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Chapter 7

Neurosurgical Options for Glioma

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Abstract

Glioma surgery has been the main component of glioma treatment for decades. The surgical approach changed over time, making it more complex and more challenging. With molecular knowledge and diagnostic improvement, this challenge became maximally safe resection of tumor, which resulted in prolonged overall survival, progression-free period, and a better quality of life. Today, the standard glioma treatment includes maximally safe resection, if feasible, administration of temozolomide, radiotherapy, and chemotherapy. Surgical resection is performed as subtotal resection, gross total resection, and supratotal resection. Subtotal resection is the resection where a part of tumor is left. Gross total resection is a complete removal of the magnetic resonance imaging (MRI) visible tumor tissue. Supratotal resection is performed as gross total resection with excising the MRI visible tumor tissue borders into the unaffected brain tissue. Before we make final decision on which type of resection should be performed, many factors have to be considered. The main question has to be answered: what the actual impact of resection on the progression of glioma is and what the functional risk of resection is.

Keywords: glioma biopsy, subtotal resection, gross total resection, supratotal resection, oncofuntional balance

1. Introduction

Glioma is the most frequent malignant tumor of the brain, with a high mortality as the grade of glioma gets higher [1]. World Health Organization in 2016 classified glioma into four grades, where I and II grades are classified as low grade glioma and III and IV grades as high grade glioma [2]. Glioma surgery is one of the most common and challenging

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surgeries for every neurosurgeon. The history of glioma surgery changed during the past century following all technical progresses. One of the biggest technical improvements started with the discovery of nuclear magnetic resonance in the 1950s, now known as magnetic resonance imaging [3]. After MRI introduction, the concept of maximal MRI visible tumor resection started to be the standard approach to glioma surgery. Nevertheless, this concept had a significant rate of morbidity, and it stranded to be valid for decades. During the past 25 years, the concept of surgical removal of gliomas has changed from a maximally aggressive for high grade glioma to minimally invasive but maximally efficient resection. The concept for low grade glioma changed also from "watch and wait" to active surgical treatment [4].

In the course of years, *subtotal resection* (STR) and *gross total resection* (GTR) evolved to *supratotal resection,* which became the surgical option especially for low grade glioma in the eloquent area and younger patients. With supratotal resection, neurosurgeons are trying to utilize minimally invasive surgery for the preservation of life quality as much as possible, but resecting most of tumor tissue using brain monitoring techniques, intraoperative imaging, awake surgery options, etc. The overall survival period with this approach was extended. As the new surgical concept, supratotal resection, which is actually also aggressive but selective, controlled, and monitored approach, over the years confirmed the highest level of general development of glioma surgery. In this respect, supratotal resection is probably becoming the most important part of *state of the art* in glioma management generally, but we are waiting for the results of big clinical trials. When the tumor infiltrates eloquent brain areas the challenge is how much to resect in balance of maximal safe resection and possible neurological deficit or worsening of functional status [4].

In this review, we are going to discuss surgical options for glioma treatment and the impact of it on the patient's life.

2. Different surgical options

Gliomas represent 30% of all brain tumors and 80% of all malignant brain tumors [1]**.** The origin of gliomas are the transformed glioma cells of the central nervous system. Gliomas can be classified by cell type, localization, and grade. The grade classification is performed by World Health Organization (WHO) in 2016 and widely used [2].

There are four grades of gliomas:

Grade I—pilocytic astrocytoma;

Grade II—diffuse astrocytoma, oligodendroglioma;

Grade III—malignant glioma: anaplastic astrocytoma, anaplastic oligodendroglioma;

Grade IV—glioblastoma multiforme (IDH wild type and mutant), diffuse midline glioma, H3 K27M-mutant.

Grade I and II gliomas are classified as low grade glioma (LGG) and grade III and IV as high grade glioma (HGG). Surgical treatment options are different for every group of gliomas, LGG and HGG, due the glioma life cycle [2].

2.1. Surgical techniques

In this review, we will present contemporary surgical techniques used in treatment of both glioma groups: LGG and HGG and the impact on patient's life. Surgery remains the core treatment for management of gliomas. Surgical resection of pathological tumor mass, almost nonfunctional brain region, is common, standard, and the oldest neurosurgical approach to contemporary neuro-oncology. Historically, glioma surgery was a controversial topic, but many recent studies have demonstrated the crucial place of glioma resection in the management of low and high grade gliomas [5]. Concerning glioma surgery, there are two big questions: what the actual impact of resection is on progression of glioma and what the functional risk of it is [6]. To improve the outcomes of these two questions in past decades, a huge improvement has been made in intraoperative techniques (neuronavigation, intraoperative MRI, intraoperative ultrasound, stimulation mapping techniques, and fluorescence-guided surgery; **Figure 1**) [7, 8]. These techniques were developed to maximize the resection of glioma and preserve or improve the quality of life [6, 7]. Before glioma surgery, the neurosurgeon must calculate all benefits and possible hazards which could influence on morbidity, mortality, and quality of the rest of life.

