The prognosis and clinical manifestation depend on multiple factors which share together according to their severity and their stage, namely; tumor size, location, infiltration range, eloquent area involvement, and the extent of the surgical resection. The main histopathological features include micro vascular proliferation, pleomorphic cells, necrosis, increased cellularity ,mitoses and microscopic intra-tumoral hemorrhage.(3)

Intracerebral hemorrhage (ICH) is defined as bleeding into the brain parenchyma.(4) ICH is a common neurological emergency in patients with intracranial tumor, which usually occurs late in the course of disease, in some point of time it heralds the cancer diagnosis. The presence of ICH in patients of GBM usually occurs by unique mechanisms, especially intratumoral hemorrhage or coagulopathy, whereas hypertensive hemorrhage is rare.(5) A highly vascularized, malignant primary brain tumor (BT) like a GBM and metastatic BT tends to bleed spontaneously. Glioblastoma multiform should be included in the differential diagnosis of non-traumatic ICH.(6)

In pathogenesis of sudden massive bleeds into cerebral tumors, the ischemic necroses areas are formed, invasion of the large blood vessel wall by turnout tissue which leads to rupture of the thin-wall, and tortuous tumor vessels occurred in anaplastic gliomas.(7) Before the introduction of computed tomography (CT scanning), clinical diagnosis and non-invasive confirmation were difficult. The CT scan is one of the best modalities to diagnose ICH.(4)

The general, prognosis for GBM associated with ICH worsens with increasing age in elderly patients. The surgical removal of both the hematoma and the tumor with adjuvant treatment are associated with prolonged survival rate.(8) Despite the presence of adjuvant therapy including microsurgical resection and radiotherapy and chemotherapy, about 75% of patients die within 18 months from the diagnosis.(9)

Head injury is one of many causes of intracerebral hemorrhage; this can range from a contusion on the cortical surface to a deep parenchymal hematomas. If the patient had a tendency to bleed, he/she can develop a large intracerebral hematoma after minor trauma. As mentioned above, GBM with its altered histological structure of the blood vessels makes them more prone to bleed and shear during the trauma.(10)

The rationale behind this study is to determine if GBM survival rate changes with ICH, and to see if the associated complication comes with primary brain tumor at KFMC data as well as Saudi Arabian neurosurgery research. Moreover, the study determined the effect of hemorrhage on the diseases prognosis. Finally, the current study explored the prevalence and predisposing factors to find out whether they can help to get good prognosis for patients and can prevent the complication development.

Literature Review :

The Glioblastoma multiforme is the most common intracranial neoplasm of all primary central nervous system tumors.(2) Intracranial tumors are said to account for 8% of nontraumatic intracerebral hemorrhage. About half of this may be the first manifestation, and in a small proportion of these cases the patients die suddenly.(11)

The pathology of GBM is linked to the molecular basis of this disease. The most common genetic abnormalities that can lead to gliomagenesis is complete deletion of chromosome 10. The presence of tumor suppressor genes on various loci on this specific chromosome leads to heterozygosity (LOH) of chromosome 10 and to the induction of GBM. p16INK4a deletion, p14ARF and p53 mutation, RB1 methylation, and MGMT methylation are other common mutations present in GBM.(12)

The “mutator phenotype” in glioma cells is raised by these molecular and genetic mutations. The DNA repair mechanisms will be mutated in this “mutator phenotype” which will include base excision repair, nucleotide excision repair as well as recombination and mismatch repair. The gliomagenesis will happen because of a combination of specific genetic mutations and mutations in DNA repair mechanisms.(13)

Amplification of epithelial growth factor receptor (EGFR) on chromosome 7 is another common mutation in GBM. Cellular development, proliferation, migration, and vascularization within the cell is normally regulated by EGFR. The binding of EGFR and the growth factor ligands activate signaling cascades that include the infamous RAS protein, which leads to alteration of the transcription of cellular regulation genes within the nucleus. Eventually, the mutations in EGFR can easily cause cancer.(12)

Cytogenetic and molecular genetic studies of GBM have shown loss of heterozygosity on chromosome arm 10q (60%–90%), mutations in p53 (25%–40%), *PTEN* mutations (30%), overexpression of MDM2 (10%–15%), and epidermal growth factor receptor (EGFR) gene amplification that the most frequent alterations encountered in these tumors.(14)

The specific cause of GBM is unknown and identifying various risk factors has proven difficult. Many factors that could increase the risk of developing GBM have been suggested; however, only the directly impact GBM development by radiation have been shown. Other factors have been suggested as possible risk factors for GBM including increased cell phone use and pesticide exposure.(13)

