INTRODUCTION

Primary brain tumors account for about 2% of all malignant neoplasms in adults. Approximately half of them represent gliomas. Glioblastoma multiforme (GBM) derived from neuroepithelial cells is the most frequent and deadly primary malignant central nervous system (CNS) tumor in adults ***(Stupp et al., 2005).*** GBM accounts for 60%e70% of all gliomas in the adult population ***(Li et al., 2015)***. According to the National Database of Central Brain Tumor Registry of the United States (CBTRUS), the age-adjusted GBM incidence rate is 3.97 cases per 100,000 for men and 2.53 cases per 100,000 for women. GBM cases represent about 20% of all primary CNS tumors in the adult population and about 75% of all anaplastic gliomas. Patients younger than 20 years have a lower incidence rate and frequency rapidly increases starting in the fifth decade of life ***(Furnari et al., 2007).***

Epidemiologic studies of glioma have examined many risk factors over the past several decades; however, there are few consistent findings. GBM remains one of the most challenging treatment tasks in clinical oncology. The median survival of patients with GBM treated only with the use of neurosurgical procedures and supportive care is 4.2 months ***(Arvold et al., 2014).*** The median survival time after surgical treatment followed by chemoradiation therapy also remains poor at 14.6 months ***(Stupp et al., 2005).***

A close study in adults age recognized four prognostic subgroups based on age, extent of surgery (biopsy versus resection), and KPS; median survival ranged from 2.3 months in subgroup IV (biopsy only, KPS <70) to 9.3 months in subgroup I (surgical resection, age <75.5) ***(Scott et al., 2012).***

Clinically, patients with GBM may exist with headache, focal neurologic deficits, confusion, memory loss, personality changes or with seizures. Diagnosis and treatment response is suggested by magnetic resonance imaging (MRI) and the use of adjunct technology such as functional MRI, diffusion-weighted imaging, diffusion tensor imaging, dynamic contrast-enhanced MRI, perfusion imaging, proton magnetic resonance spectroscopy and positron-emission tomography ***(Wen and Kesari, 2013).***

Maximal surgical resection, post-operative concomitant chemo-radio therapy and adjuvant temozolomide or carmustin wafers after that is the standard of care in patients younger than 70 years old with newly diagnosed GBM. Although, recurrence seems to be the rule despite standard care. Lately, attention has been given to understand the primary molecular pathogenesis of these tumors involving alterations in cellular signal transduction pathways, the existance of resistance to therapy and to find methods to penetrate easier the natural blood-brain barrier (BBB). Regardless of these efforts to treat but, it remains an incurable disease and the prognosis falls in a poor survival range of 12–15 months (median 14.6 months) and a

mean survival rate of only 3.3% at 2 years and 1.2% at 3 years ***(Stupp et al., 2005).***

Glioblastoma (GBM), the most common malignant primary brain tumor in adults, has a diverse prognosis despite aggressive therapeutic intervention ***(Dolecek et al., 2012).*** There has been a great increase in the understanding of molecular alterations, both genetic and epigenetic, in GBMs. However, the number of clinically relevant molecular markers for GBM prognostication remains limited. Also, the best panel of molecular markers to be used in routine practice remains debatable. Among the molecular alterations, isocitrate dehydrogenase 1 (IDH1) mutation has been shown to be a prognostic marker associated with longer overall (OS) as well as progression-free survival (PFS) ***(Nobusawa et al., 2009).*** The methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) promoter is another well-established prognostic and predictive marker ***(Hegi et al., 2005).*** Recently, mutations in the promoter region of telomerase reverse transcriptase (TERT), the gene encoding catalytic subunit of telomerase, have been described in gliomas especially in GBMs and correlated with poor clinical outcome ***(Huang et al., 2013)***. Few recent studies have suggested various prognostic subgroups. Thus, ***Molenaar et al. (2014)*** reported a two-gene predictor for GBM survival and, based on the combination of IDH1 and MGMT status, stratified GBMs into three prognostically distinct genotypes. Another study by

Kellia et al. (2014) demonstrated three prognostic molecular subgroups of GBMs based on TERT and IDH1 status. Recently, ***Eckel-Passow et al. (2015)*** combined TERT mutation with IDH1 mutation and 1p/19q co-deletion status and described five distinct prognostic subgroups of gliomas. GBMs having only IDH1 mutation had the best prognosis, whereas those with TERT mutation only had the worst PFS/OS ***(Eckel-Passow et al., 2015).*** However, the drawback of all these studies is that they do not simultaneously incorporate other important genetic alterations in GBMs such as TP53 mutations and RTK and NF1 alterations for survival analysis, which may be important confounding factors in determining clinical outcomes.