There are few surgical options based on glioma type:

- glioma biopsy.
- subtotal resection.
- gross total resection.
- supratotal resection.

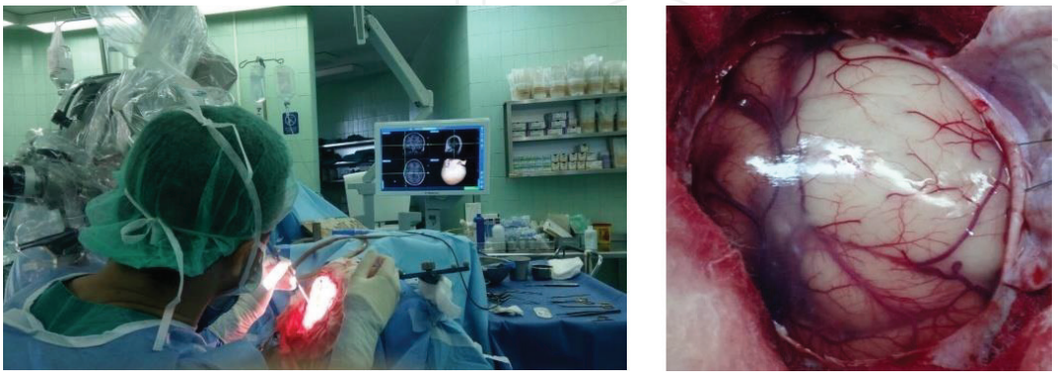


Figure 1. Typical intraoperative arrangement of the patient who undergoes tumor resection and the neurosurgeon, in the early stage of glioma surgery, immediately before dural opening. Microscope is positioned close to the surgeon's left arm and neuronavigation tool is in front (picture on the left). After the opening of the dura, characteristic findings of differently colored glioma affecting the brain cortex are presented. Tumor tissue bulks over the dural edge; it is obviously white-grayish and much lighter, with strange pathological vascularization (picture on the right).

2.1.1. Glioma biopsy

Glioma biopsy is the standard procedure for taking tissue samples of tumors with a minimally invasive approach. It consists of taking a sample of tissue through a minimum opening of the skull. Biopsy indications are tumors in difficultly accessible brain zones, multicenter lesions, and pathology where it is advisable to establish a pathohistological diagnosis, which will then determine further surgical or nonsurgical treatment (e.g., whether it is tumor glioma or lymphoma; the former will then undergo resection, while the latter is mainly nonsurgically treated). On the other hand, very advanced gliomas and gliomas in the elderly who are not candidates for a more aggressive approach (open surgery) are also indications for biopsy. Minimally invasive approaches have been favored for a long time in neurosurgery for glioma resection.

2.1.1.1. Frame-based stereotaxis

Today, Leksell G frame is still the most widely used, consisting of two parts—one fixed quadrangular and the other moving, the so-called arc. The fixed part consists of four graduated rods. On the right or left side of the patient, there is a diagonal bar in the form of the letter "N" that connects the corners.

Of the four basic geometric systems used in frame-based navigation systems, the "arc radius" system is the most commonly used, which is the base of the Leksell frame. The principle of the C arc is based on the ability to reach the center of the C arc from all directions by moving the probe along the radius of the frame. The frame itself is fixed on the patient's head, while the C arc is a movable part with the possibility of penetrating with a puncturing needle through any point on the convexity of the skull. The advantages of the Leksell frame design are the ability to reach any intracranial point with great precision and the ability to use it directly under the control of CT or MRI. One of the disadvantages is the bulkiness of the device itself, the obstruction of the operating field, and the "non-real time" procedure if there is no radiological supervision (CT or MRI).

By setting up the frame and the effect of the CT scanning, the center is first marked in anterior–posterior direction. The center is observed on axial CT scans in the form of the letter X by joining the frame corners. On the vertical plane, the center is marked by pulling the corner line through the mid-point of the letter "N." After defining the center, the target point is defined in relation to the geometric center of the frame and it can be accurately calculated, after which the C arc is moved and the probe is placed in the center of the lesion.

2.1.1.2. Frameless stereotaxis

Next evolutionary step in the development of stereotaxis was frameless stereotaxis. Frame-based stereotaxis is a clearly defined relationship between two coordinate systems (preoperative and intraoperative) and a precise position in relation to the planned procedure without further need for determining coordinates. Frameless stereotaxis, unlike frame-based, uses "point pair" registration to establish a relationship between preoperative images and surgical

field or coordinate systems relative to preoperative images and patients during surgery. To connect these two coordinate systems, "registration" is necessary to establish a common relationship between two coordinate systems [9].

