Debulking surgery and Radiotherapy versus Biopsy and Radiotherapy in patients with High Grade Gliomas.

A systematic review.

A research submitted for partial fulfillment of the conditions for the Master Degree in Neurosurgery.

By

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2017

ACKNOWLEDGEMENT

First of all, thanks to ***ALLAH*** who gave me the power to accomplish this work. I would like to express my sincere gratitude to my advisor ***Prof.Dr.Salah Abd Al-Khalek Hemida,*** for his continuous support, patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this review

Beside my advisor, I would like to thank ***Asst.Prof.Dr.Hesham Anwar,*** and ***Dr.Ahmed Roshdy,*** not only for their insightful comments and encouragement, but also for the hard questions which pushed me to widen my research from various perspectives.

My sincere thanks also go to ***Prof.Dr.Mohamed Tawfik Hosny,*** the chairman of neurosurgery department, Maadi Military Medical Complex for for his kind help, valuable guidance, assistance and encouragement.

No words can describe my intense gratitude to ***Prof.Dr.Emad Khattab,*** for his unconditional support, continuous motivation, absolute patience and valuable life experience he shared with me. He always pushes me forward and stands by my side in all my work problems and life issues.

For ***all the Neurosurgery staff members,*** Maadi Military Medical Complex, thank you for teaching me how to be a neurosurgeon. I will not forget the time spent serving and learning in this departement and I will be grateful for it all my life time.

My deep gratitude also goes ***to Asst.Prof.Dr.Sherif Matbouly***, and ***Dr.Mohamed A. Bashir,*** for their immense effort, valuable technical notes, unlimited support and help to complete this review.

To ***my fellow neurosurgery residents,*** I stand speechless in front of you. For all the time we spent together, for all the memories we had, for all the experience we shared, I would like to say THANK YOU.

Finally, to my lovely wife, ***Dr. Mayada Mohamed,*** thank you for the sleepless nights we were working together before deadlines, and for all the fun and pain we have had.

Ahmed Ragab Abdelsalam

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List of Abbreviations:

HGG	High grade gliomas
GBM	Glioblastoma Multiforme
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
MDT	multi-disciplinary team
NPS	neurological performance scale
CSF	Cerebrospinal fluid
ICA	Internal carotid artery
PCom A	Posterior communicating artery
ACh A	Anterior choroidal artery
PCA	Posterior cerebral artery
GST	Glutathione-S-transferase
DNA	deoxy nucleic acid
RNA	ribonucleic acid
EMF	electro-magnetitc field
AIDS	acquired immune deficiency syndrome
VEGF	vascular epithelial growth factor
AA	anaplastic astrocytomas
WHO	World Health Organization
EGFR	epidermal growth factor receptor
GC	Gliomatosis cerebri
ICP	Increased intracranial pressure
PNET	supratentorial primitive neuroectodermal tumor
DMI	diffusion-weighted imaging
DTI	diffusion tensor imaging
PWI	perfusion-weighted imaging
CBV	Cerebral blood volume
MS	multiple sclerosis
MRS	Magnetic resonance spectroscopy

1. INTRODUCTION

Gliomas are primary brain tumors that develop from glial cells. Glial cells provide the structural backbone of the brain and support the function of the neurons. Gliomas make up about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors **(Goodenberger ML et al., 2012).**

The exact causes of gliomas are not known. Different oncogenes can cooperate in the development of gliomas **(Reuss, D et al., 2010).**

Gliomas are classified by pathologists according to their appearance under the microscope into four grades (I, II, III and IV), and the treatment and prognosis depend upon the tumor grade **(Louis DN et al., 2014).**

High grad gliomas, which include anaplastic astrocytoma (WHO grade III), glioblastoma multiforme (GBM, WHO grade IV), and gliosarcoma, are the most common malignant primary central nervous system (CNS) tumors in adults **(Bondy ML et al., 2011)**.

HGG may arise through two distinct pathways of neoplastic progression. Tumors that progress from lower grade astrocytic tumors, typically display both well-differentiated and poorly differentiated foci. They develop in younger patients (fifth to sixth decade), with time to progression from lower-grade lesions ranging from months to decades. In contrast, Another pathway develop in older individuals (sixth to seventh decade), have short clinical histories (less than 3 months), and arise de novo without any evidence of a lower-grade precursor **(Ohgaki H et al., 2011)**.

The symptoms of HGG depend mainly on its location and its size and consequently on the function of areas involved by the tumor, with a variety of nonspecific symptoms typical of a mass growing inside the skull with increased intracranial pressure. Common symptoms are persistent headache, nausea, vomiting, focal deficit (hemiparesis, hemianesthesia,

hemianopsia, diplopia, aphasia) and seizures due to tumor irritation effect **(Bleeker et al., 2012).**

High-grade glioma diagnosed mainly as an irregular hypointense lesion on T1-weighted MRI with various degrees of contrast enhancement and edema. The presence of ring-like enhancement surrounding irregularly shaped areas of presumed necrosis suggests glioblastoma. Magnetic resonance spectroscopy may be used to help differentiate tumors from stroke, old trauma, radionecrosis, infection, and multiple sclerosis **(Talos IF et al., 2013).**

Management includes either biopsy or surgical resection followed by radiotherapy in the majority of cases. Additional adjuvant chemotherapy is also a treatment consideration. In general, high-grade gliomas have a poor prognosis, are rapidly progressive, and are resistant to therapy. Median survival is around 1 year for GBM, 2 years for anaplastic astrocytoma, and 5 years for anaplastic oligodendroglioma **(Bleeker et al., 2012).**

2. AIM OF WORK

The aim of this study is to evaluate the role of biopsy versus cytoreductive surgery for the management of patients radiologically diagnosed with high grade gliomas regarding the clinical outcome and survival. Prognostic factors such as age of patients, duration of symptoms, presence of seizures, neurological performance scale (NPS), as well as tumor characteristics such as localization, size, and grading will be put in consideration.