One of the suggested possible risk factors for developing GBM is head trauma. Some experimental data have shown that trauma is able to act as a carcinogen in the presence of an initiating carcinogen. Hypertrophy and multiplication are experienced when glial have a trauma, they undergo a process called gliosis. This causes a change in the blood-brain barrier and in the architecture of the brain cerebrovascular, which could cause the brain to have further exposure to carcinogens or growth factors. However, the correlation between development of gliomas and repeated head injury has been shown in several studies especially in males but there is no clear cause and effect has yet been proven. To elucidate the connection between head trauma and GBM more research needs to be done in this area.(15)

Exposure to ionizing radiation is the only risk factor that has been proven to increase the risk of developing GBM, which is energetic enough to excite electrons and damage DNA, by radiation

therapy or radiosurgery. Radiation can result in damaging the DNA and therein causes cell death, another side effect of radiation developing a tumor that includes necrosis of tissue by the radiations itself. Over than 116 cases of GBM have been reported since the 1960s, that have been caused by radiation and overall the risk of developing GBM following radiotherapy is approximately estimated with 2.5 percent. For acute lymphoblast leukemia (ALL) patients, it has been reported that they develop GBM more frequently because of the radiotherapy. All in all, it is clear that exposure to the ionizing radiation is linked to glioblastoma development.(16)

GBM is considered as the most common and the most malignant type of primary brain tumors in adults. More than 50% of GBM patients present in the sixth or seventh decade of life. The reported incidence of GBM cases in Europe and North America were 2 to 3 cases per 100000 per year.(9) In the US each year 17,000 cases diagnosed as brain tumors, approximately 60% are GBM.(14)

Glioblastoma multiforme contributes to the most common type of glioma which forms about 51.9% of all brain tumors (17).In primary brain tumors, glioblastoma multiforme is commonly associated with ICH, because it is considered the most frequent primary brain tumor and its tumor cells are highly invasive and destructive.(5) A highly vascularized, malignant primary brain tumor (BT) like a glioblastoma and metastatic BT tends to bleed spontaneously.(6)

The incidence of ICH in GBM patients was variable among different studies, some studies report as few as 1 % to 2 % of spontaneous ICH are due to an underlying cancer while other studies report as high as 7 % to 10 %.(5)

The significant prognostic variable in patients with glioblastoma was patient age, Karnofsky performance score, and location of tumor especially frontal tumor having some clinical relevance. Threshold level of age that determines the significant differences in the clinical outcomes have reported 50 years as a cut-off age for prognostic differences. It has been established that the prognosis for patients with GBM is determined by a complex interaction between age and genetic alterations.(18)

Morphologically, high grade tumor has more malignant which has worse prognosis. GBM patients survival rate depends on different clinical and biologic parameters which include size of tumor and location, using different kinds of combination treatments, presenting age, Karnofsky performance score (KPS) at presentation, histological features of the tumor, and molecular genetic factors.(14)

The genetic differences among GBM patients contribute to the differences in survival and prognosis. By studied molecular markers and its associations with the clinical outcomes of patients with glioblastoma in different age groups, the reported findings advocate clinical significance of a complex interrelation between the molecular biology of genetic alterations in glioblastoma and patient age.(17)

The median survival rate for GBM patients is less than one year, and about 2% of patients survive three years.(14) Some patients have a significantly better prognosis and outcome than the majority of GPM patents who return due to several factors including young patients' age, high performance score of (KPS \geq 70), macroscopically total tumor resection, radiotherapy of at least 54 Gy in total, and chemotherapy. Despite the presence of adjuvant therapy including microsurgical resection and radiotherapy and chemotherapy, about 75% of patients die within 18 months from the diagnosis.(9)

Intracranial hemorrhage is considered as a highly morbid neurological disease that accounts for nearly half of the cerebrovascular events in patients with brain tumors. Prognosis in patients with

GBM and ICH was poor including an underlying malignancy, multiple hemorrhagic foci, hydrocephalus, and absence of ventriculostomy.(9)

In the short-term prognosis of ICH patients with GBM the report demonstrated about 22% to 31% mortality at 1 month, and 48% to 75% had partial or complete independence at discharge. However, in the long-term prognosis of ICH with GBM, the underlying malignancy prognosis are often poor (78% mortality at 1 year), and ICH generally occurs late in the neoplastic course.(5)

Intracranial tumors are a well-established cause for brain hemorrhage. However, hemorrhage is believed to occur infrequently. Tumors were found in 2% of the 461 autopsied cases in which spontaneous intracerebral hemorrhage was reported. Glioblastoma multiforme was found in 7 of 8 patients with glial neoplasia. In the study, the pathogenesis of ruptured blood vessels is understandable in view of the "huge, disorderly, fistulous vessels" invariably present. Proliferation of endothelium, clusters of dilated thin-walled vessels, and areas of necrosis were common findings in tumor tissue examined microscopically. In high-grade malignancy the extensive and abnormal vascularity are considered as predisposing factors.(4)

In the differential diagnosis of intracranial hemorrhage GBM should be considered especially in the absence of predisposing factors. The association of tumors and vascular malformations should always be taken into consideration and preoperative radiological investigation should be performed explicitly in cases that have intraparenchymal hemorrhage.(2)

Brain tumour is a well recognized cause of intracranial hemorrhage, but at the same time the hemorrhage is uncommon, representing 0.8% to 10.2% with an average of 3.3% of spontaneous cerebral haematomas in large autopsy series, while among neurosurgically treated cerebral bleeds the incidence of brain tumours ranges from 0% to 11% with an average of 3.3%.