The frameless system consists of two parts, an infrared scanner and a dynamic frame, that is fixed to the Mayfield holder. The dynamic scanner transmits the coordination system data to the operating field and integrates them with software with preoperative images. The dynamic framework requires at least three fixed registration points (nasion, lateral cannula, frontal tuber, and tragus). In the further course, an additional multipoint registration on the curvature of the skull is used for the purpose of co-registration and refining the matching of the two coordinating systems. Registration is performed by marker or laser. Once the registration has been made, it is necessary to carry out a check for early identification of errors. The advantages of the frameless system are ease of use, as well as intraoperative possibility, altering the route or plan without the need for additional CT scanning, not taking up a large space, the possibility of absolute freedom of manipulation of the operating field, and no preoperative planning and determination of the coordination point on CT or MRI.

As the leading flaw of the frameless system, there is a decrease in precision compared to frame based, most likely because of less defined registration points in comparison to clearly defined points. However, these deviations from the target point in the brain do not exceed a value of 2–5 mm; they are expected and they are generally accepted when executing the procedure.

2.1.1.3. Navigation-guided glioma biopsy

Most important indications for neuronavigation in glioma surgery are:

a. Neuronavigation driven resections, subtotal resections, and reduction of gliomas (determination of tumor margins, edges of craniotomy, as well as limitations of the form and length of skin incisions)

b. Neuronavigational inducement of glioma biopsy

- early diagnosis with minimal risk
- deep lesions (thalamic gliomas, basal ganglia etc.)
- patients with a high operative risk in case of prolonged anesthesia or those with advanced diseases and poor prognosis compared to co-morbidity
- multiple lesions
- patients who reject the proposed surgery for resection
- patients with "unsafe" radiological diagnosis and suspicion of infectious or demyelinating disease

c. Setting the catheter into tumor cavity

- cyst drainage
- intratumoral chemotherapy
- intratumoral radiotherapy

Unrelated to the use of neuronavigation in oncology or the treatment of gliomas, neuronavigation can be used in ventriculostomy, electrode placement for deep brain stimulation, endoscopic neurosurgery, etc.

2.1.1.4. The present, challenges, and future of biopsy

One of the disadvantages of the established stereotaxy is deviation during the procedure and its execution at the present time in the MRI or CT preoperative images. Currently, efforts are being made to overcome the problem by real-time MRI-induced biopsy with promising results [10, 11]. In certain cases, when we have an extremely small tumor, the precision of biopsy is questionable with disappointing pathohistological results. Today, microelectrodes are used to do the microrecording of the brain electrical potential on the biopsy path and in the target tumor zone with the absence of electrical potentials, performing biopsy by the "real time" method and increasing safety and precision [10].

Since fluorescence 5 ALA has already found its use in tumor surgery and increased radicalism of resection, it is also applied in biopsy; a decrease in negativity of results was observed [11].

Because of the existence of brain blood barriers and inadequate chemotherapeutic penetration of brain tumor, convection-enhanced delivery is developed, which represents a modality of combined surgical and colon tumor treatment. Locally, the medicine (chemotherapeutic) is placed into the brains of rats by using a frameless catheter; it is used in the treatment of diffuse brain stem gliomas [12].

2.1.2. Subtotal resection

Glioma resection in which a portion of tumor can still be seen in postoperative images is called subtotal resection (STR). STR should be performed only when it is not possible to perform gross total resection (GTR). To have better results of STR, tumor mass must be removed as much as possible to preserve functionality of the patient and quality of life. All technical supports should be used to optimize STR. Intraoperative MRI should be used in every STR to optimize glioma safe removal [8].

2.1.3. Gross total resection

Some mathematical modeling studies estimated that at least 78% of preoperative tumor volume must be resected to increase survival and resection brings an incremental benefit of up to 98% [13]. The surgical resection technique that brings this benefit with clear margins is called gross total resection, **Figures 2** and **3**. Since the beginning of wide use of modern operative

