



# Surgical Resection Techniques of Central Area Gliomas

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The resection of eloquent located infiltrating brain tumors still presents one of the most formidable challenges in neurosurgery. The need to perform complete (and hence aggressive) resections of high-grade gliomas has been strongly supported by level II evidence of the impact of a complete resection on survival [1–3] and stands in contrast to the need to preserve the patients' integrity and the general principle of medicine to “first do no harm.” Fortunately, recent developments in neuro-oncologic neurosurgery provide technologies that can allow for a safe and still aggressive resection even in the central motor area. Among these developments are:

- Improved preoperative imaging (metabolic and functional/anatomic) that allows for improved planning,
- Intraoperative visualization of the tumor (5-aminolevulinic acid [ALA], ultrasound, and intraoperative magnet resonance tomography [iMRI])
- The identification of functional and nonfunctional areas (i.e., resectable areas) by intraoperative monitoring.

Once resectable tissue has been identified, technologies for a safe removal are now available (e.g., ultrasound aspirators). The introduction of subpial resection techniques allows for a more complete resection that preserves the subarachnoid vessels and therefore prevents vascular injuries. Taking advantage of these methods enables the neurosurgeon to limit the resection to functionality and not the tumor margin

per se, thereby allowing for a potential supramarginal resection concept. Based on these considerations, this chapter discusses surgical strategy and resection techniques of central area gliomas, the avoidance and management of complications, and the anticipated future development of neuro-oncologic neurosurgery.

## 21.1 The Need to Perform Complete Resections of Intrinsic Brain Tumors

### 21.1.1 The Evidence for High-Grade Gliomas

Currently available randomized and controlled studies advocate a surgical resection of malignant gliomas. The prospective randomized 5-ALA study with a total of 270 patients compared the 5-ALA-fluorescence-guided resection of glioblastomas with the conventional white light assisted surgery [1]. The 5-ALA-fluorescence-guided resections resulted in a higher frequency of complete surgical resections of the contrast-enhancing tumor parts on magnetic resonance tomography (MRT). This 29% higher frequency of complete resections after 5-ALA-guided resection resulted in a significantly improved 6-month progression-free survival [1, 2]. Although this study was not directed at an analysis of the overall survival (OAS), a non-significant trend toward a better OAS was observed in the 5-ALA-group [1]. The additional

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analysis, which included biases and imbalances, suggested a relationship between survival and degree of surgical resection of glioblastoma patients [2]. Next to the 5-ALA study, the prospective randomized and controlled Frankfurt iMRT study demonstrated the benefit of a complete surgical resection of glioblastomas on the patient progression-free survival [4]. Furthermore, it was speculated that the degree of the surgical resection may enhance the efficiency of adjunct and adjuvant therapies [3]. Therefore, this evidence suggests a significant benefit of surgical cytoreduction in malignant gliomas.

### 21.1.2 The Evidence for Low-Grade Gliomas

Based on the fact that the majority of low-grade glioma (LGG) patients are young adults without major neurologic deficits who enjoy normal life [5], historically these patients have been offered a “wait-and-see” observation of the lesion or just a diagnostic biopsy [6]. But this approach does not take into account the nature of LGGs as a slow-growing process, invariably progressing to high-grade gliomas. LGGs grow continuously about 4–5 mm per year [7], with an inverse correlation between

