The impact of surgery in high grade gliomas - a literature review

Adriana Baritchii[1], A. Gubian[1,*], St.I. Florian[1,2]

[1]University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Department of Neurosurgery
[2]Cluj County Emergency Hospital, Department of Neurosurgery
*Student

Abstract: Malignant gliomas are aggressive brain cancers. After many decades of intensive research they represent a major cause of cancer related mortality and morbidity. Management of malignant gliomas is very difficult. None of the current treatments are curative. High grade gliomas are optimally treated with surgery followed by radiotherapy and chemotherapy. The impact of surgery on progression free survival and overall survival was a constant preoccupation and debate for decades among neurosurgeons. Different studies published in the last 25 years have provided evidence that the extent of resection of high grade gliomas can influence time to progression and median survival, although so far there is no class I prospective randomized trial to fully answer this question. Some of the most important studies are reviewed here. The modern neurosurgery relay on some tools that proved to be very helpful in guiding the surgeon to achieve the maximal tumoral cytoreduction with minimum impact on the brain's eloquent areas. iMRI has been proved to be safe and became an important tool during tumor surgery, used alone or in conjuction with other important techniques: intra-operative neurophysiology, awake cortical mapping, 5-ALA fluorescence etc. Although so far the prognostic of high grade gliomas is still disappointing, further understanding of the biology of these tumors and a patient-tailored treatment could be the keys of finding a cure in the future.

Introduction

Malignant gliomas are aggressive brain cancers. After many decades of intensive research high grade gliomas represent a major cause of cancer related mortality and morbidity. They are the most common primary brain tumors and account for about of 2% of all cancers. [36, 23].

Due to the fact that glial cells undergo mitosis, they can present with abnormal proliferation, which may result in glial tumors. The origin of the tumor is thought to be a common pluripotent neuro-ectodermal precursor. This cell has the ability to differentiate along the astrocytic lineage, up to a grade IV. Primary glioblasomas are tumors that appear de novo [10].

The World Health Organization classifies the glial tumors into four grades. Grade I is reserved for special types of astrocytomas that are better delineated. The more typical astrocytic neoplasm is graded II through IV. There are some histological criteria that affect the prognosis like: cellularity, presence of giant cells, anaplasia, mitosis, vascular proliferation with or without endothelial proliferation, necrosis and pseudopalisading [42]. Grades III and IV are the malignant ones.

They represent approximately 70% of all gliomas and affect predominantly patients between 40 and 70 years [33]. Glioblasoma multiforme (grade IV) is the most aggressive primary brain tumor. Despite all the effort of trying to improve the treatment, the median survival is 12-15 months, with a 2 year survival rate of 15% up to 26% [49].

Currently there are no prevention strategies for malignant gliomas, except reducing the exposure of the head to high doses ionizing radiation. Among other studied risk factors supposed to be involved in the development of this type of brain tumors (radiation, chemical carcinogens, infection/ viruses) only radiation exposure has been established to be causal [35, 58]. Some genetic syndromes, for exemple Li-Fraumeni, are also more frequent associated with the development of malignant gliomas [35].

Management of malignant gliomas is very difficult. None of the current treatments are curative [40]. Recent studies concentrate on understanding the molecular mechanism and gene mutation. Combined with clinical trials this work will be able to provide us a new promising and individual approach. Standard treatment consist of maximal surgical resection, radiotherapy and concomitant and adjuvant chemotherapy with temozolomide [43,15].

Among all the treatment option available for malignant gliomas the surgery is the first step and maybe the most important one. Beside the fact that it provides tumoral tissue for pathological examination and reduces the tumor volume and edema, surgery also serve the purpose of treating the patient with BCNU implantable wafers and also developing in vitro drug sensitivity assay with the goal of predicting the clinical response to chemotherapy.