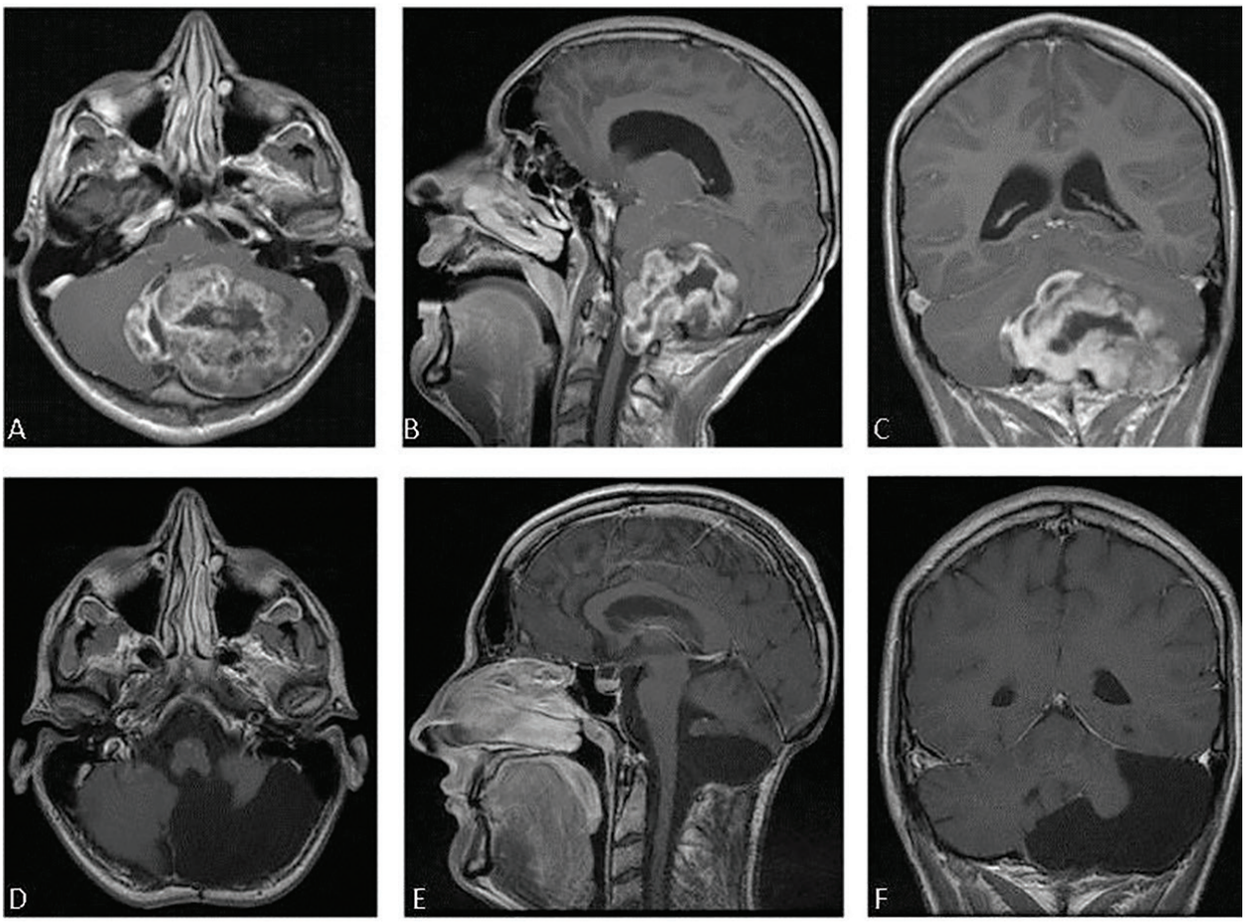


Figure 2. A 19-year-old male patient admitted to our department comatose, with Glasgow Coma Scale score—GCS 4, with respiratory dysfunction (August 2015). Urgent surgery was performed with GTR, pathohistology confirmed LGG. Three weeks later, the patient was discharged from the department in good condition—awake, walking alone with Karnofsky score 80. Preoperative axial, sagittal, and coronal postcontrast T1-weighted MRI (A-C) show a huge tumor in the cerebellum, predominantly on the left side with adherence to the brain stem and propagation down to C2 (Siemens MRI Avanto 1.5 T). Two and a half years postoperative contrast T1-weighted MRI, in March 2018 (D–F), shows complete tumor resection with no signs of tumor rest or recurrence.

techniques, the incidence of gross total resection has increased [8]. On the other hand, without technical development, microsurgical GTR of glioma cannot be always achieved because of the deep location of tumor, located in the eloquent regions, and/or both hemispheres spanned [14]. Aggressive GTR can lead to increased morbidity and complications without improving survival [15, 16]. GTR is shown to be an independent factor of overall survival (OS), but, in respect of STR, evidence is not clear for its benefit [6–8, 15]. Like for STR, in GTR also, intraoperative MRI and all technical supports should be used to have a better resection and to preserve the eloquent brain areas.

