# Effects of Cancer Treatment on the Nervous System, Volume 2

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Edited by

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# PART 1:

# EFFECTS ON THE CENTRAL NERVOUS SYSTEM

# CHAPTER 1.1

# NEUROSURGERY AND "BRAIN TOXICITY" INCLUDING NOVO TTF

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## Abstract

Neurosurgical resection of brain tumors represents an indispensable treatment option in the multimodal management of patients. In recent years there is clear evidence that the maximum safe resection of brain tumors correlates with the patient prognosis. The neurosurgical goal to achieve maximum safe resection is especially challenging for neurosurgeons in gliomas due to their diffuse infiltrative growth pattern into the normal brain and the lack of a definite tumor margin. Therefore, complete resection of brain tumors, especially diffusely infiltrating gliomas, bears the risk of postoperative neurological deterioration ("brain toxicity"). To minimize the risk of a new postoperative neurological deficit, several advancements were introduced into the neurosurgical field to optimize surgery of brain tumors and markedly increase the safety of these neurosurgical procedures in recent decades. First of all, neuronavigation with multiple preoperative image data is nowadays the current standard for preoperative planning and intraoperative image guidance during brain tumor surgery at most neurosurgical centers worldwide. Intraoperative magnetic resonance imaging (MRI) is a powerful imaging tool that is able to detect residual brain tumor tissue during surgery independent from brain-shift; it is not, however, widely available due to its high costs. Additionally, functional imaging techniques such as fiber tracking/diffusion tensor imaging, functional MRI and

transcranial magnetic stimulation are powerful techniques to visualize brain function during the preoperative investigation of tumors in eloquent brain regions. To localize and monitor the brain function during surgery of eloquent brain tumors, intraoperative monitoring and brain mapping/stimulation are powerful techniques to prevent injuring sites of motor, language and sensory function. In this book chapter, we also focus on “brain toxicity” of specific substances that support the neurosurgeon during resection of brain tumors, locally applied substances that bypass the limited permeability of the blood–brain barrier and tumor treating fields. Overall, “brain toxicity” of these substances and tumor treating fields is relatively low, however, specific side effects have to be considered.

**Keywords:** Brain tumors, gliomas, epileptic seizures, neurotoxicity, tumor treating fields

## 1. Neurosurgery of brain tumors

More than 120 different types of central nervous system (CNS) tumors are distinguished by the World Health Organization (WHO) (David N. Louis, MD Hiroko Ohgaki, PhD Otmar D. Wiestler, MD Webster K. Cavenee, 2016). These tumors are further divided, according to their behavior, into non-malignant and malignant tumors as well as primary and secondary CNS tumors. Diffusely infiltrating gliomas represent the most common primary brain tumors in adults and these tumors are further classified into slowly growing low-grade gliomas (LGG; WHO grade II) and rapidly growing high-grade gliomas (HGG; WHO grade III and IV). Within the subgroup of diffusely infiltrating gliomas, glioblastoma (GBM) is the most frequent and aggressive CNS tumor with a devastating patient prognosis. Since gliomas are characterized by indefinite tumor margins and glioma resection is thus particularly associated with the risk of potential “neurotoxicity,” this chapter will focus on diffusely infiltrating gliomas.

Neurosurgical resection or the biopsy of brain tumors represents an essential treatment option in multimodal management. After surgery, the histopathological tumor diagnosis is established according to the criteria set by the WHO. In recent years, further characterization of brain tumors with the assistance of molecular markers has gained more and more importance in routine clinical practice for postoperative treatment decisions. Depending on the histopathological diagnosis and the molecular markers, either postoperative treatment such as chemotherapy and/or radiotherapy is initiated or a follow-up treatment with regular imaging studies is conducted in patients suffering from brain tumors (Stupp et al., 2005). Over recent years,