Surgery - how much

The first step in the treatment of malignant gliomas is the surgery. The mechanical cytoreduction of the tumor mass can help the patient to gain some time for other therapeutic intervention (radiotherapy, chemotherapy). The beneficial effect of tumor resection was observed both on cerebral blood flow and metabolism even at distant sites of the tumor. 30 to 60 g of tumor mass will create a neurologic symptom while 100 g of tumor is lethal. A 90% resection of a 50 g (5X 1010 cells) tumor theoretically reduces the tumor burden to 5 g (5 X 109 cells). After the total resection of the gadolinium enhancing regions on MRI 1 g of tumor (or 1X 109 cells) may be left in place. The other therapies are also involved in the tumor destruction: radiotherapy can kill two logs of cells while chemotherapy is believed to destroy one to two logs of cells. The body immune system will reduce the tumor burden to less than 1X105 cells [32]. Although tumor cytoreduction appears to be vital, the presence of the viable tumor cells beyond the enhancing margins of the tumor- a cause for future recurrences- explain why surgery is more effective as part of multimodality treatment strategy [27,14]

The impact of surgery of high grade gliomas on progression free survival and overall survival was a constant preoccupation and debate for decades among neurosurgeons. The infiltrative nature of these tumors makes impossible the curative resection. A wider margin resection coupled with adjuvant therapy creates the condition of delaying the recurrence and prolonging the survival [4].

An early retrospective study by Simpson et al [47] included 645 patients with glioblastoma from the Radiations Therapy Oncology Group database. The authors analyzed the survival with respect to known prognostic factors, such as age and Karnofsky Performance Status, as well as extent of surgery, site, and size. The median survival was 11.3 months in patients with complete resection, 10.4 months for partial resection and 6.6 months for biopsy only. Some factors that offered survival benefit were identified: age

<40, Karnofsky Performance Score (KPS)>70, frontal lobe location and total resection. The conclusion of the study was that biopsy only yields inferior survival to more extensive surgery for patients with glioblastoma multiforme treated with surgery and radiation therapy.

In 2003 Metcalfe and Grant, after the research of 2100 documents, were unable to draw a conclusion, due to the fact that they didn't found enough randomized data for analysis. The authors underlined the idea that treatment must be considered on an individual basis. Although there was no good evidence that resection offers any clear advantage over biopsy, the indication of using biopsy for certain deep seated lesions is still standing, while small superficial placed frontal tumors can be resected completely with little difficulty [34].

Evaluation of the extent of resection and its influence on the survival using a 5-aminolevulinic acid- a non-fluorescent prodrug- was described by Stummer and al [50]. ALA is a precursor of haemoglobin that leads to the synthesis of porphyrins in malignant gliomas. The intracellular accumulation of fluorescent porphyrins- which appear in red fluorescence under blue light- enable more complete resection of contrast- enhancing tumour.. 322 adult patients with radiographically suspected malignant gliomas were randomized, comparing cytoreductive surgery using ALA (n=161) versus conventional white light (n=161). The authors concluded that surgery using 5-aminolevulinic acid enabled more complete resections of contrast-enhancing tumor. This was associated with a significant improvement in progression-free survival in patients with newly diagnosed malignant glioma undergoing cytoreductive surgery.

One of the most comprehensive studies that attempt to find a correlation between the extent of the resection and survival comes from Lacroix et al [26]. 416 patients who underwent resection for glioblastoma over a period of 6 years were included. The tumoral volume pre and postoperative was assessed using computer assisted image analyses. Five independent predictors of survival were identified by the authors following multivariate statistical analyses: age, Karnofsky Performance Scale (KPS) score, extent of resection, and the degree of necrosis and enhancement on preoperative MR imaging studies. When a resection of 98% or greater of the tumor was achieved a significant survival advantage was associated. The median survival was 13 months in patients with gross or near gross total resection (98% or greater) compared with 8.8 months for patients with less than 98% resection (p=0.02). A clinical outcome scale ranging from 0 to 5 was proposed based on age, KPS and radiographic evidence of necrosis. A significantly improved survival was observed in patients with lower scores (1-3) who underwent aggressive resections and a trend toward slightly longer survival was found in patients with higher scores (4-5). This study supports the concept of aggressive cytoreductive surgery as part of the management of high grade gliomas, yet not at the expense of neurologic function or surgical complications.