AIM OF THE WORK

This is a retrospective study of glioblastomamultiforme patients presented to Ain Shams University Hospital between the period of 1/2012 till 12/2016 aiming at detection of the prognostic factors, response to the therapy used, progression free survival and overall survival.

REVIEW OF LITERATURE

Epidemiology

Incidence and Prevalence

The SEER registry reports that the incidence of primary CNS tumors is between 2.2 and 8.3 per 100,000 people per year, based on race and gender (for all races, the incidence is 7.7/100,000 men and 5.4/100,000 women, with the extreme deviations being 8.3/100,000 white men and 2.2/100,000 American Indian/Alaska Native women). This translates to an estimated case load in 2007 of 20,500 (11,170 men and 9,330 women), with an anticipated 12,740 deaths, and an age-adjusted death rate of 4.4/100, 000. In the SEER system, the incidence rate of primary malignant brain and CNS tumors (excluding lymphomas, leukemia, tumors of pituitary and pineal glands, and olfactory tumors of the nasal cavity) for the years 2005-2009 is 6.5 cases per 100,000 ***(Howlader et al., 2012).***

Glioblastoma multiforme (GBM) is the most aggressive glioma of astrocytic lineage. According to the 2015 Central Brain Tumor Registry of the United States (CBTRUS) report, the average annual age adjusted incidence rate (IR) of GBM is 3.2/100,000 population ***(Ostrom et al., 2015).*** Anaplastic astrocytoma and glioblastoma increase in incidence with age, the peak incidence being in the fifth and sixth decades of life ***(Yongzhi and Tao, 2013).***

The National Cancer Registry Program of Egypt (NCRPE). Damietta profile over 2009, 67 Brain and Nervous System cancer cases were registered. Glioblastoma was the uppermost histological type, (35.7%) followed by astrocytoma (21.4%) ***(Ibrahim et al., 2011).***

The National Cancer Registry Program of Egypt (NCRPE). El-Minia profile Over 2009, 343 Brain and Nervous System cancer cases were registered in Minia. Out of 69 cases with registered pathological diagnosis, glioblastoma was the uppermost histological type (21.7%) ***(The National Cancer Registry Program of Egypt (NCRPE). El-Minia, 2009*).**

In the Clinical Oncology department of Ain Shams University Hospitals, all newly diagnosed cases with CNS tumors have been registered from 30 May 2012 to 1st June 2013 using the NCRPE registry form. CNS tumors accounted for 53 newly diagnosed cases (5.6%) and was classified as the fourth common cancer in both sexes. 54.7% of CNS tumors occurred in males. The mean age was 43.1 years ± 19.5 SD. 62.3% of the cases were from Cairo, 20.8% were from Upper Egypt and 8% were from Lower Egypt. 54% of the lesions were overlapping and 13% of the cases were presented with frontal lobe lesions at time of diagnosis. Glioblastoma Multiforme was the most predominant pathology occurring in about 43.3% of the presented cases ***(Anwar et al., 2014).***

Etiological Factors

i. Environmental Factors

The key epidemiologic factors of glioma risk include advancing age, male sex, and Caucasian race. Ionizing radiation is one of the few factors shown to have a powerful association with the development of brain tumors. Exposure to ionizing radiation represents the most important exogenous risk factor for childhood brain tumors. Prenatal diagnostic x-ray exposure increases the risk of childhood brain tumors. A large amount of data has been gathered on the incidence of brain tumors in patients who received cranial irradiation for the treatment of acute lymphoblastic leukemia (ALL). The evaluated cumulative risk of secondary malignant brain tumors after childhood ALL therapy is 0.5% at 10 years after completion of therapy ***(Jimmy, 2011).***

Interest has emerged in a possible relationship between use of cellular telephones and the risk of brain tumors. Case-control studies were unable to show a link between the duration of cell phone use and the development of gliomas, meningiomas and acoustic neuromas ***(Wrensch et al., 2010).***

Other large case-control studies also have failed to find any correlation between cell phone use and the risk of developing brain tumors. However, some still claim that there is a link between brain tumors and cell phone use ***(Hepworth et al., 2006).***

ii. Viral Associations

Although certain CNS tumors may have a viral association, the human evidence remains delicate. Specifically, no increase in the risk of developing a brain tumor has been associated with previous polio vaccination, which discredits claims that simian virus 40 contaminating older polio vaccine preparations cause brain tumors ***(Brenner et al., 2013).***

iii. Hereditary Syndromes

Most gliomas are sporadic, but genetic vulnerability is suspected based on the occurrence of several brain tumors in families with germline mutation of the TP53 suppressor gene and patients with neurofibromatosis type I, Li-Fraumeni syndrome as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome subscribes to less than 5% of GBMs ***(Farrell and Plotkin, 2007).***