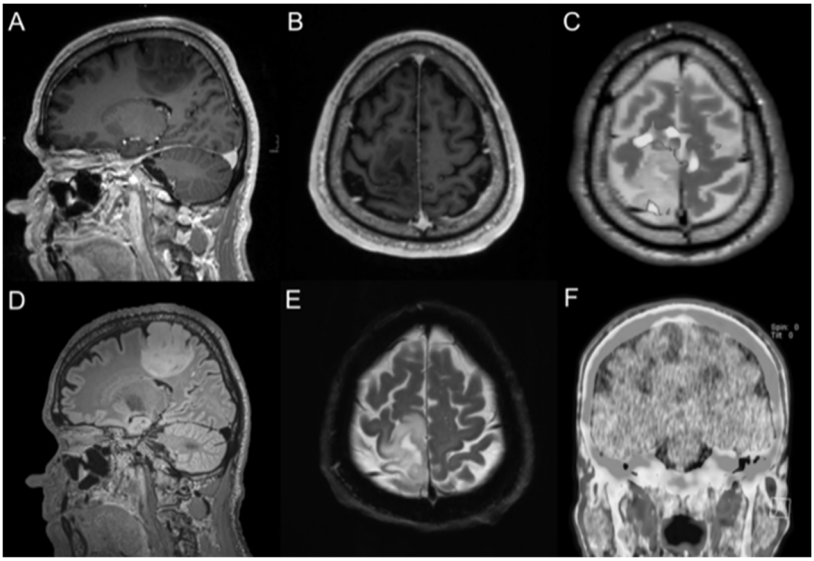


Figure 1: Preoperative investigation of brain tumors with structural MRI, functional MRI and positron emission tomography. (A) Sagittal and (B) axial contrast-enhanced T1-weighted images demonstrate a parietal/postcentral lesion with non-significant contrast-enhancement that is hyperintense on (D) sagittal FLAIR and (E) axial T2-weighted sequences. (C) Functional MRI is able to localize motor function of the lower extremity that is in close proximity to the anterior tumor margin according to T2-weighted images. (F) Positron emission tomography is capable of identifying an intratumoral region (red) of increased tracer uptake that might already be a sign of focal malignant transformation of an initial low-grade glioma.

several studies have been conducted with the purpose of clarifying the value of the extent of tumor resection in different brain tumors (Hollon, Hervey-Jumper, Sagher, and Orringer, 2015; Sanai and Berger, 2008; Sanai, Polley, McDermott, Parsa, and Berger, 2011; Soffietti et al., 2010). According to these studies, clear evidence now exists that complete resection of the vast majority of brain tumors is associated with an improved patient prognosis as compared to incomplete tumor removal (Sanai and Berger, 2008). In diffusely infiltrating gliomas, complete tumor resection is also beneficial as it prolongs the time period for the malignant transformation of initial LGG. Consequently, the neurosurgical aim is maximum safe tumor removal with preservation of neurological function whenever possible (Sanai and Berger, 2008; Stummer and Kamp, 2009;

Tonn and Stummer, 2008; Vogelbaum et al., 2012). In contrast, a neurosurgical biopsy is preferentially conducted in selected patients with deep-seated brain tumors or suspicion of a CNS lymphoma. According to the Response Assessment in Neuro-Oncology (RANO) criteria, the aim of surgery in LGG is the complete resection of the abnormality on preoperative T2-weighted/Fluid attenuated inversion recovery (FLAIR) sequences (Chukwueke and Wen, 2019). In other tumors such as HGG and brain metastases, the aim of surgery represents the complete safe resection of the contrast-enhancing tumor according to preoperative MRI.

### *1.1 Challenges of brain tumor surgery*

Since neurosurgical resection is the primary treatment for the majority of patients with brain tumors, these tumors pose a special challenge for neurosurgeons in the preoperative planning phase as well as during the procedures (Sanai and Berger, 2008). In this sense, neurosurgical resection of LGG and HGG is especially challenging due to their characteristic diffusely infiltrative growth pattern into the normal brain. Furthermore, the most common primary brain tumors frequently show only slight differences in the macroscopic appearance as compared to the normal brain parenchyma, and thus insufficient visualization of the tumor margin is frequently observed during surgery (Martin et al., 1998). Therefore, these limitations might lead to incomplete resection of brain tumors with associated unfavorable patient prognosis. In diffusely infiltrating gliomas, incomplete tumor resections are reported in the literature in up to 88% of the cases (Sanai and Berger, 2008; Smith et al., 2008; Sanai et al., 2011; Capelle et al. 2013). Although considered as well-demarcated tumors, incomplete resections in brain metastases are also reported in approximately 25% of cases with available postoperative MRI (Kalkanis et al., 2010; Kocher et al., 2011; Patchell et al., 1998).