Starting from almost 3 decades ago some authors suggested that partial tumor resection could be associated with a greater risk in terms of postoperative neurological worsening compared with radical resection or stereotactic biopsy. Today is very well known that partial resection of glioblastoma carries significant risk of postoperative haemorrhage and edema- so called wounded glioma syndrome. In the series of Ciric et al [8] 42 patients with supratentorial gliomas were studied pre and postoperatively with CT scan. A gross total or nearly gross total resection was performed in the majority of patients (86%). The postoperative neurological status was stabile or improved in 97% of these patients. 40% of patients with partial resection presented a

neurological worsening after the operation. Fadul et al [13] examinated prospectively morbidity and mortality in 104 patients who underwent surgery for supratentorial gliomas. The authors reported that patients with complete resection had fewer acute neurologic complications and no greater risk of being neurologically impaired at 1 week compared with patients that were treated with biopsy or less extensive procedures. Another retrospective analysis performed on 66 patients- Vecht et al [55]- found that extensive surgery was correlated with a better immediate postoperative performance, a lower one-month mortality rate and a longer survival in high grade gliomas. Because of the retrospective nature of the study the authors concluded that a more extensive surgery does not lead to more postoperative neurological deterioration. Abrudan et al [1] published a study on 266 patients showing that age and type of surgery were prognostic factors that significantly influenced the survival at 12, 18 and 24 months. The authors found that the global survival rate was 47 % at 12 months, 26,3% at 18 months and 16,7% at 24 months and the difference of mean survival at 12, 18 and 24 months monitoring was 2,8 months, 4,4 months and 5,1 months respectively for the patients that underwent gross total resection of the tumor. This study adds a new argument in favor of maximal cytoreductive surgery whenever possible.

Although the management of elderly patients with high grade gliomas is mainly focused on the optimal use of radiotherapy and chemotherapy, it is important first to address the patient to neurosurgical resection. Age and number and severity of additional illness are vital when considering the extent of resection in older patients, due to surgical risks and potential postoperative complication.

There are some useful data regarding management of high grade gliomas in elderly patients, namely those over 65 years. In the study of Vuorinen et al [56] 30 patients older than 65 years were randomized into two groups: stereotactic biopsy and open craniotomy and resection of the tumor. Ultimately only 23 tumors proved to be a malignant glioma (19 glioblasoma and 4 anaplastic astrocytoma). 13 patients had a stereotactic biopsy and in 10 cases a resection was performed. All the patients were referred to radiotherapy. The estimated median survival time was 85 days in the first group compared with 171 days in the second one. The estimated survival time was 2.757 longer after tumor resection. Radiotherapy had a significant effect on survival (p= 0.001). The authors didn't find a significant difference in the time of deterioration between these two treatment (p=0.057) and concluded that in this population the survival was improved by the resection of the tumor although the overall benefit is modest [56].

In 2010 Chaichana et al [7] reported a retrospective study were they found that patients who underwent surgical resection had median survival of 5.7 months, while patients who underwent needle biopsy without resection had median survival of 4.0 months. For patients aged 70 years and older median survival was 4.5 months for 26 patients with surgical resection as compared with 3.0 months for 26 patients who underwent needle biopsy (P = 0.03). The authors found no significant differences in postoperative outcomes among the two groups. As a conclusion this study demonstrates that older patients tolerate aggressive surgery without increased surgery-related morbidity and have prolonged survival as compared with similar patients undergoing needle biopsy.