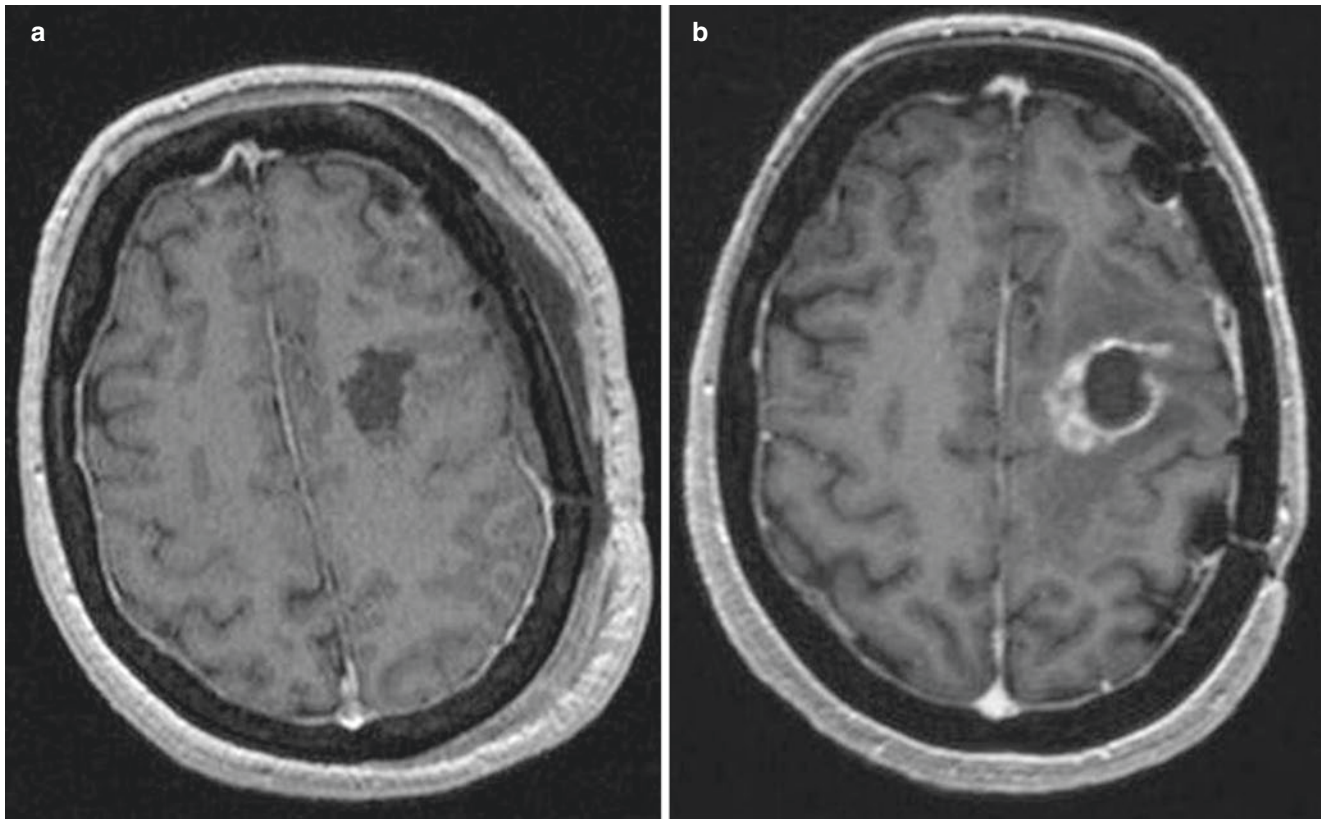
growth rate and overall survival [8]. Recent studies clearly demonstrate a significant increased overall survival following “complete” resection [6, 9–12]. The largest surgical series to date published by the French glioma network identifies the extent of resection as an independent prognostic factor significantly associated with longer survival [13]. At the same time residual tumor volume (of less than 5–10 cm<sup>3</sup>) acts as a predictor of malignant transformation [12]. Therefore, according to the current European guidelines, maximal resection represents the first therapeutic option in LGGs [14]. However, a widely accepted definition of maximal resection of LGG has yet been established. Biopsy studies detected tumor cells at a distance of 10–20 mm of the MRI-defined tumor margins [15], suggesting a supramarginal resection with a 2-cm margin around the LGG visible on MRI [16]. In recent studies an increased epilepsy control by supramarginal resection is discussed based on the hypothesis that epileptic seizures arise from the peritumoral tissue and not from the tumor core itself [17].

Therefore, our surgical aim should be to resect the T2/FLAIR-weighted MRT-affected tissue to provide the best chance for stabilizing the disease by controlling epilepsy, delaying malignant tumor transformation, and increasing overall survival.

## 21.2 The Biological Need for a Supramarginal Approach

Maximum resection of low-grade and high-grade gliomas can obviously prolong the progression-free survival (PFS) and overall survival (OAS). However, as a consequence of the infiltrating growth pattern of gliomas, local tumor recurrence surrounding the resection cavity is almost inevitable

(Fig. 21.1). Therefore, modern neurosurgical-neuro-oncology needs to address the issue of resection within the infiltration zone by adopting a supramarginal approach, extending the resection beyond the lesion itself. This approach is highly dependent on the intraoperative evaluation of tissue functionality and has therefore promoted the use of intraoperative monitoring (IOM).



**Fig. 21.1** Recurrence of a glioblastoma after complete surgical resection. (a), This illustrates the case of a 50-year-old male patient suffering from recurrent glioblastoma (glioblastoma, WHO<sup>o</sup>IV; IDH wildtype). (b), Fourteen months following complete surgical resection

### **21.3 Surgical Resection Techniques of Central Area Gliomas: Strategy and Technique**

We define the central area of the brain as the structure that involves the primary motor cortex, the superior part of the cortical-spinal tract, and the primary sensory cortex, including the thalamo-cortical areas. Surgery in these areas has therefore to take into account the potential damage to motor functions and disturbances of somatosensory functions.