In an autopsy series of 430 spontaneous intracerebral haematomas 44 cases, or 10.2 percent, were caused by a proved neoplasm, including 21 anaplastic gliomas, 17 metastases, 2 oligodendrogliomas, 2 malignant lymphomas, and one meningioma. These instances of massive bleeding into brain tumour represented 2.4 percent of about 1,800 primary and secondary cerebral neoplasms proven by necropsy.

In only four of the patients with primary brain tumours (two glioblastomas, one oligodendroglioma invading the leptomeninges, and one primary malignant lymphoma), three of them with a history of arterial hypertension, were the presenting symptoms those of a spontaneous intracerebral haemorrhage, and the tumor itself was not diagnosed until surgery or necropsy. Most of the patients showing spontaneous bleeds from a cerebral neoplasm had been presented with signs of increased intracranial pressure and other symptoms before the haemorrhage had occurred.(7)

Significant variability is known to be in the frequency of intratumoral hemorrhage (either micro- or macroscopic) according to tumor histology. Patients with glioblastoma, oligodendroglioma, and metastatic brain tumors have the highest risk for developing intratumoral hemorrhage.(6)

A study done by Shrieve, et al. to compared the outcomes in patients treated with SRS with outcomes in those treated by brachytherapy. The authors reported an overall survival time of 10.2 months for SRS-treated patients and 11.4 months for brachytherapy-treated patients. It was also documented that SRS based therapy allowed the delivery of targeted radiation to inoperable recurrent tumors and avoided an increased risk of hemorrhage.(19)

The brain tumor was first described by Rudolf Virchow in 1863. Bailey and Cushing changed the original name "spongioblastoma" to glioblastoma because of the colorful macroscopic appearance with hemorrhages and necrosis.(9)

The possibility exists that primary glioblastomas may have a significantly longer preoperative history, but to clearly distinguish between both subsets, the window of eligibility was deliberately kept small. Two biopsies taken at an interval of >6 months to avoid a sampling error and clinical as well as histopathological evidence of progression from low-grade or anaplastic astrocytoma to diagnose the secondary glioblastoma required at least. Tumor necrosis within an astrocytic neoplasm is an essential criterion used by surgical pathologists for the diagnosis of a glioblastoma. Typically two types of necrosis are encountered. Multiple small, irregularly shaped, bandlike or serpiginous necrotic foci surrounded by radially orientated, densely packed, small, fusiform glioma cells in a pseudopalisading pattern this features in the first type. In primary and secondary glioblastomas these areas of pseudopalisading necrosis are a histologic hallmark and are observed at a similar frequency.

A large area of geographic necrosis containing necrotic tumor cells and vessels is the appearance in the second type. Around intact capillaries a rim of viable tumor cells is often observed in the periphery of such foci. This type of necrosis is considered ischemic in nature apparently a result of insufficient blood supply.(20)

The various malignant supratentorial hemispheric tumors can't be distinguished from each other by a special pathognomic radiographic appearance. On cranial CT scanning, High-grade gliomas typically display irregular or ring enhancement reflecting the breakdown of the blood–brain barrier or tumor neovascularity. On T1-weighted sequences; cortical and white matter T2-signal hyperintensity, representing infiltrating tumor and reactive vasogenic edema, and the aforementioned irregular pattern of contrast enhancement, all of which are the characteristics of MR imaging–documented appearance of malignant gliomas of low intensity.