A study of Zouaoui et al [59] in 2014 describes oncological patterns of care, prognostic factors, and survival for patients with glioblastoma multiforme older than 70 years in France. 265 patients were included. 95 of them underwent surgical resection and 107 biopsy. Adjuvant therapy was also performed-chemotherapy alone (CT), radiotherapy alone

(RT) or concomitant radiochemotherapy (CRC). In the group of patients with biopsy median survival was 199 days in those who received only CT, 318 days in those who received CRC and 149 days in patients who received RT. In the group of patients that underwent surgical resection the median survival (in days) was as following: 245 with CT, 372 with CRC and 26 with RT. A hypothesis of the authors was that elderly patients are undertreated. The authors concluded that Karnofsky performance status seems to be the most relevant clinical predictive factor and RS and CRC have a positive impact on survival for elderly GBM patients in the general population, at least when feasible.

Mariniello et al [31] compared the effects of combined treatments (surgery and radiochemotherapy) on the outcome and survival between elderly (≥ 65 years) patients with glioblastoma and younger ones (<65 years). The median survival of older patients was 14.5 months, significantly lower than patients < 65 years (17 months) (p = 0.02). The conclusion of the study was that when several criteria of selection to surgery are respected (good Karnofsky performance status (KPS), largely resecable tumor, and no significant co morbidity) the difference of survival is less significant.

Age is one of the most important prognostic factor in patients diagnosed with malignant gliomas. A study of Uzuka et al [54] suggested that postoperative KPS score is an important prognostic factor for glioblastoma patients aged ≥ 76 years. Based on statistical analyses of 79 glioblastoma patients aged ≥ 76 years (median age 78.0 years; 34 men and 45 women) that were treated with tumor resection or biopsy followed by chemotherapy or radiotherapy, the authors reported a median overall progression free survival of 6.8 months and a median overall survival of 9.8 months. Patients aged ≥ 78 years were significantly less likely to receive radiotherapy (p = 0.004) and patients with a postoperative KPS score of ≥ 60 were significantly more likely to receive maintenance chemotherapy (p = 0.008). Two independent prognostic factors were identified: postoperative KPS score ≥ 60 (p = 0.017) and temozolomide therapy (p < 0.001)

Konqlund et al [24] included in their study 80 patients over 60 years old diagnosed with high grade gliomas and operated at Oslo and Haukeland University Hospitals between 2008-2009. Clinical outcome was assessed at six months and overall mortality at 2 years. Surgical morbidity included neurological sequels (10%), postoperative hematomas (3.8%), hydrocephalus (1.3%) while the surgical mortality reported was 1.3%. Median overall survival was 8.4 months. Adjuvant radiochemotherapy increased significantly the survival. In univariate analyses couple of factors were identified to reduce survival: age ≥ 80 years, subtotal resection, American Society of Anesthesiology (ASA) scores 3-4, Karnofsky performance scale (KPS) < 70, and mini-mental state examination (MMSE) score < 25. Authors conclusions were that surgical treatment of high grade gliomas carries low mortality and acceptable morbidity in patients aged ≥ 60 years and maximum tumor resection should be attempted.

The benefit of total tumor resection in elderly patients is supported by others studies in the literature. After analyzing 437 patients ≥70 years Scott et all [45] identified 4 prognostic subgroups with markedly different median survivals: subgroup I =patients <75.5 years of age who underwent surgical resection (9.3 months); subgroup II = patients ≥75.5 years of age who underwent surgical resection (6.4 months); subgroup III = patients with Karnofsky performance status of 70 to 100 who underwent biopsy only (4.6 months); and subgroup IV = patients with Karnofsky performance status <70 who underwent biopsy only (2.3 months). Grossman et al [17] published a study aiming to compare surgical outcome of elderly patients undergoing

awake-craniotomy to that of younger patients. A total of 334 young (45.4 ± 13.2 years, mean ± SD) and 90 elderly (71.7 ± 5.1 years) patients were studied. The authors found no significantly higher rate of mortality, or complications in the elderly group and concluded that gross total tumor resection in elderly patients with high grade was associated with prolonged survival. Gulti et al [18] explored the survival and treatment provided to elderly patients diagnosed with glioblastoma in a population-based setting, from the Norwegian Cancer Registry. 2882 patients who were diagnosed with glioblastoma between 1988 and 2008 were included. The following factors were identified as independent predictors of reduced survival: increasing age, no tumor resection, no radiotherapy, and no chemotherapy. In the authors opinion despite multimodal treatment the gain for the oldest seems at best very modest and the prognosis remains very poor.