2.1.4. Supratotal resection

Surgical resection of pathological tumor mass, almost nonfunctional brain region, is common, standard, and the oldest neurosurgical approach to contemporary neuro-oncology. Historically, glioma surgery was a controversial topic, but many recent studies have demonstrated the crucial

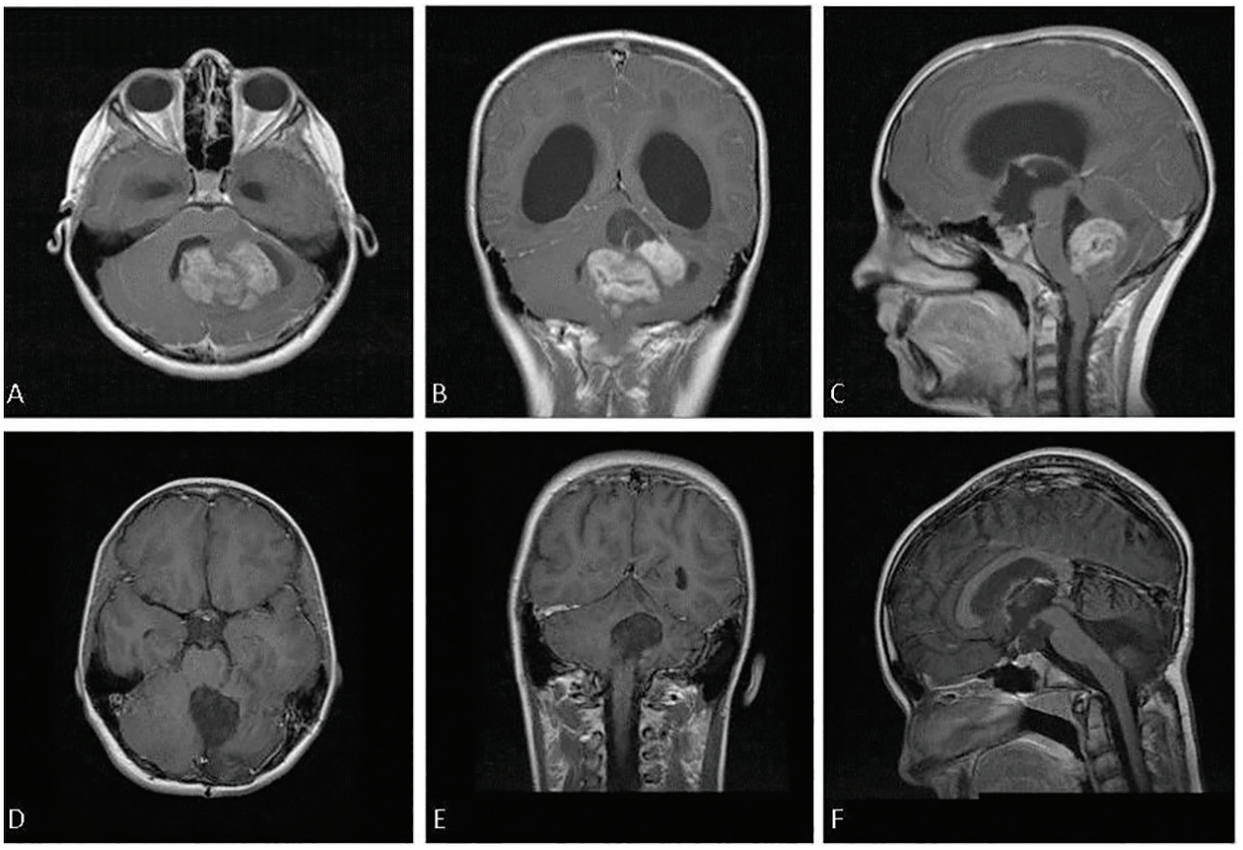


Figure 3. An 11-year old girl with glial tumor in the posterior fossa producing hydrocephalus, admitted to the neurosurgical department with impairment of consciousness, walk and gait disturbance, fully dependent on parents (June 2015). Preoperative T1W axial, coronal, and sagittal contrast brain MRI (A–C) revealed a huge glial tumor, predominantly solid, mostly located in the left cerebellar hemisphere with partial involvement of the fourth ventricular floor and compression to the brain stem (low grade glioma). Two and half years of postoperative contrast T1W MRI shows no recurrence of tumor (D–F, March 2018). The child is in full condition without any neurological deficit.