Evidence of significant local mass effect is often seen because the propensity for these lesions grows rapidly. Other malignant supratentorial hemispheric tumors, such as supratentorial primitive neuroectodermal tumors, ependymomas, and pleomorphic xanthoastrocytomas are included in the neuroimaging differential diagnosis. Pleomorphic xanthoastrocytomas, of which approximately 20% have histological characteristics typical of classical malignant gliomas, have a fairly unique neuroimaging appearance in that an enhancing solid component arising near the cortical surface is characteristically observed, in association with an underlying cyst. We should perform Gadolinium-enhanced neuroimaging of the entire neuraxis only if there is a high index of suspicion for the presence of disseminated disease at the time of initial evaluation or if a competing diagnosis is highly considered in the differential of a child's presenting complaint. Perhaps the best philosophy is to reserve such intensive neuroimaging intervention for the postoperative period, after a firm histopathological diagnosis has been established.(21)

The standard treatment of GBM includes microsurgical resection, postoperative external radiotherapy with an effective dose of 54 Gy and chemotherapy.(9) For patients with ICH, steroids should be given to decrease mass effect and vasogenic edema, the tumor also should be considered for surgical resection. The standard treatment of the BT manifesting with an ICH is surgical removal of both the hematoma and the tumor. The optimal timing of the intervention has poorly been defined, especially when the patient has stable neurological status after admission and there is only a minimal or no mass effect on the (CT) scan.(6)

The synergistic management of GBM including surgical resection, radiotherapy, chemo/immuno/gene therapy, will lead to significant prolonged survival with good prognosis and improve the quality of life.(9)

Knowledge about the relationship between GBM and ICH is important, as the presentation, management, and outcome of ICH in patients with GBM differs from the general population, which in turn will alter the further oncological therapy, goals of care, and the expected prognosis of these patients.(5)

Objectives :

- To determine prevalence of patients who are presented with intra cranial hemorrhage and non-hemorrhagic which developed as complication of GBM grade four only who attending NNI, KFMC.
- To evaluate prognosis of GBM among grade four patients only presenting with intra cranial hemorrhage in KFMC (NNI).
- To assess predisposing factors which increase the risk in the development of ICH in GBM patients.

Research Project & Methodology

Study setting:

The data set used in this study involved 530 existing data recorded in the National Neuroscience Institute. This study is reviewed by NNI at King Fahd Medical City. The inclusion criteria included any patients (age >18) diagnosed with glioblastoma multiforme world health organization grade IV both male and female were included. The exclusion criteria is patients who have any hemolytic disease such as (hemophilia).

Study subjects:

A total of 89 patients with GBM, were identified, of which 26 patients were presented with ICH. Those patients received follow-up care in the King Fahd Medical City Clinic and were included in this study.

Study design:

A retrospective medical record review was performed from 2008 through 2013. Medical records encoded for patients with GBM were cross-referenced with medical records encoded for cases of non-hemorrhagic, intracranial hemorrhage and non-traumatic cerebral hemorrhage. Only those GBM patients who were followed in the King Fahd Medical City Clinic were included.

Method:

The research team reviewed the number of patients presenting with ICH among GBM, data of the predisposing factors that is common between ICH GBM and compared it with non hemorrhagic GBM patients that included different variables. This study evaluated the effect of (receiving anticoagulant, radiation dose, chemotherapy, surgical type, tumor size and location) on being a risk factor to develop ICH on GBM. In addition, the study reviewed the prognosis of ICH GBM patients and compared it with non hemorrhagic GBM patients (post operative survival rate).

As this study is intended to end with prevalence, risk factors and prognosis of hemorrhagic and non-hemorrhagic relative with glioblastoma multiforme among adult in KFMC. The sample size is

limited to patients with GBM . It is estimated that brain oncology clinic are 530 patients from which we estimated 89 patients with GBM, and they were divided into hemorrhagic 26 patients and non-hemorrhagic 63 patients. The study was not based on any sampling technique as it was involved with the whole population in the study. We used (T-Test) to find any difference in mean among quantitative data we also used (Chi – square test) to find any association between qualitative variables.

Patient data confidentiality and autonomy maintained at all levels, and the patient care is not affected by refusal to participate in the study. The data was coded so that identifying information was eliminated and separated in a different sheet so they were not included in the data collection sheet. The access to the data was limited only to the researchers who worked on it. We encrypted the data by using a computerized method, using a password-protected computer. The principle investigator and the co-investigators are the only persons who have access to the forms. We have obtained the IRB once the proposal was approved.

Management Plan

In our research, we managed the parts of work as follows:

Dr. Ahmad Lary: supervised the students in measures of the collected data (tumor size and location).
Dr. Ali balbaid: supervised the students in the part of data entry, data analysis and reviewed the final draft of the proposal and manuscript. Students (Saad Al-Maimouni and Rabea Qutub): prepared the learning contract, the consent form as approved by the National Neuroscience Institute in KFMC, and the research proposal. This was followed by data collection from the National Neuroscience Institute in KFMC database. After that, we entered the data in a computer program and performed the data analysis. Finally, we obtained the results and wrote the final manuscript.