Prognostic factors

Of the estimated 17,000 primary brain tumors diagnosed in the US each year, approximately 60% are gliomas ***(Uddin and Jarmi, 2007).*** Glioblastoma (GB), or grade IV astrocytoma, is the most aggressive of primary tumors of the brain for which no cure is available. Management remains palliative and includes surgery, radiotherapy, and chemotherapy. With optimal treatment, patients with GBs have a median survival of less than one year ***(Bruce et al., 2006).*** About 2% of patients survive three years ***(Scott et al., 2009).*** Previously reported

long-term survivors (LTSs) of GB may have been patients who actually harbored other low-grade gliomas ***(McLendon and Halperin, 2011)***. The overall prognosis for GB has changed little since the 1980s, despite major improvements in neuroimaging, neurosurgery, radiotherapy, and chemotherapy techniques.

We found that patient survival depends on the following clinical and biologic parameters: tumor size and location, treatment, age at presentation, performance status, histologic findings, and molecular genetic factors.

- **Tumor size and location**

GB is a highly infiltrating tumor and most of the time cannot be resected completely; hence, surgery often consists of incomplete debulking. The feasibility and extent of surgical resection depends on tumor size and eloquence of the brain areas (location). Supratentorial and cerebellar tumors are more amenable to surgical treatment and thus carry better prospects than tumors in the brainstem or diencephalon. Stereotactic biopsy, followed by radiotherapy, may be a more appropriate treatment for these patients ***(Coffey et al., 2012).*** Case management with best supportive care for patients with unresectable, primary, biopsy-proven GB results in a median survival time of three months ***(Nieder et al., 2005).***

- **Treatment**

Clinical evidence suggests that an aggressive and multimodal treatment results in longer survival ***(Kleinschmidt-De Masters et al., 2006).*** Total or subtotal resection, combined with radiotherapy and chemotherapy, is the mainstay of treatment. New therapies that are still under investigation have shown some promising results. For example, in a report of a study by ***Dehdashti et al. (2007)*** brachytherapy was used as a boost to radiotherapy: three patients lived 11, 16, and 18 years, respectively, in the basic group, but unfortunately, statistics did not reveal any significant association with brachytherapy ***(Dehdashti et al., 2007).*** In another example, temozolomide has proved to significantly prolong survival when used as an adjuvant chemotherapy to radiotherapy ***(Minniti et al., 2008).*** Regarding intra-arterial chemotherapy, a survival benefit in comparison with intravenous administration was not established ***(Imbesi et al., 2006).***

- **Age at presentation**

Nearly all studies showed a significant negative relationship between advancing age and duration of postoperative survival ***(Korshunov et al., 2005).*** In a report of a study by ***Korshunov et al. (2005)*** the percentage of patients younger than age 40 years who survived more than five years was 34%, compared with 6% for patient's age 40 years old and older. The researchers suggested age 40 years as the most appropriate cutoff for dividing patients with GB into groups according to prognosis.

- **Karnofsky performance score (KPS) at presentation**

Many studies' findings show that higher KPS at presentation correlates with improved outcome ***(Krex et al., 2007).*** This is most probably linked to the factor of younger age at diagnosis.

Tumor size and location, treatment, age at presentation, and KPS at presentation allow stratification of patients into risk groups. ***Lamborn et al. (2014)*** identified four risk groups. The two lower-risk groups included patients younger than age 40 years, the lowest risk group being young patients with tumor in the frontal lobe only. An intermediate-risk group included patients with a KPS >70, subtotal or total resection, and between ages 40 and 65 years. The highest-risk group included all patients older than age 65 years and patients between ages 40 and 65 years with either KPS <80 or biopsy only. Subgroup analyses indicated that inclusion of adjuvant chemotherapy provides an increase in survival, although that improvement tends to be minimal for patients older than age 65 years, for patients older than age 40 years with KPS <80, and for those treated with brachytherapy.