place of glioma resection in the management of low and high grade gliomas [5]. Over time, the approach to glioma changed from minimally invasive biopsy to maximally possible resection (STR or GTR). Today, total resection changed from temporal lobectomy to very aggressive frontal lesion—paralesional resection of high grade glioma. In the past decade, supratotal resection became a popular approach technique for glioma resection. Supratotal resection includes, like GTR, a total tumor resection with radical resection of perilesional brain tissue, nonglioma region, **Figure 4**. Even after GTR, because of the infiltrative behavior of glioma, probably there are some cells left, which is the biggest challenge to a successful resection and increase in recurrence, OS, and progression-free survival (PFS) [5, 17]. With conventional MRI, it is almost impossible to estimate spatial extent of infiltrative glioma [5]. In low grade glioma, tumor cells are found up to 20 mm beyond MRI seen abnormalities, while in GBM, cells are found diffusely in the hemisphere on the GBM site, even contralaterally [17]. These cells lead to diffuse spread of tumor and its recurrence [5]. Visualization of these cells is beyond any known technique. With supratotal resection of the margins around tumor visible on FLAIR-weighted MRI, there is a limited possibility of leaving residual cells. This resection impacts also on the history of malignant transformation of glioma, which occurs after diagnosis in 4-year

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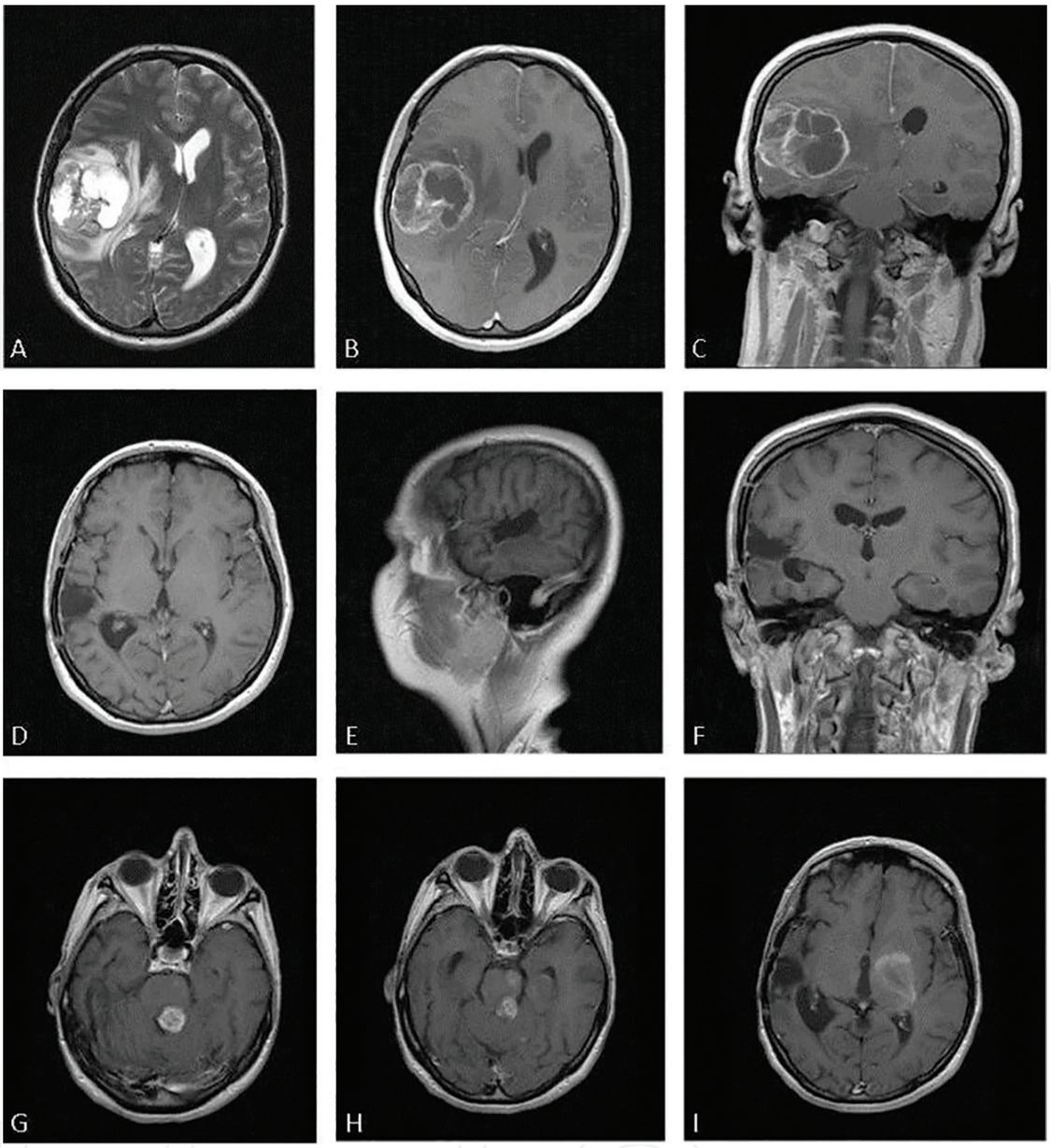