In many centers sophisticated preoperative imaging, including functional MRI, fiber tracking, and metabolic imaging, is available and enables the surgeon to define the

anatomic and functional localization of the lesion, thereby providing valuable information that helps to define the risk of causing permanent damage. At this point the detailed goals of surgery must be defined and involve several considerations. First, the individual situation of the patient must be known and considered. Especially in elective (low-grade glioma) surgery, the timing of surgery must be discussed. Is the patient able to accept a temporary deficit in this period of his or her life? Is a minor permanent deficit after a resection of a high-grade glioma compatible with an acceptable quality of life? Is the family ready to provide support if a major deficit occurs? The surgeon needs to define the goals of surgery within this social framework.

## 21.4 Defining the Surgical Strategy

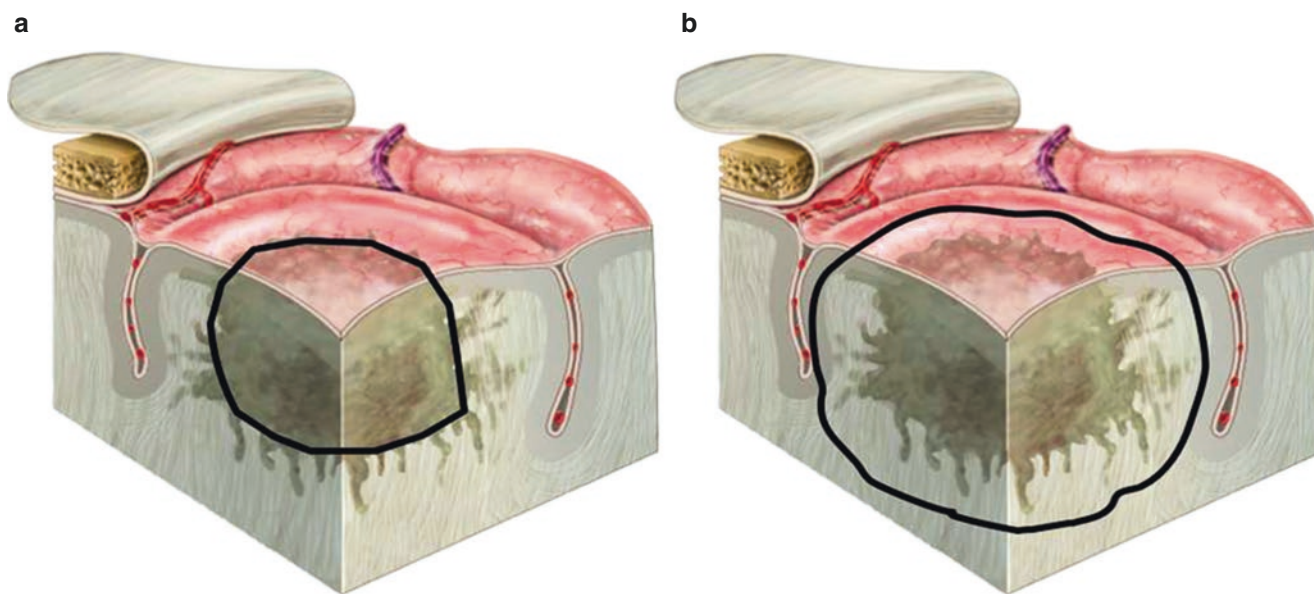
Under the perspective of maximum prolongation of survival, the primary surgical goal should be the removal of the contrast-enhancing part in the case of a high-grade glioma and the T2 or FLAIR-defined lesion in the case of LGGs. Considering the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. It is therefore necessary to consider a supramarginal approach, thus putting eloquent structures at a high risk for permanent neurologic deficits (Fig. 21.2).

By planning the resection of infiltrating tumors, the surgeon is subject to antithetical endpoints: do no harm ver-

sus the removal of deadly neoplastic tissue. Therefore the surgical strategy is aimed at a trade-off between both endpoints.

To resolve this conflict, the surgeon must involve several technical and ethical aspects:

- the indications for surgery and informed consent,
- optimized surgical planning aiming at a supramarginal resection,
- avoidance of permanent neurologic injuries by minimizing the risk of vascular or tissue-related neurologic deficits.