- **Histologic findings**

The higher the grade of tumor, the more malignant the tumor is and the worse the prognosis is. Tumors are graded mainly on the basis of their proliferation index, which is an important prognostic factor in GB. The Ki-67 protein is expressed in all phases of the cell cycle except G0 and serves as

a good marker for proliferation. Studies that have evaluated proliferation index by Ki-67 immunohistochemistry in GB have shown a significant correlation between high proliferation rates and shorter disease-free and overall survival ***(McLendon and Halperin, 2011).***

The cytologic and histologic composition of glioblastoma has an impact on survival. Microcystic change, the presence of cells with obvious astrocytic differentiation (fibrillary astrocytes), and the subjective impression that areas of better differentiation are present has been associated with a better outcome. Another histologic factor, calcification, was in one study associated with a better prognosis. A significant relationship also exists between the presence of necrosis and poor outcome ***(Burger and Green, 2011). Korshunov et al. (2002)*** found that some histologic and genetic markers that were significant for outcome appeared to be closely related to biology of single cytologic subsets. So they divided GB into three cytologic subsets: small-cell GB (SGB), pleomorphic-cell GB (PGB), and gemistocytic GB (GGB).

- **Molecular genetic factors**

Cytogenetic and molecular genetic studies of GB have shown that the most frequent alterations encountered in these tumors are 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. More p53 expression was reported in LTSs (>3 years) and overexpression of MDM2 in short-term survivors (<3 years) ***(Burton et al., 2002).***

Korshunov et al. (2002) found that the number of p53-positive tumors prevailed among the PGB, whereas the number of tumors with EGFR and MDM2 positivity was significantly greater in SGB. GGB contained the significantly lowest mean proliferating cell nuclear antigen (PCNA) labeling index (LI), greater number of p21*ras*-positive cases, and higher mean apoptotic index (AI). Thus, there is a relationship between histologic and genetic markers. Survival time in patients with SGB, EGFR, and MDM2 positivity and PCNA LI >40% was found to be significantly shorter, whereas presence of p21*ras* and AI >0.5% were associated with prolonged survival. In another study, ***Korshunov et al. (2005)*** found that being younger than age 40 years is strongly associated with a favorable prognosis. EGFR amplification, loss of 9p21, and gain of chromosome 9 had prognostic significance for all patients, whereas gain of chromosome 7 and loss of 10q23/*PTEN* showed clinical importance only for patients age 40 years and older. ***Krex et al. (2007)*** studied 55 patients with GB who lived more than three years. They found significantly more frequent O6-methylguanine–DNA methyltransferase (MGMT) hypermethylation in LTSs ***(Krex et al., 2007).*** Interestingly, the protein product of MGMT gene, 06

alkylguanine–DNA alkyltransferase, was shown to be involved in tumor resistance to alkylating agents. Silencing of the MGMT gene by promoter methylation compromises DNA repair and has been associated with longer survival in patients with glioblastoma who receive alkylating agents ***(Crinière et al., 2007).*** Clinical trials for malignant gliomas now often include determination of MGMT expression status.

Recently, ***Marko et al. (2008)*** identified a set of 1478 genes with significant differential expression ($p < 0.01$) between long-term and short-term survivors and, with additional mathematic filtering, isolated a 43-gene "fingerprint" that distinguished survival phenotypes. Gene ontology analysis of the fingerprint demonstrated pathophysiologic functions for the gene products that are consistent with current models of tumor biology, suggesting that differential expression of these genes may contribute etiologically to the observed differences in survival.

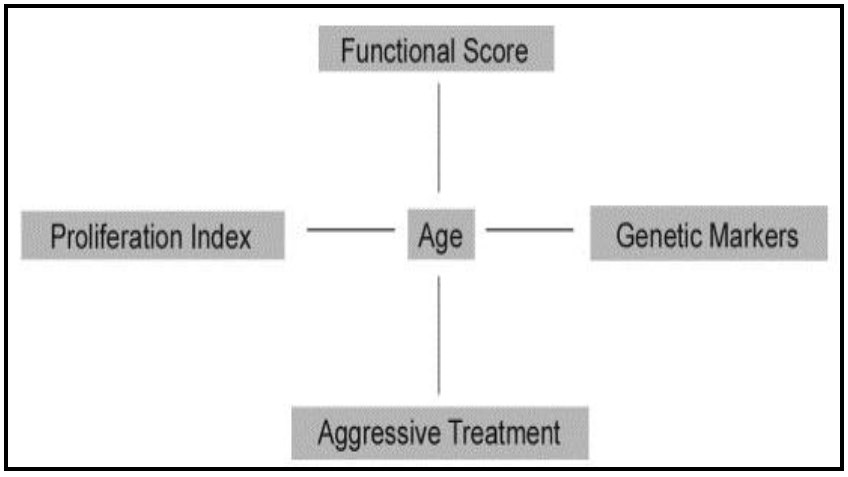

Figure (1): Interaction of prognostic factors for patients with glioblastoma.