Figure 4. A 38-year old female patient admitted to our neurosurgical department after a large glioma was found in the right temporal region. The patient was with mild left-sided hemiparesis and dizziness (January 2016). Supratotal resection was done and tumor completely resected with 1 cm perilesional tissue. She was discharged from hospital 5 days after the surgery without any neurological deficit. Chemotherapy (temozolomide) and the whole brain irradiation were done immediately. Brain MRI (A–C) was performed prehospitally, T2W axial sequence and T1W axial and coronal postcontrast sequence show extensive, solid cystic tumor located right temporoparietally, surrounded by peripheral edema with compression signs on the right side of the cerebral chamber and signs of mediosagital structure shift to the left. Twelve months after the surgery (March 2017), there was no recurrence on control MRI (middle row, pictures D-F). The same patient 16 months after the surgery (G–I). It was IDH negative glioblastoma multiforme, Grade IV, wild type. Although a complete neurosurgical resection was performed, recurrence was revealed on 16 months follow-up MRI (July 2017), not even on the site of the previous surgery but on the contralateral side as multicentric lesion in the brain stem. MRI T1W axial postcontrast sequence showed multicentric lesions in the left cerebellar pedunculate area, left parietal paraventricular, and left parietal supraventricular areas. The postoperative area on the right did not show any recurrence of the primary tumor. Despite all given therapy, the patient died 17 months after the surgery. This example confirms the thesis that glioblastomas are a diffuse disease, and probably, even after extremely vast surgery, tumor reoccurrence will occur relatively soon. IDH, Isocitrate dehydrogenase.

periods on average [5]. Currently, a randomized controlled clinical trial of supratotal resection for all grade gliomas in noneloquent areas is being conducted with 120 participants; primary results are expected soon (2 years OS, PFS, and Karnofsky Performance Score (KPS)) [18]. The evolution of supratotal surgery from gross total to supratotal was possible due a number of technological advances (light microscope, microneurosurgical tools, magnetic resonance imaging, neuro-navigation, brain mapping, 5-ALA fluoroscency technique, tractography, etc.). Supratotal resection, concerning recently published findings of a few independent authors, resulted in better survival of glioma patients [13, 19].

2.2. Low grade glioma surgical options

For grade II glioma, the recommended treatment is maximally safe resection, with or without radiotherapy followed by procarbazine, lomustine, and vincristine administration or temozolomide plus radiotherapy followed by temozolomide depending of glioma features [20]. When it comes to low grade glioma in the meta-analysis, 5-year OS was markedly increased after resection of low grade glioma, increasing from 50–70% in STR to 80–95% in GTR [7]. GTR has superiority over STR and biopsy with increased OS and PFS [6, 21, 22]. But in another large study, they did not find any difference between STR and GTR in 5-year OS [23]. The impact of STR on OS must be more clearly defined. One study has shown that in younger patients with supratentorial low grade glioma, OS after GTR at 2 and 5 years was 99 and 93%, respectively. The PFS rates at 2 and 5 years were 82 and 48%, respectively [13].

In addition to greater OS GTR for low grade gliomas, it may impact on alerting process from low grade to high grade glioma [7]. In children after GTR, low grade glioma often does not need any further therapy, with 10 years OS rates of 90% or greater, with rare tumor recurrences [24]. In a study including patients with supratotal resection of low grade glioma with 11-year mean follow up, malignant transformation to high grade glioma did not occur. In the control group of total resection, 24% of the patients had malignant transformation from low to high grade glioma ($p = 0.037$) [19]. These promising results come from a pilot study including only 16 patients with performed supratotal resection; a larger study is needed to give a more relevant overview of the behavior of lower grade glioma after supratotal resection.

2.3. High grade glioma surgical options

Recommended treatment for grade III and IV glioma, glioblastoma multiforme (GBM), includes maximally safe resection, if feasible, administration of temozolomide with combination of radiotherapy and chemotherapy depending of favorable and unfavorable prognostic factors and glioma features [20]. The median OS for GMB is 15 months and for grade III tumors between 3.5 and 10 years [14, 25]. In surgical treatment, STR shows better OS compared to biopsy without increasing morbidity [8]. As shown in a meta-analysis of 12,607 high-graded glioma in elderly patients, biopsy OS *vs*. STR was 5.71 months *vs.* 8.68 months, respectively, with lower morbidity rate and longer progression free survival in STR patients [21]. In studies assessing the extent of resection (EOR) in high-grade glioma, in the so-called volumetric studies, STR showed a shorter OS of 2 to 8 months; in nonvolumetric studies, OS was also shorter by 0.9 to 8 months [7]. In their study, Chaichana et al. showed that residual volume and EOR