Another study published in 2012 underlines the importance of total resection regardless of age. Oszvalt et al [37] collected data from 361 patients with newly diagnosed cerebral glioblastoma. Depending on tumor size, location and Karnofski Performance Scale score the patients underwent resection (complete, subtotal and partial) or biopsy. After the surgery all the patients received adjuvant treatment. The overall survival of elderly patients (>65 years) (9.1 ± 11.6 months) was significantly lower than that of younger patients (<65 years) (14.9 ± 16.7 months; p = 0.0001). Age was a negative prognostic factor in patients undergoing biopsy (4.0 ± 7.1 vs 7.9 ± 8.7 months; p = 0.007), but not in patients undergoing tumor resection (13.0 ± 8.5 vs 13.3 ± 14.5 months; p = 0.86), which lead the authors to conclude that resection should not be withheld from patients only on the basis of age.

One of the most extensive study comparing biopsy, partial resection and gross total resection in older patients was published by Almenawer et al at the beginning of this year [2]. The authors undertook a meta-analysis of the outcome, overall survival (OS), postoperative Karnofsky Performance Status (KPS), progression-free survival (PFS), mortality, and morbidity in patients over 60 years old after the surgical procedure. 12607 participants from 34 studies were included. When comparing the tumor resection (of any extent) with biopsy overall survival (MD 3.88 mo, P < .001), postoperative KPS (MD 10.4, P < .001), progression free survival (MD 2.44 mo, P < .001), mortality (RR = 0.27, P = .002), and morbidity (RR = 0.82, P = .514) were in favor of the resection group. Gross total resection was found to be superior to subtotal resection in terms of overall survival (MD 3.77 mo, P < .001), postoperative KPS (MD 4.91 mo, P = .016), and progression free survival (MD 2.21 mo, P < .001) with no difference in mortality (RR = 0.53, 95% CI: 0.05-5.71, P = .600) or morbidity (RR = 0.52, 95% CI: 0.18-1.49, P = .223). These findings support the idea of increasing extent of safe resection in elderly patients, which can lead to an upward improvement in survival time, functional recovery, and tumor recurrence rate at this group of age (>60 years).

Recurrent glioma resection has also been debated in the literature and there are many class III studies that show the improvement of survival with re-resection. A study of Rostomily et al [41] was focused on 51 adult patients with recurrent malignant gliomas that were treated in a Phase II trial of multidrug chemotherapy. 31 patients underwent radical tumor resection before chemotherapy. Higher Karnofsky scores, lower grade initial histology, lack of prior chemotherapy, greater degree of myelotoxicity, smaller postoperative tumor volumes, greater extent of surgical resection, and a local versus diffuse recurrence pattern were associated with a longer overall median time to tumor progression. The overall median survival time was increased in patients with higher Karnofsky scores, lower grade

histology at the time of recurrence, greater degree of myelotoxicity and lobar versus deep tumor location. Helseth et al [19], after studying 516 patients with glioblastoma who underwent primary surgery in 2003-2008 found an overall survival (OS) of 9.9 months and negative prognostic factors like increasing age, poor neurological function, bilateral tumor involvement, biopsy instead of resection, and radiotherapy alone compared to temozolomide chemoradiotherapy. The authors concluded that in a carefully selected group of patients, repeat surgery significantly prolongs OS. Park et al [38] based on clinical and radiographic data of 34 patients who underwent re-operation of recurrent GBM tumors validated a preoperative scale that identifies patients likely to have poor, intermediate, and good relative outcomes after surgical resection. The authors found that the factors associated with poor postoperative survival were: tumor involvement of prespecified eloquent/critical brain regions (P = .021), Karnofsky performance status (KPS) < or = 80 (P = .030), and tumor volume > or = 50 cm (3) (P = .048). Sughrue et al [53] published a paper where they showed that repeat surgery for glioblastoma is beneficial in many cases providing the patient with a satisfying disease free period but is difficult to reliably predict who these patients are.

