



Recent Advances in the Treatment of Gliomas: The Multimodal Care Therapy

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Abstract

Edited by: Branislav Filipović
Citation: Ibrahim O, Hafez MA, Haleem HA, El Maghraby H. Recent Advances in the treatment of Gliomas: The Multimodal Care Therapy. Open Access Maced J Med Sci. 2021 Jul 02; 9(B):503-508. <https://doi.org/10.3889/oamjms.2021.6229>
Keywords: Glioma; Molecular biology; Awake surgery; 5ALA; Neuronavigation; Extent of resection; Disease-free survival
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Received: 23-Apr-2021
Revised: 18-Jun-2021
Accepted: 21-Jun-2021
Copyright: © 2021 Omar Ibrahim, Mohamed A, Hafez, Helmy Abdel Haleem, Hussein El Maghraby
Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists
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BACKGROUND: Glioblastoma (GBM) is the most devastating primary malignancy of the central nervous system in adults. At present, standard treatment consists of maximal safe surgical resection followed by radiotherapy (60 Gray) with concomitant daily temozolomide chemotherapy. Low-grade gliomas constitute approximately 15% of the nearly primary brain tumors diagnosed in adults each year. Extent of tumor resection has become a strong predictor of patient outcomes, alongside patient age, performance status, tumor histology, and molecular genetics (isocitrate dehydrogenase-1 and 1p/19q codeletion status). Over the past two decades, surgeons have emphasized the importance of maximizing extent of resection and its impact on overall survival, progression-free survival, and time to malignant transformation.

AIM: We aimed to present recent advances in the treatment of gliomas.

METHODS: This is a prospective analysis of 50 patients diagnosed with gliomas which are enrolled in a joint supervision between Kasr Al Aini Hospital, Cairo University, Egypt, and Coventry University Hospitals, England.

RESULTS: The study included 50 patients, 31 males and 19 females, ages ranged from 21 to 75 years (mean age 47.5 years). Gross total resection was achieved in 28 patients (56%). The most common surgical complication in our series was post-operative transient weakness in 4 patients (8%). Mean true survival of low-grade glioma patients was 40.5 months while the mean true survival for anaplastic astrocytoma (Grade 3) patients was 38 months and that of GBM (Grade 4) patients was 18.8 months.

CONCLUSION: Despite persistent limitations in the quality of data, mounting evidence suggests that more extensive surgical resection is associated with longer life expectancy for both low- and high-grade gliomas.

Introduction

Gliomas are a class of tumors which arise from the supporting structures of the brain which are astrocytes and oligodendrocytes. They range in behavior from benign lesions with distinct borders such as juvenile pilocytic astrocytoma, curable with surgical resection alone, to more diffusely infiltrative cancerous lesions, astrocytoma, oligodendrogliomas, and glioblastoma (GBM), all uniformly lethal in a matter of several to many years [1].

They are the most common primary brain tumors in adults; they represent nearly 80% of all primary malignant brain tumors, with poor prognosis in their high-grade histotypes [2].

According to the current WHO grading system, high grades include Grade III and IV lesions. One-year survival rate for high-grade gliomas (HGG) is 53.7%, while the 2-year survival rate for these patients is only 14.6% [3].

GBM is the most devastating primary malignancy of the central nervous system in adults. At present, standard treatment consists of maximal

safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Grays) with concomitant daily temozolomide chemotherapy, followed by maintenance treatment with temozolomide for 6–12 months [1].

Low-grade gliomas (LGGs) constitute approximately 15% of the nearly primary glial brain tumors diagnosed in adults each year [4]. The majority of LGGs are detected in healthy patients with good neurologic status following a seizure [5]. LGGs tend to occur in locations adjacent to eloquent areas of the cortex [6]. A common location for these tumors in adults is in the supratentorial region, frequently involving the supplementary motor cortex and insula [7].

Due to their infiltrative nature and their appearance looking like normal brain, LGGs require a combination of regimens from resection, chemotherapy, and radiation. Most LGGs will gradually evolve into higher-grade gliomas and likely patients will die from the disease [8], [9].

