A Retrospective analysis of high grade glioma cases treated in N.C.I in the period from 2000-2009

Thesis submitted for partial fulfillment of master degree in clinical oncology

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2012

Abstract

This is a retrospective analysis of high grade glioma cases treated in N.C.I during the period from 2000-2009.

The most important prognostic factors in literature were tumor grade, performance status, radiation dose, extent of surgery and use of concurrent and adjuvant temozolamide.

The independent prognostic factors in this study were tumor grade, performance status and radiation dose.

Extent of surgery & effect of temozolamide were not evident in our study due to very limited no. of patients who received temozolamide or underwent GTR.

Limitations in this study were bad recording in files, selection bias, improper assessment of performance status and grading of toxicity and irregular follow up of the patients.

Key Words :

glioma cases - primary brain - gliomas requires .

Acknowledgement

Foremost, I would like to express my sincere gratitude to my advisor Prof. Tarek Shouman for the continuous support of thesis, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my thesis.

Besides my advisor, I would like to thank the rest of my thesis committee: Prof. Iman Abd El Hady and Dr. Sherwif Abd El Fattah, for their encouragement, insightful comments, and hard questions.

Last but not the least, I would like to thank my family: my parents & my wife, for supporting me spiritually throughout my life.

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Introduction

Malignant astrocytoma; glioblastoma multiforme (WHO grade IV), and anaplastic astrocytoma (WHO grade III) are the most common primary brain tumors in adults. Glioblastoma multiforme (GBM) comprises 80% of malignant gliomas. While malignant astrocytomas comprise only 2% of all adult tumors at a rate of 5 cases per 100,000 adults per year, their malignant nature makes them the fourth greatest cause of cancer death ***(Davis F et al., 1998).***

Treatment of high grade gliomas requires a multimodality approach with combination of surgery, radiation therapy and chemotherapy.

Surgery aims at (1) to establish the histology of the lesion (2) to debulk the mass effect of the tumor to correct a neurologic deficit and to prevent imminent death in patients with large tumors and early herniation syndromes; and (3) to debulk the tumor to increase efficacy of radiation therapy and chemotherapy, which produce the best response rate when they are used with minimal tumor burden ***(Jackson RJ et al., 2001).***

Radiation therapy in addition to surgery is a standard of care based on results of at least three randomized trials conducted in the 1970s, which showed significant improvement in overall survival compared to observation ***(Walker MD et al., 1978, 1980& Andersen et al., 1978).***

Recent advances in radiation technology aims at more precise dose delivery and minimizing dose to normal structures.

Concurrent and adjuvant chemotherapy role has emerged as a standard of care after the results of the landmark EORTC trial, which showed significant

survival improvement in the favor of the arm of chemoradiation ***(Stupp R.,et al.,2005).***

Poor treatment outcomes of high grade gliomas remain a challenging issue for the physicians which need more efforts in order to improve treatment results.

Aim of work

This is a retrospective analysis of high grade gliomas cases treated in radiation therapy department in N.C.I, Cairo University, in the period from 2000-2009.

All treatment data & results will be collected and correlated with the different prognostic factors, in order to compare our results with the internationally recognized results.

Epidemiology& Molecular biology

In the year 2008, an estimated 21,810 new cases of primary CNS tumors will be diagnosed in the U.S. These tumors will be responsible for about 13,070 deaths ***(Maher EA., et al, 2003).***

In Egypt, there is no clear data about the incidence of high grade gliomas in the population, but in NCI, this group constituted only 0.21% of total malignancy with a slight adult predominance of 54.44% and no sex predilection (50% each). The low number of such tumors could be attributed to the lack of neurosurgery practice at NCI. ***(Mokhtar N. et al, 2007)***

Malignant astrocytoma; glioblastoma multiforme (WHO grade IV), and anaplastic astrocytoma (WHO grade III) are still the most common primary cerebral neoplasms in adults. These highly invasive tumors have a strong predilection for cerebral hemispheres. Glioblastoma multiforme (GBM) comprises 80% of malignant gliomas. While malignant astrocytomas compromise only 2% of all adult tumors at a rate of 5 cases per 100,000 adults per year, their malignant nature makes them the fourth greatest cause of cancer death ***(Davis F et al., 1998).***

Malignant astrocytomas are associated with a slight male to female preference (1.6:1.0). The peak age at onset for GBM is in the sixth or seventh decade, whereas anaplastic astrocytoma (AA) usually presents in the fourth or fifth decade. GBM (0.2/100,000 per year) and AA (0.5/100,000 per year) rarely occur in children less than 14 years of age. While malignant astrocytomas occur less commonly in African-Americans, no national differences in incidence have been consistently demonstrated after racial and age correction. Recent evidence suggests that the incidence of GBM and AA have doubled over the past decade. While the significance of this

observation is unclear, many believe this to be a result of the increased use of MRI and CT ***(Davis F et al., 1998).***