Results

Table 1 and 2 illustrate patients' demographic data. The mean age of the non-hemorrhagic patients 50.3 ± 16.6 years, where the hemorrhagic patient's mean age 62.9 ± 18.1 years with T-test = -3.2 and P value = 0.002 . The mean of survival time in non-hemorrhagic patients is 2.5 ± 1.1 year while the mean of survival time in hemorrhagic patients is 1.8 ± 1.2 year with T-test = 2.7 and P value = 0.009. the mean of tumor size diameter in non-hemorrhagic patients is 4.1 ± 1.5 CM while the mean of tumor size diameter in hemorrhagic patients is 4 ± 1.3 CM with T-test = 0.19 and P value = 0.85

The female patients in the study account for 27 patients (30.3%) while the male patients account for 62 patients (69.7%). The alive patients account for 18 (20.2%) while the dead patients account 71 (79.8%). The hemorrhagic patients account for 26 (29.2%) while the non-hemorrhagic patients account for 63 (70.8%).

The radiological location of the tumor divided in to frontal lobe account for 34 patients (38.2%), partial lobe 21 patients (23.6%), temporal lobe 18 patients (22.2%), thalamus 5 patients (5.6%), occipital lobe 3 patients (3.4%), pineal body 3 patients (3.4%), cerebellum 2 patients (2.2%), basal ganglia 2 patients (2.2%) and hypothalamus 1 patients (1.1%).

In the surgical type gross total resection of the tumor account for 47 patients (52.8%), subtotal resection 29 patients (32.6%), biopsy 6 patients (6.7%) and patients with non-surgical intervention 7 (7.9%). Patients who have history of anticoagulants medication usage are 42 (47.2%) while patients who does not use anticoagulant medication are 47 (52.8%). Patients who had adjuvant chemotherapy

are 63 (70.8%), patients how had new adjuvant chemotherapy are 7 (7.9%), patients how had concurrent chemotherapy are 4 (4.5%) and patients how did not take chemotherapy are 15 (16.9%). The patients received radiation dose 30 GY and less were 17 (19.1%), patients who received dose range from 31- 59 GY were 31 (34.8%), patients how received 60 GY were 41 patients (46.1%).

Table 1. Illustration of patients' demographic data.

variable	count	column N %
gender	female	27 30.30%
	male	62 69.70%
event	alive	18 20.20%
	dead	71 79.80%
surgical type	gross total resection	47 52.80%
	subtotal resection	29 32.60%
	biopsy	6 6.70%
	no surgery	7 7.90%
hemorrhagic or non	non hemorrhagic	63 70.80%
	hemorrhagic	26 29.20%
chemotherapy	adjuvant	63 70.80%
	new adjuvant	7 7.90%
	concurrent	4 4.50%
	non	15 16.90%
history of anti-coagulant	no	47 52.80%
	yes	42 47.20%
radiation dose	≤30 GY	17 19.10%
	31-59 GY	31 34.80%
	60 GY	41 46.10%
radiological location	frontal lobe	34 38.20%
	parietal lobe	21 23.60%
	temporal lobe	18 20.20%
	thalamus	5 5.60%
	occipital	3 3.40%
	pineal	3 3.40%
	basal gangilia	2 2.20%
	cerebellum	2 2.20%
hypothalamus	1 1.10%	
variable	mean	Std. deviation
age	53.93	17.9
survival time	2.3	1.2
tumor diameter Cm	4.05	1.4

Table 2. Illustration of patients' demographic data.

variable	mean	std. deviation	t-value	p-value
age	Non-hemorrhagic	50.25	-3.2	0.002
	hemorrhagic	62.85		
survival time	Non-hemorrhagic	2.5	2.7	0.009
	hemorrhagic	1.8		
tumor diameter Cm	Non-hemorrhagic	4.1	0.19	0.85
	hemorrhagic	4		

Table 3 illustrates gender, radiological location and radiation dose in relation to hemorrhagic or non-hemorrhagic. The female who had hemorrhagic GBM were 8 patients (29.6%) while the non-hemorrhagic accounts for 19 patients (70.4%). The male who had hemorrhagic GBM were 18 patients (29%) while the non-hemorrhagic accounts for 44 patients (71%). We used chi-square test to find the significance of gender in relation to hemorrhagic GBM P value= 0.57

In radiological location of tumor, patients with frontal lobe hemorrhagic GBM account for 6 patients (17.6%) while patients with frontal lobe non-hemorrhagic GBM account for 28 patients (82.4%). Patients with parietal lobe hemorrhagic GBM account for 8 patients (38.1%) while patients with parietal lobe non-hemorrhagic GBM account for 13 patients (61.9%). Patients with temporal lobe hemorrhagic GBM account for 5 patients (27.8%) while patients with temporal lobe non-hemorrhagic GBM account for 13 patients (72.2%). Patients with other lobes (occipital, cerebellum, basal ganglia, thalamus, hypothalamus and pineal body) hemorrhagic GBM account for 7 patients (43.8%) while patients with other lobes non-hemorrhagic GBM account for 9 patients (56.2%). We used chi-square test to find the significance of tumor radiological location in relation to hemorrhagic GBM P value= 0.19