Median survival for patients with LGGs ranges from 5.6 to 13.3 years and is dependent on specific histology and molecular characteristics [10].

Treatment options include surgery, radiotherapy, and chemotherapy. Surgical intervention

is generally performed with the goal of maximum safe resection and aids in diagnosis by providing tissue for molecular testing (1p19q codeletion, IDH, ATRX [α -thalassemia/mental-retardation- syndrome-X-linked] mutations).

Radiation is typically reserved for patients considered to be at "high risk" (for example, patients over 40 years old or patients with an incomplete resection) or with progressive disease [11].

Several variables positively affect the prognosis for patients diagnosed with gliomas: These include young age, tumor location, radiological features, recurrence, and the opportunity to perform an adjuvant therapy in the postoperative course [12].

Patients and Methods

This is an observational prospective study of 50 patients of glioma that was treated through microscopic resection at University Hospitals Coventry and Kasr AL Ainy University Hospitals. All cases were not operated on before. Careful history taking, thorough neurological examination, and pre- and post-operative radiological evaluation were done for all patients. Patients with an unstable neurological condition or who were considered a poor medical risk after surgery resulting in Karnofsky Performance Scale score of below 70 were excluded from the study.

Pre-operative computed tomography (CT) scans of brain, magnetic resonance imaging (MRI) scans with IV contrast, perfusion-weighted imaging, and MR spectroscopy were performed to all patients, while functional MRI studies were done only for patients with lesions affecting eloquent areas of the brain.

Low-grade glioma patients were operated on using awake craniotomy technique, while high-grade glioma patients were operated on using intraoperative fluorescence-guided technique.

Before awake surgeries, the tasks that will be performed during surgery were rehearsed in the ward. Simulation of the surgical posture, equipment setup, and role sharing, as well as rehearsal of the tasks for the patient, surgeons, and anesthesiologists were also performed in the operating room.

In awake surgeries, a complete scalp block was done along the incision and around the incision using 1:1 mixture of 2% xylocaine with adrenaline (20 ml) and 0.5% Marcaine (20 ml).

Neuronavigation was used for optimizing the surgical approach to the tumor in the majority of our patients as well as cortical mapping for preservation of eloquent areas of the brain. Electrocortical stimulation mapping and subcortical

white matter stimulation are used to establish a real-time functional map of the brain surface that allows the surgeon to delineate a safe boundary for tumor resection.

Resection was then performed, sparing the functional areas detected by stimulations, regularly given during the resection, to define precisely the interface between lesion and functional areas. At the end of the resection, cortical stimulations were repeated using the same electrical parameters (particularly, the same intensity) as before, to check the functional integrity of the pyramidal pathways again, with the same clinical criteria of evaluation used previously.

In fluorescence-guided surgery, a Zeiss OPMI Pentero microscope for neurosurgery with alternating white and blue light visualization mode was used. 5ALA was given orally to patients with a dose of 20 mg/kg. One gram of 5ALA (Gliolan) was dissolved in 50 ml of water and given 4 h before surgery to the patients.

Resection was carried out by switching liberally between white light and blue light modes of the surgical microscope. Because GBMs frequently feature necrosis, which either fluoresces weakly or not at all due to missing metabolism, resection was performed by dissecting marginal, fluorescing tissue outside of the area of frank necrosis. This strategy allowed surgery to be as efficient and quick as possible.

Post-operative CT scans and MRI were performed to all patients to detect the radiological extent of resection.

Tumors were subject to histopathological assessment and molecular biology studies for diagnostic and prognostic purposes. Low-grade glioma patients were put under oncological surveillance while high-grade glioma patients received a combination of radiation and chemotherapy.

All patients had regular follow-ups for the assessment of functional outcome following surgery, disease-free survival, and true survival status.

Results

The study included 50 patients, 31 males and 19 females, ages ranged from 21 to 75 years (mean age 47.5 years). The mean follow-up duration was 6 months with a range of 1–24 months.

The chief complaint was seizures in 22 cases (44%), headache in 13 cases (26%), dysphasia in 6 cases (12%), and weakness in 5 cases (10%) (Table 1).

