ULTRASOUND GUIDED VERSUS CONVENTIONAL MICROSCOPIC RESECTION OF SUPRATENTORIAL ASTROCYTOMA: A COMPARATIVE STUDY

Thesis submitted for the partial fulfillment of MD degree in Neurosurgery by

Aly Ibrahim Soliman Mohamed Abdo Ibrahim, M.B.Ch. B
M.Sc. Surgery, Ain Shams University, 2009
Assistant lecturer of neurosurgery, Ain Shams University

Under supervision of

Prof. Dr. Mohamad Alaa Fakhr
Professor of neurosurgery, Ain Shams University

Prof. Dr. Hisham Abd-Al Salam Simry
Professor of neurosurgery, Ain Shams University

Prof. Dr. Ayman Abdel Raouf El-Shazly
Professor of neurosurgery, Ain Shams University

Prof. Dr. Walid Ahmed Abdel Ghany
Assistant Professor of neurosurgery, Ain Shams University

Ain Shams University
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List of abbreviations

AA	anaplastic astrocytoma
BBB	blood brain barrier
CBV	cerebral blood volume
CC	corpus callosum
Cho	choline
Cr	creatine
CSF	cerebrospinal fluid
DTI	diffusion tensor imaging (on MRI)
DWI	diffusion-weighted images (on MRI)
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EOR	extent of resection
fMRI	functional magnetic resonance imaging
GBM	glioblastoma multiforme
GFAP	glial fibrillary acidic protein
GTR	gross total resection
HGG	high-grade glioma
ICU	intensive care unit
IDH	isocitrate dehydrogenase
IL	interleukin
iMRI	intraoperative magnetic resonance imaging
IOUS	intraoperative ultrasonography
JPA	juvenile pilocytic astrocytoma
KPS	Karnofsky performance scale
LGG	low grade glioma
LGG	low-grade glioma
MA	malignant astrocytoma
MPFS	malignant progression free survival
MRS	magnetic resonance spectroscopy
mTOR	mammalian target of rapamycin
NAA	N-acetyl aspartate
NF1	neurofibromatosis type 1
NTR	near total resection
PDGF	platelet derived growth factor
PI3K	phosphatidylinositol-3-kinase
STR	subtotal resection
T1WI	T1-weighted image (on MRI)
T2WI	T2-weighted image (on MRI)
US	Ultrasound
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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Abstract

Background

Astrocytomas are the most common primary brain tumors with glioblastoma being the most frequent and most aggressive among them. Surgical resection remains the only surgeon modifiable determinant of outcome in patients harboring astrocytomas. Maximum safe resection has shown to improve outcome by extending survival and relieving tumor pressure. Multiple intraoperative aids have been introduced over the last two decades to help surgeons achieve maximum safe resection. In this study we compared the use of intraoperative ultrasound guidance to conventional surgery. Ultrasonography is a cheaper alternative to intraoperative magnetic resonance imaging and is more suitable for limited resources neurosurgical practice.

Patients and methods

We conducted a cohort study comparing ultrasound guided resection with conventional surgery. We included patients with high and low grade supratentorial astrocytoma that is amenable to gross total resection. The primary outcome was the degree of cytoreduction measured by both a conventional categorical method as well as three-dimensional volumetric analysis. Other outcomes included the postoperative functional status and the rate of operative complications.

Results

There were 17 patients in the ultrasound group and 13 patients in the control group. The extent of resection was significantly better in the ultrasound group with both the conventional categorical method (P=0.01) and the volumetric method (P=0.03). Patients in the ultrasound group had a significantly better postoperative performance score (P=0.01). The general rate of complications was low to draw conclusions. It was not possible to measure survival trends due to high attrition rate.

Discussion

Ultrasound was superior in the control of resection. This was seen through its ability to detect small residual tumor and help its subsequent resection. Intraoperative High-grade and focal low-grade gliomas were both well localized and well defined with ultrasound while this was less clear with diffuse low grade gliomas. Ultrasonography guided resection also appears to be safer than non-image guided surgery, probably due to better localization of the tumor.

Conclusion

We recommend the use of ultrasound in surgical resection of high-grade and focal low-grade gliomas to achieve a higher and safer extent of resection. Further studies are needed to compare ultrasonographic

guidance to neuronavigation and intraoperative magnetic resonance imaging.