In the radiation dose, the hemorrhagic GBM patients who received 30 GY or less account for 6 patients (35.3%) while non-hemorrhagic GBM who received 30 GY or less account for 11 patients (64.7%). In the radiation dose, the hemorrhagic GBM patients who received 31-59 GY account for 8 patients (25.8%) while non-hemorrhagic GBM who receive 31-59 GY account for 23 patients (74.2%). In the radiation dose, the hemorrhagic GBM patients who received 60 GY account for 12 patients (29.3%) while non-hemorrhagic GBM who received 60 GY account for 29 patients (70.7%). We used chi-square test to find the significance of radiation dose in relation to hemorrhagic GBM P value= 0.79

Table 3. Illustration of gender, radiological location and radiation dose in relation to hemorrhagic or non-hemorrhagic.

variable		count	%	p-value	
gender	female	non-hemorrhagic	19	70.40%	0.57
		hemorrhagic	8	29.60%	
	male	non-hemorrhagic	44	71%	
		hemorrhagic	18	29%	
radiological location	frontal lobe	non-hemorrhagic	28	82.40%	0.19
		hemorrhagic	6	17.60%	
	parital lobe	non-hemorrhagic	13	61.90%	
		hemorrhagic	8	38.10%	
	temporal lobe	non-hemorrhagic	13	72.20%	
		hemorrhagic	5	27.80%	
other lobes	non-hemorrhagic	9	56.20%		
	hemorrhagic	7	43.80%		
radiation dose	≤ 30 GY	non-hemorrhagic	11	64.70%	0.78
		hemorrhagic	6	35.30%	
	31-59 GY	non-hemorrhagic	23	74.20%	
		hemorrhagic	8	25.80%	
60 GY	non-hemorrhagic	29	70.70%		
	hemorrhagic	12	29.30%		

Table 4 illustrates all variables in relation to the survival time by using cox-regression test. The relation of age to survival time has P value =0.75, which is not significant but in the odds ratio = 1.003 which means every year increasing age will have (0.3%) to increase survival time. We found that all variables in relation to survival time (by using cox-regression) do not have a significant effect on survival time.

Table 4. Illustration of all variables in relation to the survival time by using cox-regression test.

variable		p-value	OR	95.0% CI for OR	
				lower	upper
age		0.75	1.003	0.98	1.023
gender	male	0.406	1.29	0.708	2.35
	female*				
surgical type	gross total resection	0.075	0.362	0.12	1.107
	subtotal resection	0.305	0.565	0.189	1.68
	biopsy	0.822	1.16	0.315	4.28
	no surgery*				
tumor diameter Cm		0.074	1.19	0.983	1.44
hemorrhagic or non	hemorrhagic	0.081	0.578	0.312	1.071
	non-hemorrhagic*				
chemotherapy	adjuvant	0.194	1.75	0.752	4.07
	new adjuvant	0.396	1.75	0.481	6.36
	concurrent	0.645	1.42	0.31	6.27
	no chemo*				
history of anti-coagulant	yes	0.99	0.996	0.53	1.86
	no*				
radiation dose	≤ 30 GY	0.234	1.64	0.726	3.7
	31-59 GY	0.11	1.62	0.9	2.91
	60 GY*				
radiological location	frontal lobe	0.702	1.17	0.508	2.74
	parietal lobe	0.749	1.15	0.477	2.8
	temporal lobe	0.075	0.412	0.156	1.09
	other lobes*				

*female = censor *no surgery = censor *non-hemorrhagic = censor *no chemo = censor
 *no history of anti-coagulant = censor *60 GY = censor *other lobes = censor

Figure 1 illustrates survival time of hemorrhagic and non-hemorrhagic population in the study. The graph shows survival time for all population ranging from 0.3 to 4.9 years, with a severe sudden drop in the survival time of hemorrhagic GBM patients at the first year of diagnosis. In general, the five-year survival time decreased in both groups simultaneously after the second year of diagnosis but more in hemorrhagic GBM group.

Figure 1. Illustration of survival time for hemorrhagic and non-hemorrhagic population in the study.