The most common tumor location was found to be in the frontal lobe in 29 patients (58%) followed by the temporal lobe in 12 patients (24%), parietal and

occipital lobe in 4 patients each (16%), and only one patient with a cerebellar tumor (2%).

Thirty-six out of 50 patients (72%) had a tumor affecting an eloquent area in the brain while only 14 patients had their tumors in non-eloquent areas (28%). The left side of the brain was affected in 30 patients (60%) while the right side tumors were found in 20 patients (40%).

Table 1: Pre-operative presenting symptoms in 50 patients with glioma

Symptom	Number of patients	Percentage
Seizures	22	44
Headache	13	26
Dysphasia	6	12
Weakness	5	10
Visual problems	4	8

Gross total resection was achieved in 28 patients (56%), while debulking more than 50% was achieved in 22 patients (44%) patients. A routine post-operative contrast-enhanced MRI and MRI perfusion were done in most patients within 72 h from surgery to determine the radiological extent of resection and the presence of any residual tumor.

In our series, 38 out of 50 patients (76%) had not encountered any significant post-operative complications, while 4 patients (8%) had transient weakness which improved during hospital stay, 4 patients (8%) had post-operative wound collection, and only 1 patient (2%) had post-operative photosensitivity following the use of intraoperative fluorescence.

Table 2: Lesion characteristics in 50 patients with glioma

Characteristic	Types	Percentage
Pathology	LGG	10 patients (20)
	AA	5 patients (10)
	GBM	35 patients (70)
Location	Frontal	29 patients (58)
	Temporal	12 patients (24)
	Parietal	4 patients (16)
	Occipital	4 patients (16)
	Cerebellar	1 patient (2)
Eloquence	Eloquent	36 patients (72)
	Non eloquent	14 patients (28)

GBM: Glioblastoma, LGGs: Low-grade gliomas.

Thirty-five patients (70%) had their tissue pathology revealing GBM multiforme, 5 patients (10%) were diagnosed with anaplastic astrocytoma, and 10 patients (20%) with astrocytoma Grade 2 (Table 2). Molecular biology studies were only done to a certain number of patients due to financial reasons, so 21 out of 35 patients with GBM were found to be IDH wild type and 5 patients were IDH mutant type. Only five among low-grade glioma patients did molecular biology studies and four out of them were IDH mutant type and only one was IDH wild type.

As regards post-operative oncological treatment, 45 patients (90%) needed to receive adjuvant therapy in the form of radical radiotherapy, chemotherapy, or a combination of both while only 5 patients (10%) were put under oncological surveillance with no need for further intervention.

Mean true survival as well as disease-free survival of low-grade glioma patients were 40.5 months

and all of our patients are still alive. On the other hand, the mean true survival for anaplastic astrocytoma (Grade 3) patients was 38 months and that of GBM (Grade 4) patients was 18.8 months.

Discussion

The management of glioma patients remains challenging and is often based on clinician experience and patient preference [42]. Treatment options have been limited and current research endeavors have not led to a cure for gliomas, however, clinical trials have contributed to a better understanding of the disease progression and improvements in patient outcomes to treatment [43].

It has been demonstrated that the patient factors (age, comorbidities, and Karnofsky score), tumor factors (tumor grade, tumor location, and lobes), and treatment factors (surgical methods and adjuvant therapy) were among the most significant predicting factors influencing overall survival [44].

As for LGG, early maximal safe resection is considered standard of care. Factors favoring early resection are the uncertainty about the radiological diagnosis, the assumption that resection will postpone malignant transformation and will improve overall survival [45].

In recent years, there has been a trend of favoring GTR in the treatment of LGGs and relevant studies published up to 2017 showed that GTR greatly increased the 5-year and 10-year survival of patients with LGGs. Twenty studies assessing the surgical outcomes of LGGs were analyzed, and results showed that patients with LGGs are expected to benefit from a greater extent of resection if their safety during the surgery can be ensured [46].

To achieve maximal safe resection, awake craniotomy technique was performed in our study for all eligible patients with low-grade glioma affecting an eloquent area in the brain as the precentral gyrus (motor strip), corticospinal tracts, Broca's speech area, Wernicke's speech area, or the brain stem.