Keywords

Astrocytoma, glioblastoma, ultrasound, extent of resection

Introduction

Astrocytomas are the most common primary tumors of the nervous system, and glioblastoma (GBM) is the most common and most aggressive of these tumors.(1) Despite the vigorous basic and clinical research, survival trends have remained largely static for many years, reflecting the general lack of effective therapeutic options for patients with these tumors.(2) Current median life expectancy for patients with GBM with optimal treatment is 12–14 months.(3) The estimated survival in cases of malignant astrocytomas (MA) varies depending on many factors, the most important of which are: tumor grade, the degree of resection, patient's age and Karnofsky performance score (KPS), with a worse prognosis for patients more than 60 years of age and for a KPS < 80%.(4)

Low-grade diffuse astrocytomas (World Health Organization [WHO] grade II) usually progress to malignant variants over years.(5) Malignant astrocytomas are infiltrative lesions, with tumor cells found outside the radiological tumor margin, which makes them surgically incurable.(6,7) Yet, surgical resection is the main stay of treatment followed by adjuvant chemoradiotherapy.(3)

Maximum safe resection remains the primary goal of surgery. A multitude of studies have shown that gross total resection can prolong survival bearing in mind that the extent of tumor resection should not negatively affect the post-operative functional status of the patient.(8–12)

Classic surgical planning relies on preoperative imaging and indirect localization methods. This is limited by the quality of preoperative images, the surgeon's anatomical knowledge and his accuracy in making preoperative calculations. Even in optimal conditions, classic methods are still hampered by human errors, which cannot be tolerated when dealing with such a sensitive structure as the human brain and which makes gross total resection, without intraoperative image assistance, an unsafe alternative.(13)

The introduction of intraoperative navigation and imaging techniques have improved the neurosurgeons' ability to tackle brain tumors in a safer manner while achieving higher extent of tumor resection.(14,15) Magnetic resonance imaging (MRI) has great soft tissue resolution and

thus, its intraoperative use, offers accurate assessment of residual tumor. But MRI is expensive and requires a special setting and extra time for image acquisition.(15–17) Intraoperative ultrasonography (IOUS) on the other hand is cheap, fast and flexible but with a poorer image resolution. IOUS images can be better interpreted through some modifications and a learning curve.(18,19) One of the best advantages of IOUS is that it gives a real-time image, unlike neuronavigation that relies on preoperative images and is liable to the inaccuracy of brain shift.(14,20) Other adjuncts to surgery have also been introduced including cortical mapping, fluorescence-guided surgery and awake craniotomy; the aim being a safer surgery and a higher extent of resection.(21–23)

Due to its low profile and easy access, IOUS seems ideal for intraoperative guidance when other modalities are not available. Also, it is a useful additional tool even in the presence of other sophisticated albeit more expensive tools, due to some unique features that will be discussed in the study.(18,19)

Aim of the Study

The aim of this study was to assess the impact of intraoperative ultrasonography on surgery for supratentorial intra-axial brain lesions represented in astrocytomas. This impact is particularly important in neurosurgical centers where no other intraoperative imaging modalities are available, which is the case in many medical centers in the developing world. This was assessed through the extent of tumor resection and the patient's postoperative neurological and functional outcomes.

It is also important to mention that this study represents an initial experience following the introduction of IOUS in our department, which is a unique opportunity to assess the learning curve and the ease of use associated with its introduction.

I- Epidemiology

Primary malignant central nervous system (CNS) tumors account for 2% of all causes of cancer, but due to their aggressive nature and sensitive location, they produce a disproportionate rate of cancer related morbidity and mortality.(24,25) The incidence of brain tumors in the USA is 14.8 per 100,000 person/year, with about half of them being malignant.(25) Malignant brain tumors are the leading cause of death from solid tumors in children and the third most common cancer-related death in the 14-35 age group.(25) Gliomas represent about half of all newly diagnosed brain tumors, with low grade gliomas (LGG) accounting for about 15% of all brain tumors in adults and 25% of brain tumors in children.(26)

LGG in adults refers to diffuse gliomas that are WHO grade II, specifically diffuse astrocytoma, oligodendroglioma and mixed oligoastrocytoma. (27) These tumors show a slight male predominance and a biphasic age distribution, with the first peak occurring in childhood (ages 6-12) and the second peak in adulthood (20s to 40s). The median age of diagnosis of LLG in adults is 35 years.(28)

Anaplastic astrocytoma (AA) usually develops earlier than glioblastoma multiforme (GBM). The mean age of diagnosis of AA is 40 years, as opposed to GBM, with a mean age of 53 years and a peak incidence of 65 to 74 years. GBM is more common in men, with a male to female ratio of 1.5 to 1. (29) There has been a significant increase in the incidence of malignant astrocytomas (MA) since the 1980s but this has been attributed to improved diagnosis due to the introduction of high resolution imaging modalities, mainly magnetic resonance imaging.(24)

Gliosarcoma represents between 2-8 % of GBM cases. Unlike the common notion, they have a similar clinical findings and prognosis as GBM, with the additional rare ability to affect infants. (30,31)