Malignant gliomas, like most aggressive cancers, exhibit aberrant proliferation, diminished apoptosis, avoidance of both external growth control and immunoregulation, and striking rates of de novo and acquired resistance to therapeutic intervention. An enigmatic and unique behavioral feature, however, is a nearly absent rate of metastatic dissemination beyond the CNS, despite highly robust invasive and angiogenic capabilities. Another distinguishing characteristic is marked histopathologic and genetic heterogeneity across and within tumors***. (Burger PC et al.,1995 & Klelheus P et al., 2000).***Many molecular genetic abnormalities associated with phenotypic features are being increasingly characterized and include multiple abnormalities that span several critical regulatory arenas, such as genomic instability, cell cycle control, and intracellular communication via signal transduction pathways***(Rich JN et al.,2004).***

Disruption of p53 function, a key regulator of genomic stability, occurs frequently in malignant glioma due to either direct mutation or loss (***Von Deimling A, 1992).*** *P14ARF* mutation ***(Nakamura M et al., 2001)*** or human double-minute 2(*HDM2*) amplification ***(Biernat W et al., 1997)*** Additional genetic abnormalities contribute to dysregulation of cell cycle control, including *CDK4* amplification or loss of either RB1, p16INK4A or P15INK4B, due to either inactivating mutation or promoting hypermethylation ***(Jen J et al.,1994).***

Malignant gliomas also frequently exhibit abnormalities of signal transduction pathways that control key cellular processes including proliferation, angiogenesis, apoptosis, and invasion. Dysregulation of the PI3K/AKTpathway, the most prominent abnormal signaling cascade

(Vivanco I et al., 2002 & Choe G et al., 2003) is associated with adverse outcome and has been linked with two primary, triggering genetic defects. First, increased activity of growth factor receptor tyrosine kinases (TKIs), due to receptor overexpression, amplification, or mutation, can increase PI3K/AKT activity. The most common abnormally active growth factor TKIs in malignant gliomas include the epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (*PDGFR*), c-kit, and insulin-like growth factor-1 receptor (IGF1R). ***(Libermann TA et al., 1995)*** The most common *EGFR* mutation in malignant glioma, *EGFRvIII*, is created by intragenic deletion of exons 2 to 7, and exhibits ligand independent, constitutive signaling ***(Wong AJ et al., 1987 & Sugawa N etal., 1990)*** A second genetic defect linked with aberrant PI3K/AKT signaling is loss of the tumor suppressor gene, and negative regulator of AKT, phosphatase, and tensin homolog deleted on chromosome 10 (*PTEN*), which occurs in approximately 30% of GBM tumors ***(Li J et al.,1997 & Raffel C et al.,1999).***

Traditionally, GBMs are classified into either primary or secondary subtypes based on clinical and genetic features, although morphologic and microscopic characteristics of both subtypes are indistinguishable. Primary GBMs, which account for 95% of cases, arise de novo after a short clinical history, typically affect older patients, exhibit a male predominance, and frequently display aberrant PI3K/AKT signaling due to EGFR overexpression or PTEN loss.

In contrast, secondary GBMs are relatively rare, arise from preexisting

lower grade gliomas, are more commonly seen in younger patients, exhibit a female predominance, and are characterized at the molecular level

by mutation of *TP53* and *RB1*, as well as either amplification or increased expression of PDGFR ***(Ohgaki H et al., 2004)*** Of note, a recent population-based analysis revealed that the most common genetic abnormality in newly diagnosed GBM patients is loss of the distal region of chromosome 10q. This finding occurs with equal frequency among both primary and secondary GBMs. Furthermore, in this extensive analysis, loss of distal 10q was the only genetic abnormality shown to confer a negative prognosis independent of clinical factors ***(Ohgaki H et al., 2004).***

Pathology

Several grading systems have been formulated that rely solely on cytological and histological characteristics. Currently, the World Health Organization system is the most widely used and differentiates three grades of astrocytomas: WHO grade 2 (low-grade astrocytoma), WHO grade 3 (anaplastic astrocytomas), and WHO grade 4 (glioblastoma multiforme). WHO grade 3 (AA) and WHO grade 4 (GBM) are considered malignant or high-grade gliomas. The spectrum from grade 2 to 4 is characterized by increased cellularity and pleomorphism, higher mitotic rate, and the presence of vascular proliferation and necrosis. The finding of vascular proliferation and necrosis is required for the diagnosis of grade 4 ***(Burger PC et al., 2002).***

WHO grade is one component of a combination of criteria used to predict a response to therapy and outcome. Other criteria include clinical findings, such as age of the patient, neurologic performance status and tumour location; radiological features such as contrast enhancement; extent of surgical resection; proliferation indices; and genetic alterations. For each tumour entity, combinations of these parameters contribute to an overall estimate of prognosis. Despite these variables, patients with WHO grade II tumours typically survive more than 5 years and those with grade III tumours survive 2–3 years. The prognosis of patients with WHO grade IV tumours depends largely upon whether effective treatment regimens are available. The majority of glioblastoma patients, particularly the elderly, die within a year. For those with other grade IV neoplasms, the outlook may be considerably better. For example, cerebellar medulloblastomas and germ cell tumours such as germinomas, both WHO grade IV lesions, are rapidly fatal

if untreated, while state-of-the-art radiation and chemotherapy result in 5-year survival rates exceeding 60 and 80%, respectively.