are independent values for OS and GBM recurrence. They found that the residual volume of <2 cm^3 with 95% resection has the greatest reduction in death in GBM patients [14]. Because of this EOR feature, it is mandatory to perform GTR always when possible, depending on tumor location and quality of life after GTR. GTR has superiority over STR in elderly patients with high grade glioma. GTR resulted in better OS, PFS, and Karnofsky performance score [21]. In children with mean age of 11 years, GTR of high grade glioma resulted in better OS than STR, 3.4 years *vs.* 1.6 years, respectively. Female patients with GTR also had a better OS than male patients, 8.1 years *vs.* 2.4 years, respectively [26]. Concerning higher grade glioma, supratotal resection can have some benefits. In a study of Li et al. of 876 patients who had a GTR (100% EOR), 643 underwent resection of T2 FLAIR abnormality region. Approximately, 18% of them had negative EOR due to postoperative edema, and in positive patients—more than 53.21%—FLAIR resection was associated with improved OS compared with patients with less than 53.21% FLAIR resection (20.7 months *vs.* 15.5 months, $p < 0.001$) [27]. With supratotal resection, the usage of chemotherapy and radiotherapy was reduced after supratotal resection.

3. Surgical technique and oncofunctional balance

As mentioned before, the overall technical development has made supratotal resection possible, with adequate balance between maximal resection of tumor with paralesional region and functional consideration for the eloquent region of the brain. To increase the extent of resection, before surgery, functional MRI, white-matter tractography is performed; during the surgery, intraoperative MRI or ultrasound and 5-ALA-guided resection are used [5]. All these techniques give a rich fund of information, but when the leak of functional information occurs, it signals to us that, while operating, we approached the eloquent brain areas resection [5, 28]. Electrostimulation mapping during supratotal resection is the most important technique used to identify cortical areas and subcortical pathways involved in eloquent functions (especially motor, sensory, language, and cognitive functions) [5, 28, 29]. The usage of electrostimulation in humans started in the 19th century, but the first one in neuro-oncology was used in the 90s of the 20th century by Mitchel Berger. He applied electrostimulation for the mapping of eloquent cortical areas. Hugues Duffau extended and summarized the indication of electrostimulation usage at cortical and subcortical levels intraoperatively [29].

Intraoperative bipolar electrostimulation mapping has become a mandatory tool in neuro-oncology allowing to:

a. study real time individual cortical functional organization;

b. study subcortical connectivity along resection;

c. perform resection according to individual corticosubcortical functional boundaries;

d. make a better neuro-oncological impact, with preservation of the quality of life [28, 30].

With intraoperative electrostimulation, resection is extended into the regions which were considered inoperable. By this extension, a great functional outcome has been documented with

more than 95% of patients recovering to the normal neurological status in 3 months after the surgery, while some patients had improvement in comparison with their preoperative status. In respect of epilepsy, 80% of the patients with preoperative epilepsy did not report it after the surgery [28]. Electrostimulation is a safe, easy, accurate, and reliable technique of individualization of resection for each patient aiming to achieve the "oncofunctional balance."

"Oncofunctional balance" is the term used by Duffau to illustrate the approach to glioma resection through interaction with the patient to determine the best therapeutic sequence according to the patient's needs [31]. Intraoperative electrostimulation is used during the awake glioma surgery, which allows studying interactions between the natural history of tumor and the brain reorganization. With this approach, we are able to preserve the eloquent functions of the brain. Each patient who will undergo supratotal resection should be informed about possible deterioration of the eloquent functions, which of them are most important to him/her to achieve maximal oncofunctional balance. With this approach, glioma surgery becomes an individual surgery, especially designed for each patient.

4. Conclusion

Glioma surgery is one of the most impacting surgical interventions to human health, life, and quality of it. As the molecular knowledge of the life circle of gliomas and techniques improves, it increases our dream that potential curing glioma will come true. Today, the most important treatment option for preserving the quality of life and overall survival is surgical resection. If possible, maximal surgical resection with preservation of neurological functions should be first option in treatment of low and high grade glioma. The resection should be performed with the balance of maximal resection and maximal preservation or improvement of the quality of life. The new promising approach in glioma surgery is supratotal resection with the use of electrostimulation mapping, which makes glioma surgery an individual treatment option for each single patient. But there is a need of more clinical evidence to make supratotal resection widely used. Supratotal resection today is still reserved for individual cases. However, if it is impossible to perform GTR, then STR should be performed. Glioma biopsy is only the last option to confirm the diagnosis for gliomas without possible surgical resection as treatment option.

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Conflict of interest

The authors do not declare any conflict of interest.

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