3. LITERATURE REVIEW

Epidemiology

Malignant gliomas are the most common primary central nervous system tumors in adults and are subdivided into anaplastic gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) and glioblastoma which represents the most aggressive and prevalent subtype **(Jeyapalan et al, 2013).** Their epidemiology has focused on identifying the factors that can be modified to prevent this disease **(Judith et al, 2016).**

Aetiological factors

(A)Genetic Factors: Diseases or syndromes that are associated with rare mutations in highly penetrant genes like neurofibromatosis types 1&2, tuberous sclerosis are known to increase risk of glioma **(Fisher et al, 2011).**

Cytogenetic studies have shown that the loss of chromosome 10 in the astrocytomas is associated with increasing grade of malignancy (Lim& Harsh, 2005). Also allelic deletion of chromosome 17 occurs in astrocytomas of all grades of malignancy, but not in gliomas such as oligodendroglioma and ependymoma **(He et al, 2001).**

DNA stability and repair, and cell cycle regulation have produced some persuasive results with respect to risk for cancer; there is association of glutathione-S-transferase (GST) T1 deletion and glioma with p53 mutations **(Wrensch et al, 2014).**

(B) Virus induced-gliomas: Viruses known to induce tumors are classified as either deoxy nucleic acid (DNA) as papoviruses and adenoviruses or ribonucleic acid (RNA) viruses as retroviruses subfamily of oncoviruses **(Meyer MA, 2008).**

(C) Radiation-induced brain tumors: radiation types are possible mutagens; survivors from atomic bomb explosion have higher incidence rates of gliomas and other tumors **(Fisher et al, 2011).**

D) Chemical-induced brain tumors: Chemical mutagens include both endogenous and exogenous agents, which may react directly with DNA or exert their effect through a metabolite. These agents cause structural DNA damage by altering DNA bases **(Fisher et al, 2011).**

Epidemiology of anaplastic astrocytomas and glioblastomas

Malignant astrocytomas comprise more than 50% of astrocytic tumors which are more than 70% of gliomas. Glioblastoma comprises 80% of malignant gliomas. These highly invasive tumors have a strong predilection for cerebral hemispheres **(Larkavelas&Tascos, 2011).**

Malignant astrocytomas are associated with 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 astrocytomas (AA) usually presents in the fourth or fifth decade. GBM rarely occurs in children less than 14 years of age. Malignant astrocytoma is not believed to be a familial disease **(Weingart et al, 2006).**

Epidemiology of oligodendrogliomas

Approximately 5% of all primary brain tumors are oligodendroglial tumors. They represent up to 4-8% of cerebral glial Tumors. The median age at diagnosis is 40-50 years old. It is primarily a tumor of adult, but with smaller earlier peak in childhood between 6-12 years. Ratio of male to female is 3:2. CSF metastases occur in up to 10%. Spinal oligodendrogliomas comprise only 2.6% of intra-medullary tumors of the cord and filum **(Weller M, 2012).**

Epidemiology of ependymomas

Ependymomas arise from ependymal cell lining of the cerebral ventricles and the central canal of the spinal cord. They may occur else anywhere along the neuroaxis. Intracranial ependymomas comprise only 5-6% of intracranial gliomas, 69% occur in children. Spinal ependymomas represent 60% of spinal cord gliomas, 96% occur in adults. In pediatrics they are most common in the posterior fossa **(Greenberg M, 2016).**

In adults, they tend to occur intraspinal and less frequently supratentorial (intraventricular or periventricular) and with tendency to occur ectopically intraparenchymal, somewhere in the hemispheres **(Westphall M, 2013).**

They have the potential to spread via CSF through the neuroaxis, a process known as seeding or drop mets in 11%. The incidence is higher with high grade. Systemic spread occurs on rare occasion **(Greenberg M, 2016).**

PATHOLOGY

Gliomas constitute the most common type of primary brain tumor. They are derived from glial cells of astrocytic, oligodendroglial and ependymal origin. According to histologic type, the most frequently reported neoplasms are the astrocytic tumors, which account for approximately 70% of the cases reported **(Drevelegas&Karkavelas, 2011).**

Histological Classification and Grading

The current World Health Organization Classification of Tumors of Central Nervous System, Fifth edition (2016 WHO) lists more than 120 types of brain tumors. Current advances in molecular methodologies, particularly in the field of genomics, transcriptonomics, and proteomics, have revolutionized brain tumors classification, although the present classification which remains based on morphology and histology is increasingly being complemented by genetic characterization of neoplasms **(Louis DN et al, 2016).**

WHO classification of tumors of the nervous system (gliomas including astrocytomas, oligodendrogliomas, and ependymomas) ***(Louis DN et al, 2016)*** **(Table 1):**

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II