Useful tools in the surgical treatment of high grade gliomas

The use of intra operative fluorescence in gliomas surgery is a recent innovation. In living mammalian cells 5-ALA is a natural biochemical precursor for heme synthesis [12]. Each cell metabolizes 5-ALA along a set pathway toward heme production. The synthesis of the endogenous fluorescent molecule, protoporphyrin IX (PpIX), is induced through metabolic conversion in the mitochondria [5]. Given via oral route 5 ALA does not usually cross the intact blood-brain barrier but it can easily pass through the disrupted BBB found in gliomas [51]. The principle is simple: 5-ALA acts as a diagnostic fluorescent marker; given orally it assists the surgeons to visualize directly the extent of tumor resection when lighting up the operative field with a specific wavelength light source. The tumor cells that accumulates PpIX can be easily discerned from the surrounding normal cell. The fluorescent dye peak is 2-6 hours after oral administration and disappears from the tumor tissue after 12 hours [28].

5-ALA mediated-photodynamic therapy (5 ALA mediated PDT) has revealed a promising adjuvant tool in the treatment of malignant gliomas [43]. The rapid PDT response in vivo is due to three types of mechanisms: 1. PDT can directly damage and kill the cancer cells; 2. alteration of the tumoral blood flow: stasis, vascullar collapse/ leakage; 3. the induction of an inflammatory response due to the release of cytokines and other inflammatory mediators from target cells [30]. Other studies have shown that 5–ALA PDT causes mitochondrial and nuclear DNA damage with cytochrome c release and activation of caspase-3 and caspase-9 in glioma cells [22]. The lack of randomized controlled trials and an optimal 5-ALA-PDT regimen may be the reason why 5-ALA-PDT is not a standard treatment for malignant gliomas. Some challenging side effects that neurosurgeons have to deal with are cerebral edema and long-lasting skin photosensitivity. 5-ALA- PDT could be regarded as a promising alternative in glioma treatment if the specificity and selectivity of 5-ALA-PDT in glioma tissue would be improved [28].

Hirschberg et al [21] evaluated the effects of 5-aminolevulinic acid (ALA)-mediated photodynamic therapy (PDT) on the invasiveness of human glioma cells migrating from implanted multicell human tumor spheroids. The authors found that 5-ALA mediated PDT inhibited the invasiveness of

the gliomal cells by a migratory inhibition effect rather than by a cytotoxic one

A study of Puppa et al [9] showed that 5-ALA guided resection of high grade gliomas permits an overall gross total resection of 90% in 100% of patients, and 98% in 93% of patients. In the same study the authors found that in 43% of patients the boundaries of fluorescent tissue exceeded those of tumoral tissue detected by neuronavigation and concluded that 5-ALA fluorescence in the surgery of high grade gliomas enables a gross total resection in 100% of cases even if selection of patients remains a main bias. Stummer et al [52] published a study where they showed that fluorescence appears superior to contrast enhancement on MRI for indicating residual tumor. A systemic review and meta-analysis of 10 studies from the literature made by Zhao et al [58] showed a level 2 evidence of superior efficiency of fluorescence guided resection to neuronavigation guided surgery with respect to diagnostic accuracy, extent of tumor resection, safety and survival. Finally, a study of Slof et al [48] showed that 5-ALA guided resection is a cost effective option for the treatment of high grade gliomas.