Survival and prognostic factors in patients with astrocytomas

Overall survival refers to the interval of time from diagnosis (or surgery) to the time of death due to any cause. The median overall survival (Interval at which 50% of patients are still alive) and mean survival are the most important outcome measured to assess behavior, prognosis and management of tumors. Progression free survival refers to the interval of time from an intervention for the disease (e.g. surgery) until there is recurrence of the disease either clinically or radiologically. Malignant progression free survival (MPFS) is especially important in grade II gliomas and refers to time from diagnosis (with or without treatment) to malignant progression. Survival times vary greatly by histological grades, genetic profile, and age at diagnosis. In fact, many factors affect survival. These factors can be divided into patient-related, tumor-related and treatment-related. The most important patient related factors are age and functional neurological status (Karnofsky performance scale [KPS]).(9) The most important factors related to tumor are the histological grade and genetic profile. The most important factors related to treatment are the extent of surgical tumor resection and radiotherapy in case of high-grade tumors.(4)
LGG typically has a 6-8 years median overall survival; again there is variability based on specific tumor types and other factors mentioned above. AA has a median survival of 3-5 years and in GBM, median survival remains less than 2 years despite aggressive treatment. (24,32–34)

Clinical manifestations

Malignant Astrocytomas

Malignant astrocytoma most commonly occurs in the supratentorial compartment of the brain, although they can affect any part of the central nervous system. The symptoms and signs are usually those of a space occupying lesion including, headache, nausea, vomiting, blurring of vision, seizures and neurological deficits according to location. The neurological deficits may be focal or global (altered mental status). The symptoms are usually not specific to MA. Symptoms usually progress over months, but in case of AA, they may take longer, with a remote

history of seizures being the first presentation. GBM can develop de novo (primary GBM) or as a progression from AA (secondary GBM). The latter usually affect a younger population (40s and 50s) as opposed to primary GBM, usually occurring in the 60s and 70s of age. (35) Headache is the most prominent symptom and is usually more severe in the morning. GBM and gliosarcoma maybe multifocal, presenting with spatially unrelated neurological deficits. They can also spread to other parts of the neuraxis, usually through the cerebrospinal fluid. Gliosarcoma is more common in the temporal lobe and has a tendency to involve and invade the dura. Extracranial metastasis is rare, although more common with gliosarcoma (15%), and can lead to unexpected peripheral symptoms.(36)

Low Grade Astrocytoma

Low-grade gliomas rarely cause focal symptoms even if found in eloquent areas due to their slow growth. Seizure and headaches are among the most common presenting symptom. A rapid progression of symptoms may indicate tumor progression to malignancy. History of epilepsy was found to be a good prognostic factor with LGG, probably due to early diagnosis.(37)

Risk Factors

Like all neoplasms, it is difficult to pin specific risk factors to the development of astrocytomas. Yet some environmental risk factors as well as genetic factors have been linked to a small percentage of tumors. Ionizing radiation exposure, especially in large doses, like after radiotherapy to the head, has shown to increase the risk of developing both meningiomas and gliomas in addition to other tumors like schwannomas and pituitary adenoma. There is strong evidence from prospective studies showing a linear increased risk of developing radiation-induced glioma in patients who received previous radiotherapy. There is also data that suggest increase incidence of glioma in survivors of the Hiroshima bombing and in patients who received scalp radiation for tinea capitis.(38). The relationship seems to be dose dependent and usually occurs > 15 years after exposure. Studies studying the risk of short-term use of cellular phones have not shown an associated increased risk of glioma, but long-term studies are lacking or inconsistent.(39–41)

Only 1-3% of brain tumors have been attributed to inherited high-penetrance genes. One example is the rare inherited Li-Fraumeni

syndrome known for brain tumors as one of its many components. Li-Fraumeni syndrome is characterized by a germline mutation in the TP53 tumor suppressor gene. In these cases tumors usually arise at a younger age and are multiple in more cases than the general population.(42) Interestingly, some studies showed a lower incidence of glioma in patients who self reported allergies. This may arise from the activity of interleukin-4 (IL-4) and IL-13 cytokines in patients with allergy and autoimmune disease as well as increased tumor immunosurveillance in these patients. (43) Recently, two genome-wide association studies for glioma described the following regions for glioma risk: 5p15.33 (TERT), 9p21.3(CDKN2B), 8q24, 11q23 (PHLDB1) and 20q13.3 (RTEL1).(44) These discoveries represent a great opportunity for discovering the mechanism of glioma development.

II- Pathology, classification and molecular biology of astrocytomas

Molecular biology and pathogenesis

Low-grade diffuse astrocytoma

Diffuse astrocytoma (WHO grade II) is the earliest stage of infiltrating astrocytic tumors. No premalignant stage of this tumor has been recognized. Most of these tumors exhibit over expression of the platelet derived growth factor receptor (PDGFR), mutation of isocitrate dehydrogenase (IDH1) gene, and up to one half will exhibit gene mutation or deregulation of the expression of the TP53 tumor suppressor gene. A majority of these tumors will exhibit polysomy of the epidermal growth factor receptor (EGFR) gene.(45)

Anaplastic astrocytoma

Anaplastic astrocytoma (WHO grade III) represents an intermediate stage in the progression of diffuse astrocytoma to GBM both histologically and in molecular features. The WHO grading system suggests the use of mitotic activity to distinguish between diffuse and anaplastic astrocytomas. TP53 and IDH1 mutation persist in AA in addition to increase in cells exhibiting EGFR polysomy.(45)