**Fig. 21.2** Different surgical approaches to resect an infiltrating intracerebral tumor. **(a)**, A common neurosurgical approach to resect infiltrating intracerebral lesions is to remove only the lesion. This approach might result in a complete surgical resection as defined by complete removal of the contrast-enhancing part in the case of a high-grade glioma and the T2 or FLAIR-defined lesion in the case of low-grade gliomas. In the light of the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. **(b)**, A supramarginal approach addresses the infiltration zone but

has a higher risk for causing permanent neurologic deficits. (Under the perspective of maximum prolongation of survival, the primary surgical goal should be the removal of the contrast-enhancing part in the case of a high-grade glioma and the T2- or FLAIR-defined lesion in the case of low-grade gliomas. In light of the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. It is therefore necessary to consider a supramarginal approach, thus putting eloquent structures at a high risk for permanent neurologic deficits

## 21.5 The Indications for Surgery and the Informed Consent

It is crucial for the surgical strategy that the risks of causing a permanent deficit must be discussed with the patient and the family and adapted to the patient's individual situation. It is very important to weigh the potential course of the disease without cytoreductive surgery versus the likely outcome of an aggressive surgical approach. Finding the indications for surgery of an infiltrating brain tumor is often more difficult and lengthy than the surgery itself. In this discussion adjuvant treatment options must be considered as well (i.e., glioma with 1p19q co-deletion, isocitrate dehydrogenase-(IDH) mutated and yet no chemotherapeutic treatment). The patient must also be prepared for the possibility of a temporary deficit, which may occur from a high-risk procedure. If the patient agrees in a surgical approach in principle, details of the surgical strategy need to be discussed, such as an awake approach.

## 21.6 Optimized Surgical Planning Aiming at a Supramarginal Resection

By treating infiltrating brain tumors and thus resecting highly malignant tissue, a pure lesionectomy as defined by the removal of the CE/FLAIR-defined lesion is insufficient. By thoroughly analyzing the preoperative functional and anatomic imaging available, the risks of a pure lesionectomy versus a supramarginal approach versus only a biopsy may be defined.

We recommend a systematic approach:

- cortical or subcortical lesion?
- relationship to the landmarks of the central region: pre-central sulcus, M1/S1
- central veins
- relationship to subcortical structures: fiber tracts/vessels.

This analysis should answer the following questions:  
Which neurologic functions are at risk by

- approach to the lesion,
- resection of the lesion only (lesionectomy),
- supramarginal resection.

If supramarginal resection seems feasible, the extent of additional resection (until functional tissue is involved) must be defined.

We recommend performing this analysis at the latest the day before surgery. This will allow for a final check with the patient and better preparation of the surgical team. In the postoperative phase it is important that the team checks whether the surgical endpoint has been reached (early postoperative MRI) or if a second look operation should be considered.

## 21.7 Technical Aspects

### 21.7.1 Presurgical Preparation of the Patient for Awake Craniotomy

The patient must be thoroughly prepared if awake surgery is being considered. This involves training of the tasks he or she will have to perform during surgery. For central area tumors these tasks will mainly involve motor skills and simple motor language tasks (e.g., counting, naming) that will monitor facial, lip, and laryngeal motor involvement. Simple motor tasks for upper and lower extremities must be taught. We suggest training movements that globally screen the relevant motor functions and in addition prepare specific tasks evaluating single muscle functions. The patient should be completely aware of the details of positioning, potential pain management, use of a bladder catheter, and duration of the awake phase. In our experience, a specific neuropsychological preparation of the patient is not necessary [18].

### 21.7.2 Presurgical Preparation of the Patient for IOM

The neurophysiologist or technician who is responsible for the IOM setup must be briefed about the specific requirements for IOM in the individual case. Depending on the localization of the lesion, it may be necessary to vary the standard setup. For example, planning the resection of a lesion near the midline may require motor-evoked potentials (MEP) monitoring for the lower extremity compared to planning for a more lateral lesion.



### 21.7.3 Positioning

We recommend the lateral position (Fig. 21.3) for central region tumors with a parallel position of the anteroposterior line to the floor. The advantages of this positioning are:

- simple and fast to perform,
- brain shift in one dimension only,
- good anatomic orientation.

In cases of awake surgery strict axial positioning provides for easy access to laryngeal structures if reinsertion of a laryngeal mask or intubation is required.