Intra operative MRI (iMRI) is an imaging tool used primarily to increase the extent of tumour resection (EOTR) while minimizing the impact of the surgery on the brain's eloquent areas. With stereotactic frameless neuro-navigation, iMRI shows changes occuring in the brain as the resection goes on. This is very important as changes occur during the resection: brain shift diminishes, the effect of gravity may be different than on the pre-op scans, etc. Those factors render the "conventional" navigation inaccurate and the extent of resection may suffer from it. A review by Liang and Schulder [29] showed that iMRI enabled a significant increase of EOTR, and was a safe tool used in combination with other techniques such as intra-operative neurophysiology, awake cortical mapping, 5-ALA fluorescence, etc. for the treatment of high grade gliomas. The same ideea is supporterd by Schatlo et al [44] in a recent article focusing on the impact of gross total resection on progression and survival in patients with high-grade glioma and how this can be achieved using iMRI in combination with 5-ALA. Although some studies like the one published by Senft et al [46] showed evidence supporting the use of the technology in gliomas, other studies seem to disapprove this use or at least to show its limits. It is the case of Kubben et al [25] which states that there is, at best, a level 2 evidence to support the use of this technology compared with conventional neuronavigation-guided surgery in increasing EOTR, enhancing quality of life, or prolonging survival after resection of glioblastoma multiforme. On the other side iMRI is an extremely expensive technology and require the upgrading of the operating room, thus inducing a huge cost to the health system.

Intra operative mapping is a technique which aims to delimitate the tumoral margins and thus to limitate the resection to non eloquent tissues. It is of great importance because of the infiltrative nature of gliomas, where these lesions not only grow but also migrate along white matter tracts. This technique helps maximize the extent of tumor resection while minimizing postsurgical morbidity, in order to increase the median survival as well as to preserve quality of life [11]. A review from Garrett et al [16] shows the utility of this technique in the resection of gliomas in eloquent brain regions. Another study of Hervey-Jumper SL et al [20] analyzed retrospectively a single surgeon experience on 859 patients undergoing awake brain tumor surgery between 1986 and 2014. Perioperative risk factors like ASA classification, body mass index, smoking status, psychiatric or emotional history, seizure frequency and duration and tumor site, size, and pathology were assessed. The overall perioperative

complication rate was 10% and the authors concluded that awake brain tumor surgery can be safely performed with extremely low complication and failure rates. Brown et al [6] found that awake craniotomy results in a shorter hospital stay and less frequent postoperative deficits compared with general anesthesia. The data collected retrospectively from 1970 until 2012 suggests an expanded role for awake craniotomy in brain tumor surgery regardless of tumor location.

Different techniques used for functional mapping of the brain have largely replaced invasive techniques such as awake craniotomy [39]. Non invasive evaluation of the brain include BOLD-functional MRI (fMRI) magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). A case study by Asim F. Choudri et al [3] showed that tri-modality functional brain mapping allows non-invasive localization of motor, sensory, and language centers as well as white matter pathways helping the surgical planning.

Conclusions

After three decades of intensive research the prognosis for patients with HGGs is still disappointing. The infiltrative nature of these cancers precludes a surgical cure but nevertheless surgery remains the first and more important step for achieving a good quality of life. Different studies published in the last 25 years have provided evidence that the extent of resection of high grade gliomas can influence time to progression and median survival, although so far there is no class I prospective randomized trial to fully answer this question. A maximal resection is preferred but not with any cost.

The standard of care for elderly patients with high grade gliomas remains controversial and undefined. Although high grade gliomas can develop at any age, elderly population represents half of the glioblastoma population. The increasing age remains the most powerful negative prognostic factor in high grade gliomas, being related with less favorable tumor biology, less aggressive care and co morbid disease

In order to achieve a maximum resection current concept of surgical decision-making takes in consideration multimodal pre and intraoperative information. iMRI has been proved to be safe and became an important tool during tumor surgery. Used in conjuction with other important techniques, such as intra-operative neurophysiology, awake cortical mapping, 5-ALA fluorescence etc., iMRI can help the surgeon to obtain the highest levels of tumor resection while minimizing neurologic injury.

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