The use of awake craniotomies in brain tumor surgery has been shown to decrease post-operative neurologic deficits and surgical morbidity while safely delineating an operative margin for resection [4].

Among our low-grade glioma patients, 8 out of 10 had an awake surgery using neuronavigation when available or needed. The integration of standard neuronavigation with functional non-invasive neuroimaging such as functional MRI or diffusion tensor imaging was helpful to improve post-operative functional outcome.

Over the past decade, there was a large global interest in fluorescence-guided surgery (FGS) in patients with malignant brain tumors with the majority of these studies focusing on the use of 5-aminolevulinic acid (5-ALA) as a fluorescent pro-agent for FGS of malignant gliomas [27].

In this study, FGS was used in all patients with HGG to help the neurosurgeon to better distinguish the tumor margin and to improve the likelihood of complete resection.

During tumor resection, 5-ALA-induced fluorescence provides the neurosurgeon with real-time information for differentiating tumor from normal tissue that is independent of neuronavigation and brain shift [27].

5-ALA-induced tumor fluorescence helps in identification and resection of infiltrative glioma regions at the tumor margin which are typically not shown with pre-operative MRI in patients with malignant gliomas as gadolinium contrast enhancement relies on disruption of the BBB [27].

Using 5-ALA, the tumor is clearly visible in the surgical field; therefore, the only reason to leave tumor tissue behind should be that the tumor affects an eloquent area of the brain or areas whose lesion could produce a neurological deficit for the patient [26].

Surgical resection remains a critical component of the multimodality management of HGGs in local practice. The completeness of tumors resection significantly improves the effectiveness of adjuvant therapy [44].

The use of these advanced techniques played a big role in achieving maximum safe resection with no significant post-operative neurological deficit. Nine out of 10 patients with LGG had a gross total resection of their tumors while this was achieved in 24 out of 40 patients with HGG. The extent of resection was proved by post-operative MRI with contrast enhancement and perfusion MRI showing no residual.

A key prognostic factor in neurosurgical oncology is the extent of resection and despite limitations in the quality of data, mounting evidence suggests that more extensive surgical resection is associated with longer life expectancy for both low- and high-grade newly diagnosed gliomas [15], [43].

Early radiation for LGG has not demonstrated a survival benefit, but is associated with improved progression-free survival at 2, 5, and 10 years. The role of chemotherapy only remains less certain because no single chemotherapy regimen has yet emerged as the undisputed standard of care for patients with LGGs. A trial by Buckner *et al.* in 2016 demonstrated a 5.5-year median survival advantage and a progression-free survival benefit from the addition of PCV chemotherapy to radiotherapy [42].

However, only three of the low-grade glioma patients included in this study had post-operative

adjuvant therapy due to the presence of residual tumor on post-operative follow-up MRI and molecular biology studies revealing IDH wild-type LGG.

While in HGG, the addition of temozolomide to radiotherapy early in the course of the tumor provides a statistically significant and clinically meaningful survival benefit [1]. This was the standard oncological treatment for all HGG patients in this study.

The median survival of LGG in our study was 40.5 months while that of AA and GBM patients was 38 months and 18.8 months, respectively. These numbers were comparable with the median survival of GBM and AA which were 12 months–15 months and 2 years–5 years based on current published data [44].

Conclusion

Advances in intraoperative technique, including neuro-navigation, intraoperative magnetic resonance imaging, intraoperative ultrasound, stimulation mapping techniques, and fluorescence-guided surgery, have all been developed to maximize tumor resection and minimize surgical morbidity for both low- and high-grade glioma.

Our study showed a significant clinical benefit for HGG patients in terms of overall survival by using 5 ALA guided surgery with better post-operative functional outcome when compared with the conventional surgical method.

The use of awake craniotomies in LGG surgery has been shown to decrease postoperative neurologic deficits and surgical morbidity while safely delineating an operative margin for resection.

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Author Queries???

AQ6: Kindly provide expansion if needed.

AQ7: Please note some reference (13,14, 16-25 and 28-41) are not cited in text part and also Please check and cite all references in chronological order.