**Fig. 21.3** Positioning of patients with central region tumors in the operating room. We recommend the lateral position for patients suffering from central region tumors with a parallel position of the anteroposterior line to the floor. (a), lateral view. (b), coronal view

#### **21.7.4 Skin Incision and Planned Craniotomy**

The craniotomy should be sufficient to expose all superficial parts of the tumor. In addition, the craniotomy should also expose the primary motor cortex. This is of utmost importance for the positive control of MEP or bipolar stimulation (see farther on). In most cases linear incisions are sufficient. Since transcranial stimulation is influenced by the position of the electrode placement, a potential shift of electrode position after the skin incision and insertion of the spreader must be anticipated.

#### **21.7.5 Use of Intraoperative Ultrasound**

We recommend the use of intraoperative ultrasound as an available and very efficient tool for exact tumor localization. For superficially located lesions the identification of the tumor-bearing gyrus can be performed with high precision, independent of intraoperative brainshift. In more experienced hands the ultrasound might also serve for resection control.

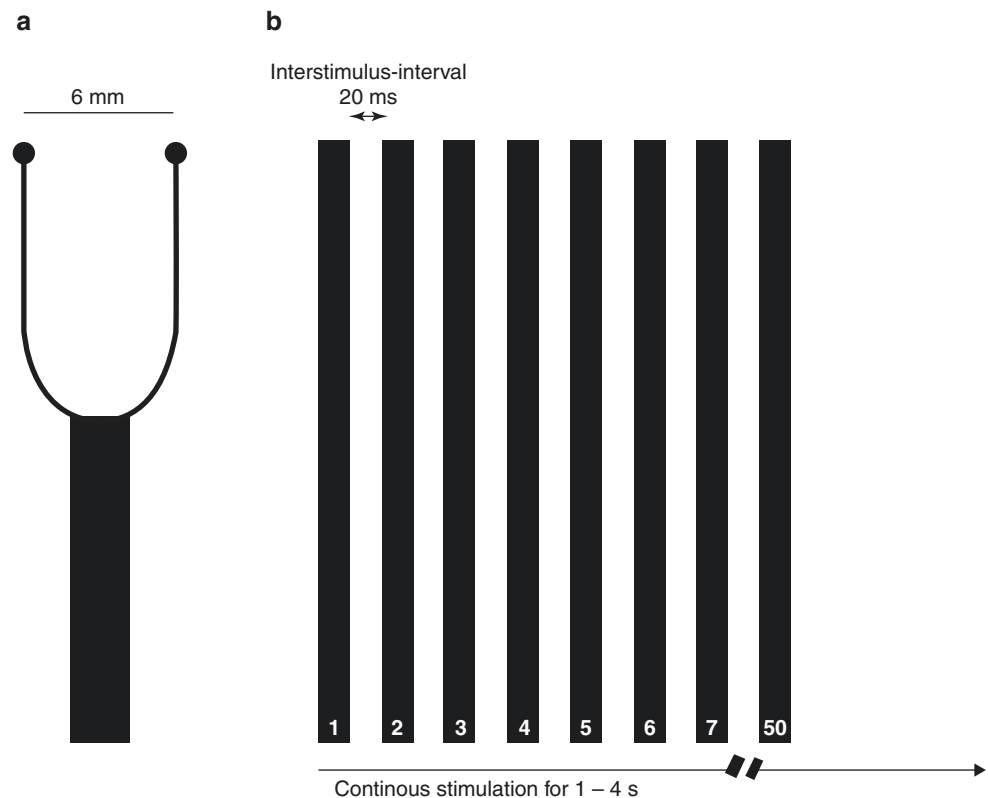


### 21.7.6 Intraoperative Monitoring: Awake Surgery

Although awake craniotomies are most often indicated for monitoring of higher cortical functions (i.e., language perception, calculation, reading), this method can also be employed for monitoring of pure motor functions. For evaluation of post central lesions, mapping of somatosensory functions is best done in the awake setting. Here we will focus on motor mapping. Awake surgery is most commonly performed in the asleep/awake/asleep or lightly sedated setting. Usually a laryngeal mask under total intravenous anesthesia (TIVA) with propofol and remifentanyl is used for the initial asleep phase. In combination with a field block (0.5% bupivacaine plus adrenalin for local vasoconstriction), this provides for sufficient pain control in the initial phase of the operation. As soon as the dura is exposed and palpation of the brain indicates a relaxed brain, the patient can be awakened and the dura opened. The patient will usually require several minutes to awaken after cessation of TIVA. After sufficient compliance is established, testing of the relevant motor functions is started. It is essential that a steady rhythm of movement is established, and quality of performance is communicated with the neurophysiologist and the surgeon.

Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator (Fig. 21.4). Stimulation intensity varies between 1 and a maximum of 6 mA. The exposed area should be subdivided into 5-mm<sup>2</sup> areas corresponding to the 5-mm distance between both poles of the stimulator.

Systematic mapping of the cortical areas is performed by gradually increasing the stimulation intensity by 0.5 mA, starting with 1 mA. Stimulation should be performed 2 s before a motor task is initiated. Application time of the probe is usually 4 s for testing of motor functions. Since bipolar stimulation blocks motor functions, the observer needs to immediately report changes in motor performance. The initial testing aims at identification of the motor cortex. The minimal intensity that blocks functions is the reference intensity or threshold that is used to evaluate the functionality of the tested tissue. As this reference intensity might change because of increased or decreased awareness of the patient, it is important that repeated stimulation of the motor cortex is performed to identify changes. For subcortical stimulation in the fiber tracts, the surgeon should be able to mentally visualize the assumed course of the tracts. It is important to define cut-off values for the stimulation intensity that identify the tissue as resectable. Usually a stimulation intensity of an additional 2 mA of the intensity established on the motor cortex is sufficient for a safe subcortical resection. Because every stimulation can induce a focal or even generalized seizure, the team must be prepared to stop the seizure by irrigation of the exposed brain with ice-cold sodium chloride (NaCl) solution that needs to be available in sufficient quantities (>6 l). Only in very rare cases will irrigation not control the seizure, and treatment with a bolus application of propofol will be needed. Seizure treatment with barbiturates should be avoided due to their longer half-life.

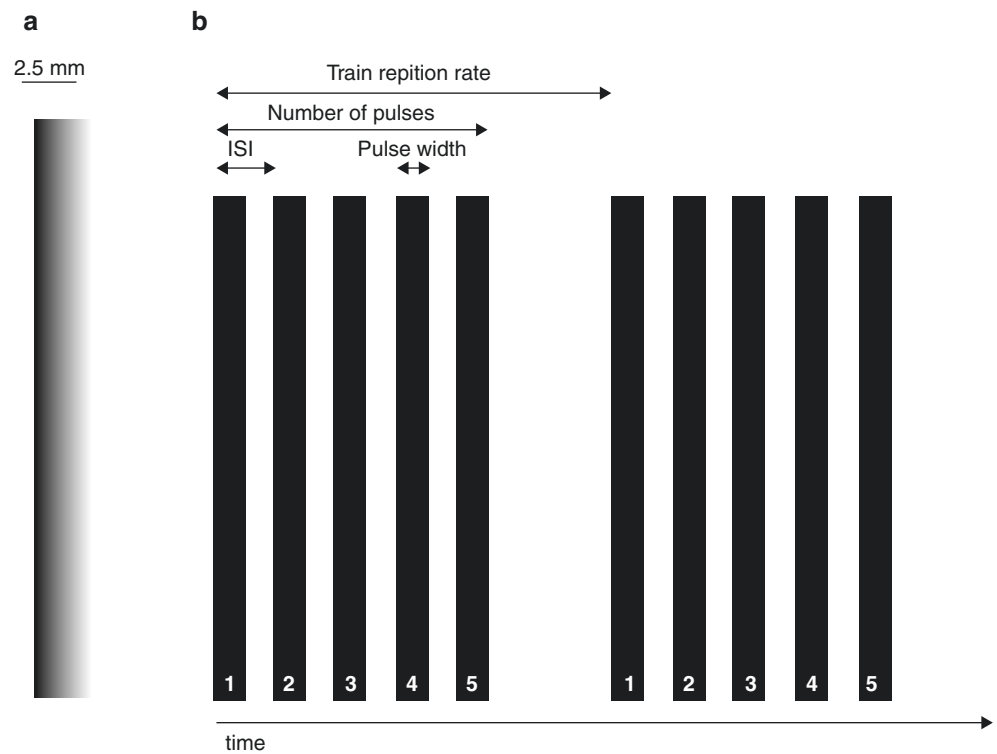


**Fig. 21.4** Method of bipolar stimulation. (a), Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator. (b), A cortical area of about 5 mm<sup>2</sup> is stimulated with a stimulation intensity of up to 6 mA over about 4 s