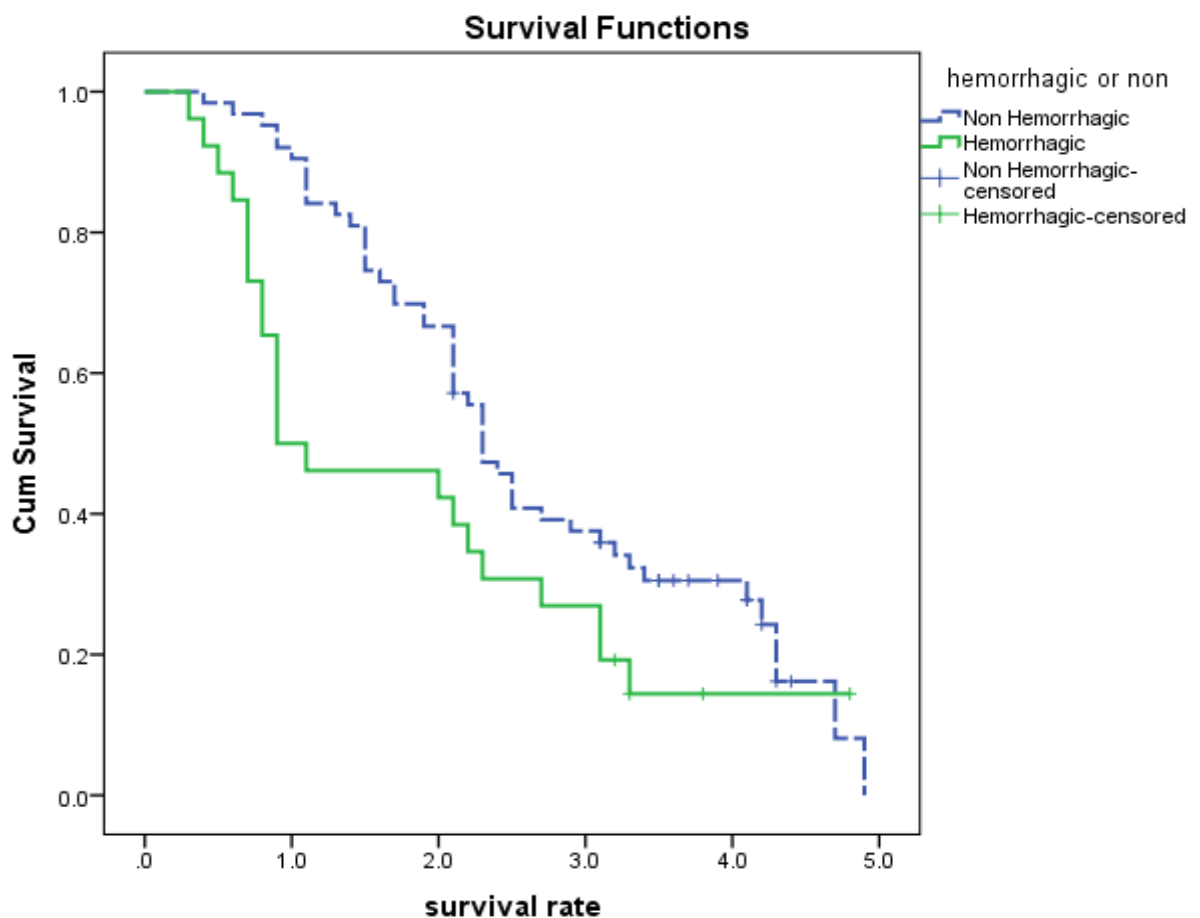


Table 5 illustrates all the variables in relation to the development of hemorrhagic GBM by using logistic regression. The relationship between age and the development of hemorrhage has P value =0.047, which is significant and in the odds ratio = 1.04, which means that every year that increases in age will account for (4%) of the development of hemorrhage.

The relationship between the total surgical resection of tumor that develops hemorrhage and no surgical intervention patients (censor) has a P value =0.25, which is not significant. However, the odds ratio = 4.15 which means that patients who had total surgical resection have more 4 times risk to develop hemorrhage than patients with no surgical intervention.

The relationship between frontal lobe location of tumor that develops hemorrhage and other lobes location(censor) has a P value =0.005, which is significant and in the odds ratio = 0.035 , which means that patients who have frontal lobe location of tumor are 96.5% less likely than other lobes to develop hemorrhage. The relationship between using anti-coagulant agent and the development of hemorrhage has a P value =0.05, which is significant and in the odds ratio = 1.80, which means that (80%) of the patients will have risk to develop hemorrhage.

We found no variables except (age, using anti-coagulant agent, and frontal lobe location of tumor) in relation to the development of hemorrhage by using logistic-regression were significant.