Table1: World Health Organization Classification of Primary Central Nervous System Tumors

Major Classification of Tumors	**WHO Grade**
Astrocytic tumors	
Pilocytic astrocytoma	I
Diffuse astrocytoma	II
Anaplastic astrocytoma	III
Glioblastoma	IV
Gliosarcoma	IV
Oligodendroglial tumors	
Oligodendroglioma	II
Anaplastic oligodendroglioma	III
Oligoastrocytic tumors	
Oligoastrocytoma	II
Anaplastic oligoastrocytoma	III
Ependymal tumors	
Ependymoma	II
Anaplastic ependymoma	III
Choroid plexus tumors	
Choroid plexus papilloma	II
Atypical choroid plexus papilloma	III
Tumors of the pineal region	
Pineocytoma	I
Pineoblastoma	IV
Neuronal and mixed neuroglial tumors	
Anaplastic ganglioglioma	III
Tumors of the Pineal region	
Pieneocytoma	I
Pineoblastoma	IV

Embryonal tumors Medulloblastoma	IV
CNS primitive neuroectodermal tumors(PNETs)	IV
Tumors of the cranial and paraspinal nerves Schwannoma	I
Neurofibroma	I
Meningeal tumors Meningioma	I
Anaplastic meningioma	II
Hemangioblastoma	I
Tumors of the sellar region Craniopharyngioma	I
Pituicytoma	I

Prognostic factors:

A recursive partitioning technique was applied to an analysis of 1578 patients accrued to three successive Radiation Therapy Oncology Group (RTOG) trials ***(Curran WJ Jr. et al., 1993).*** Age, histological appearance, Karnofsky performance status (KPS), mental status, duration of symptoms, neurological functional class, extent of surgery, and radiation dose were identified as significant partitioning covariates. Six patient classes were defined with different prognosis as favorable (classes I and II), intermediate (classes III and IV) and poor (classes V and VI). A subsequent reanalysis of data in glioblastoma patients showed no statistical difference between class V and VI with a median survival of 7.5 months. ***(Shaw EG et al., 2003).***

Table 2: RTOG recursive partitioning analysis

Class	Definition
I	Age< 50,anaplastic astrocytoma, and normal mental status
II	Age ≥ 50, KPS 70-100, anaplastic astrocytoma, and at least 3 months from time of onset of symptoms till initiation of treatment
III	- Age< 50, anaplastic astrocytoma and abnormal mental status. - Age< 50, GBM and KPS 90-100
IV	- Age<50, GBM and KPS < 90 - Age ≥ 50, KPS 70-100, anaplastic astrocytoma, and 3 months or less from time of first symptoms to initiation of treatment. - Age>50, GBM, surgical resection and good neurological function
V	- Age>50,KPS 70-100, GBM either surgical resection and neurological function that inhibits the ability to work or biopsy only followed by at least 54.4 Gy of RT. - Age ≥ 50, KPS < 70, normal mental status
VI	- Age ≥50, KPS< 70, abnormal mental status. - Age ≥50, KPS 70-100, GBM, biopsy only and receiving less than 54.4 Gy of RT.

Clinical Presentation

Symptoms or signs of brain tumors are produced by the tumor mass, the adjacent edema, or the infiltration and destruction of normal tissue. However, these symptoms and signs and are best appreciated by considering the tumor location and growth rate. For example, rapidly growing tumor located in eloquent cortex or along the ventricular system may manifest after only a small amount of growth. Those in less eloquent areas of the brain may manifest only after substantial growth. Moreover, no specific sign or symptom is pathognomonic for a brain tumor.

Brain tumor symptoms may be general, localizing, or falsely localizing. General symptoms include headache, lethargy, nausea, vomiting, and vague balance difficulties. These symptoms tend to be manifestations of increased ICP from a combination of expanding tumor volume and the production of associated vasogenic cerebral edema. Tumors also may cause raised ICP by obstruction of the ventricular system or blockage of the venous sinuses. Abrupt headache and exacerbation of neurologic signs may accompany the plateau waves of sudden increased ICP.

Headache results from traction on pain-sensitive structures of the intracranial contents including the large cerebral vessels, the dura and meninges, the venous sinuses, and cranial nerves V and IX. Headache is the most common symptom of a brain tumor and occurs in approximately 50% of patients at some time during the course of the illness ***(Forsyth PA et al., 1993)*** Headache more frequently accompanies rapidly growing than slowly growing tumors. Tumors located in neurologically noneloquent brain areas such as the nondominant frontal and temporal lobes may manifest with