### 21.7.7 Intraoperative Monitoring: Asleep

The traditional monitoring with transcranial somatosensory-evoked potential (SSEPs) and MEPs is needed and useful but not sufficient for state of the art resection in the central area. This method only offers passive monitoring and identifies problems that are often at an irreversible stage. Monopolar stimulation (Fig. 21.5) should be employed for direct identification of functional cortical or subcortical structures. To this end, in the asleep setting a systematic cortical mapping with a monopolar stimulator should be the first step after dural opening. The technique is in principle similar to the approach described for 60 Hz stimulation. Again, given the considerable risk of stimulation-induced seizures, the surgeon should start with a low current intensity and have an ample quantity of ice-cold irrigation available. As for 60-Hz stimulation, the first

step is the reliable identification of the primary motor cortex to determine the minimal current necessary to stimulate the motor system and thus establish the threshold for stimulation. If the motor cortex is identified, a grid can be placed on the exposed cortical area and if necessary subdurally following the respective gyrus. This provides for the options of direct cortical monitoring with MEPs and SSEPs and can compensate for technical problems of transcranial stimulation such as increasing distance between the cortex and skin caused by brain shift. A systematic mapping of the cortical structures identifies the region of safe corticotomy. In due course of the resection subcortical functional areas may be reached and will be identified by subcortical monopolar mapping. Again, a threshold for safe resection needs to be defined. We usually stop if electromyographic (EMG) responses are triggered by stimulation with 2 mA.

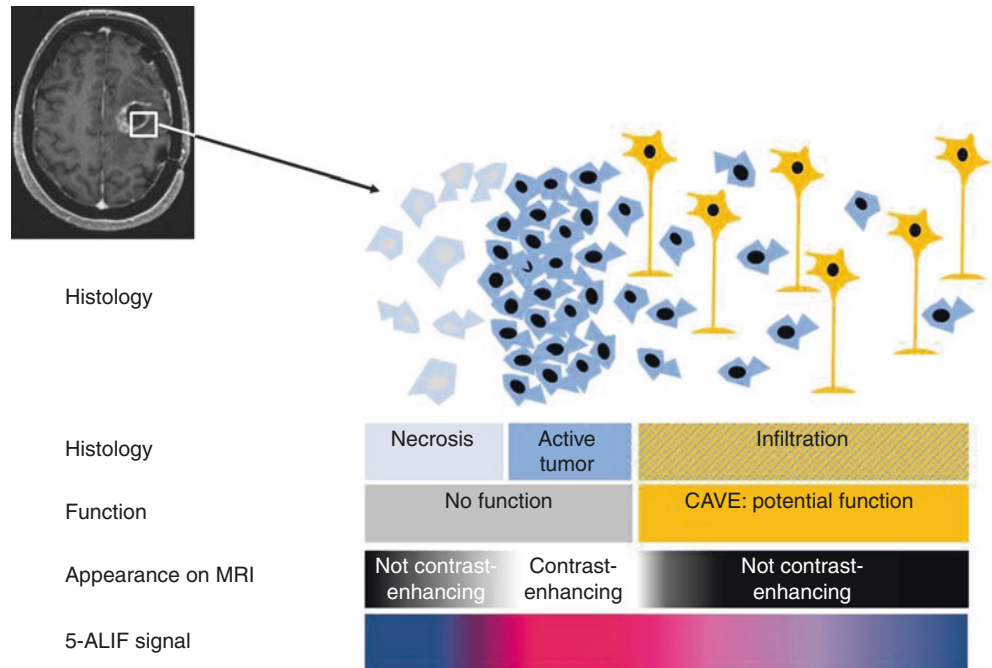


**Fig. 21.5** (a), Method of monopolar stimulation. Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator. (b), A cortical area of about 5 mm<sup>2</sup> is stimulated with a stimulation intensity of up to 6 mA over about 4 s

### 21.7.8 Use of 5-Aminolevulinic Acid

For high-grade gliomas the use of 5-aminolevulinic acid (5-ALA) is correlated with an increased rate of gross total resection and thus with a higher mPFS and mOAS [1–3]. The fluorescence-guided resection of high-grade gliomas with 5-ALA has thus become the standard of care in many centers. An experienced user of 5-ALA can distinguish different qualities of 5-ALA-induced fluorescence (ALIF) [19, 20]:

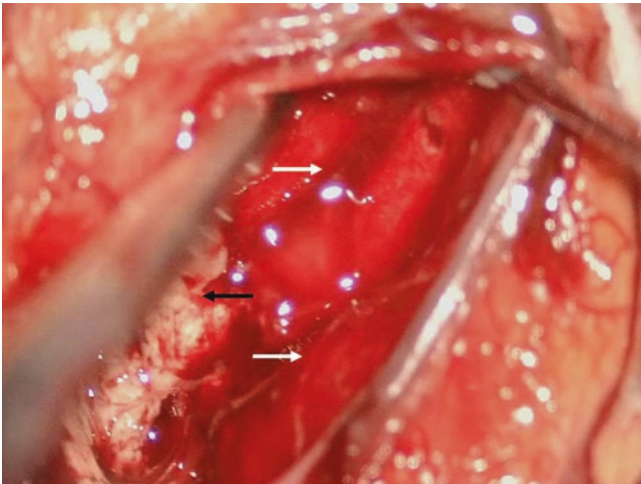
the high intensity “deep red” fluorescence correlating with malignant tumour tissue areas with very high tumor cell content. Here functionality of the tissue can be nearly excluded. At the margin of the lesion the ALIF diminishes to a faint “salmon-like” staining (Fig. 21.6). Here ALIF is helpful to identify the infiltration zone of the tumor as well as functional “danger zones.” When approaching these regions the aggressiveness of the resection must be adapted and stimulation should be employed.



**Fig. 21.6** Correlation of the tumor histology, appearance on MRI, neurologic functioning of the particular tissue, and 5-ALA signal in malignant brain tumors

### 21.7.9 Resection Technique/Tissue Ablation/ Cavitron Ultrasonic Surgical Aspirator

Once resectable tissue has been identified, the removal techniques need to be so precise that only the identified target is removed and vascular injuries are avoided. The traditional resection techniques with bipolar coagulation, suction, and dissector are often too blunt to allow for the necessary precise limitation of tissue ablation. In addition, vascular injuries are often caused by crossing the pial border and thus interfering with the sulcal arteries. We therefore recommend using ultrasound aspiration. This technology allows for the efficient resection of non-eloquent parts of the lesion, and if the right parameters are employed offers a gentle, controlled, and precise ablation of the targeted tissue. In addition, with low-power settings the pia can be preserved and a safe resection can be performed up to the pial border of the adjacent gyrus (Fig. 21.7).



**Fig. 21.7** Technique of subpial resection, during which tumor tissue (*black arrow*) is completely removed until the pial boarder appears. Malignant gliomas usually respect the pial boarders without infiltrating them. Vascular injuries of sulcal and pial vessels have to be avoided as they may lead to infarction and subsequent neurologic deficits. Use of the ultrasound aspiration device may help to prevent injury of the pial layer

### 21.7.10 Hemostasis

In patients with intact coagulation, bleeding usually stops after tumor removal. Since rebleeding in eloquent localizations is almost inevitably associated with severe deficits, a safe hemostasis is compulsory. Because of the destructive tissue effect of and permanent closure of vessels, bipolar coagulation is often not an option. We recommend that for final hemostasis the blood pressure should be raised at least 20 mm Hg above the assumed constitutional blood pressure of the patient. If severe arterial bleeding occurs, bipolar closure of the vessels must be carefully considered. However, in many cases gentle irrigation and covering the area with cottonoids are sufficient. For minor arterial and venous oozing, the application of a hemostat (i.e., oxidized cellulose) is feasible.

## 21.8 Associated Complications of Surgical Resection Techniques of Central Area Gliomas: Avoidance and Management

Complications associated with the resection of eloquent located lesions often result in severe and disabling neurologic deficits. Measures to prevent this have been described previously. In summary:

- Careful planning with precise definition of danger zones: preoperative identification of eloquent areas (cortical/subcortical) and of potential vascular conflict,
- Intraoperative identification of functional tissue by employing cortical and subcortical stimulation techniques,
- Safe tissue ablation techniques that allow for preservation of pial borders,
- Meticulous hemostasis.

Even with strict adherence to state-of-the-art procedures, complications occur at a rate of approximately 6%. Unfortunately, since most of the complications are caused by vascular injury, an effective causal therapy is not available.

## 21.9 Future Developments of Surgical Resection Techniques of Central Area Gliomas

To improve progression of the tumor and overall survival in patients with central area gliomas, the resection limits should be pushed toward a supramarginal resection. However, this is dependent on the quality and availability of intraoperative monitoring. Neurosurgeons should make every effort to have IOM available. Understanding and being able to practice IOM should be part of basic resident training. Recent advances in the understanding of molecular genetic subtyping of gliomas will lead to a more differential prediction of prognosis. This could influence resection techniques; for example, a tumor with 1p/19q mutation with a likely response to adjuvant treatment might need a less aggressive surgical approach than a non-deleted IDH-1 negative glioma.

In addition, as advances in the understanding of brain connectivity have been identified, the shift from evaluating the functionality of brain areas by topologic considerations to additional hodologic aspects might also influence surgical strategies.

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