Table 5. Illustration of all the variables in relation to the development of hemorrhagic GBM by using logistic regression.

variable		p-value	OR	95.0% CI for OR	
				lower	upper
age		0.047	1.047	1.001	1.09
gender	male	0.677	1.35	0.327	5.59
	female*				
surgical type	gross total resection	0.25	4.15	0.368	46.89
	subtotal resection	0.926	0.893	0.082	9.67
	biopsy	0.16	9.87	0.405	240.5
	no surgery*				
tumor diameter Cm		0.169	0.701	0.422	1.16
survival time	dead	0.219	3.82	0.452	32.19
	alive*				
chemotherapy	adjuvant	0.988	0.987	0.186	5.25
	new adjuvant	0.298	0.204	0.01	4.09
	concurrent	0.071	28.61	0.753	1086.35
	no chemo*				
history of anti-coagulant	yes	0.05	1.80	0.410	5.92
	no*				
radiation dose	≤ 30 GY	0.473	0.511	0.082	3.2
	31-59 GY	0.176	0.327	0.064	1.65
	60 GY*				
radiological location	frontal lobe	0.005	0.035	0.003	0.354
	parietal lobe	0.224	0.258	0.029	2.29
	temporal lobe	0.153	0.214	0.026	1.77
	other lobes*				

*female = censor, *no surgery = censor, *alive = censor, *no chemo = censor, *no history of anti-coagulant = censor, *60 GY = censor, *other lobes = censor

Discussion

Little JR et al. (4) performed a study on brain tumor hemorrhage, the sample size was 13 adult patients, and the prevalence of intracranial hemorrhage among GBM was 6% diagnosed by CT scan. In our study, the prevalence of ICH in GBM was 29.2%. This variant in prevalence because of the sample size difference. Hou LC et al. (19) reviewed management options in GBM, he found that patients' survival ranged between 12 and 18 months with treatment, but patients without any intervention had less survival time. Scott found that the 2 years GBM patients survival time was 2.2% while the 5 years survival rate was less than 10%, and the final mortality rate was around 100%.

Tanaka S et al. (8) found that the median of overall survival in the study population was 5.5 months, and the 2 years survival rate was 6%. Stark AM et al. (9) reported on 267 GBM patients, they found that the median survival time was 47 weeks, ranging from 5-305 weeks.

In our study, the overall population mean survival, time was 2.3 ± 1.2 years, specifically in non-hemorrhagic GBM. The mean survival time was 2.5 ± 1.1 years while the hemorrhagic GBM mean survival time was 1.8 ± 1.2 years.

In 2005 a study by Korshunov et al. (14) demonstrated negative relationship between advanced age and post-operative survival. The 5 years survival of patients younger than 40 years old was 34% while patients older than 40 years had 6% for 5 years survival time.

Hou LC et al. (19) in a review of studies focused on GBM resection Nieder found that the median survival rate after total resection of GBM was 14 - 50 weeks. In a review of 222 patients of GBM, the study divided the population into 2 groups, one had surgical resection, chemo and radiation therapy, and the other group had chemo and radiation therapy. They found that the median survival time was 36 weeks following resection while the other group's median survival time was 23 weeks.

Tanaka S et al. (8) the study demonstrated that the patients who received chemotherapy with radiation therapy had significant longer survival time compared to patients who received radiation therapy alone. The study summarized the predisposing factors associated with poor survival time. The factors included, older age, deep lesion, multifocal lesions, lack of adjuvant treatment, and surgical intervention (biopsy only). Stark AM et al. (9) suggested that variables which prolonged survival time significantly were age younger than 61, total surgical resection of tumor, and radiotherapy ≥ 54 GY combined with chemotherapy.

In our study, we found that the relationship between age and survival time was not significant. We also found out that the relationship between total surgical resection and the survival time was not significant; however, according to odds ratio total, surgical resection will increase survival time by 64% compared to non-surgical intervention patients.

Moreover, we found out that radiation therapy and chemotherapy do not significantly improve survival time; however, according to the odds ratio, different types of chemotherapy can improve the survival time from 42% to 75% compared to patients who did not receive chemotherapy.

In addition, the radiation therapy also did not significantly improving the survival time. This might go back to the limited number of patients admitted in king Fahad Medical City neurosurgery department; however, the odds ratio showed that radiation dose ≥ 30 GY will improve the survival time by 64%.

Tanaka S et al. (8) demonstrated the highest percentage of ICH in patients diagnosed with GBM how had surgical biopsy. In our study, the relationship between biopsy surgical intervention and the development of hemorrhage was not statistically significant. However, odds ratio showed that

biopsy can increase the development of ICH by nine times compared to patients who had no surgical intervention.

Conclusion

The prevalence of hemorrhagic GBM in the study population 29.2%, where the non-hemorrhagic GBM accounted for 70.8%. The prevalence of hemorrhagic GBM in relation to the gender was almost the same between males and females (29 %). Hemorrhagic GBM patients' mean survival time was (1.8 years), and they had worse prognosis (less survival time) than non-hemorrhagic GBM patients did.

The predisposing factor, which increased the risk of the development ICH in GBM patients, was increasing age of the patient and using anticoagulant agent. Frontal lobe location was the least prognostic factor to develop ICH in GBM patients comparable to other lobes locations.

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