### *1.2 Potential perioperative neurological deficits (“Neurotoxicity”)*

Maximal safe neurosurgical resection is considered to be the gold standard for the initial treatment in the majority of brain tumors. Nonetheless, neurosurgery for brain tumors is associated with potential perioperative morbidity and mortality. The rate of perioperative morbidity ranges from 9% to 40% as well as the mortality rate in neurosurgical procedures which must be taken into account (Cinotti et al., 2018; Trinh et al., 2015; Wong et al., 2012). During the perioperative period, a large diversity of postoperative complications might occur that are mainly

dependent on the tumor localization and the tumor type. Since brain tumors are frequently localized in the proximity of functional brain structures such as cortical motor or speech areas and the visual pathway, complete tumor removal bears the risk of new postoperative neurological deficits. This has a special relevance in diffusely infiltrating gliomas due to the lack of a distinct tumor margin.

Common neurological deficits after brain tumor surgery include sensory/motor deficits, visual perceptual deficits, impaired cognition and epileptic seizures (Mukand et al., 2001). Moreover, cranial nerve palsy, aphasia, dysarthria, dysphagia, ataxia and diplopia might occur after resection of brain tumors. Further intracranial complications comprise infarction, hemorrhage, postoperative peritumoral edema, intracranial hypertension and hydrocephalus (Trinh et al., 2015; Wong et al., 2012). Additionally, adverse medical conditions such as deep venous thrombosis and pulmonary embolism, pulmonary complications as well as renal and cardiac complications, and local or systemic infections may occur. Moreover, the removal of brain tumors located in the skull base can bear the risk of cerebrospinal fluid leak through insufficient dural closure as dural repair may be challenging in these cases.

Also, the urgency of surgery (elective or emergency surgery) plays an important role in the occurrence of postoperative complications such as intracranial hematoma, which have a higher incidence in emergency patients. Furthermore, it is well established that the neurosurgical institution and the performing neurosurgeon have major impacts on postoperative patient outcome (Trinh et al., 2015). The fact is that high-quality institutions with well-experienced neurosurgeons, who have improved access to advanced surgical resources, significantly reduce the risk of increased postoperative mortality and morbidity.

### 1.2.1 Epileptic seizures

Epileptic seizures represent common initial symptoms in patients with brain tumors, especially patients suffering from diffusely infiltrating gliomas. Interestingly, epileptic seizures are a favorable prognostic factor for survival in patients with LGG (Chang et al., 2008; Lote et al., 1998; Schaller and Rüegg, 2003). Chang et al. (2008) referred to their data of 332 LGG patients in which epileptic seizures had a high impact on the patients' quality of life (QOL). Furthermore, surgical resection and a short preoperative history of seizures reduced the number of seizures in this patient group postoperatively. In detail, 90% of these patients were seizure-free or had "meaningful improvements" after surgery. In contrast,

a long history of preoperative therapy of refractory epileptic seizures and simple partial seizure types showed an increased tendency to poor postoperative seizure control. The authors further illustrated that freedom from seizures after surgery and a return of epileptic seizures over time was associated with tumor progression. Pallud et al. argued that not only epileptic seizures but also antiepileptic drugs (AED) might result in cognitive impairment (Klein et al., 2003; Pallud et al., 2014; Ruda et al., 2012).

## 2. Techniques to minimize neurological deficits

Routinely, resection of brain tumors is performed with the assistance of an advanced neurosurgical microscope. In recent decades, several advancements were introduced into the neurosurgical field to optimize surgery of brain tumors and markedly increase the safety of neurosurgical procedures by minimizing the risk of new postoperative neurological deficits.

### *2.1 Neuronavigation*

One of the greatest advancements in neurosurgery in recent decades was the introduction of neuronavigation systems. In this sense, Roberts et al. reported the first application of a neuronavigation system during resection of brain tumors approximately thirty years ago (Roberts et al., 1986). Such navigation systems are capable of including imaging data acquired in the preoperative course and thus facilitate the preoperative approach to planning and precise localization of brain tumors and adjacent brain structures during tumor resection. Primarily, only single image data such as computerized tomography (CT) or one selected MRI sequence - mostly contrast-enhanced T1-weighted MRI images - was usually integrated into neuronavigation. The advanced neuronavigation systems are nowadays also capable of integrating multiple image data that are co-registered mostly with standard MRI. As a consequence, navigation with multiple imaging data such as positron emission tomography (PET), multivoxel magnetic resonance spectroscopy (MRS) and functional images is feasible (G. Widhalm et al., 2011). Therefore, neuronavigation systems are nowadays an essential component of neurosurgical procedures in brain tumors and are considered as standard in the neurosurgical daily routine in most neurosurgical centers worldwide. However, loss of cerebrospinal fluid after craniotomy, brain edema and gravity effects result in distinct changes in brain structure during resection of brain tumors, which is called “brain-

shift." This well-known phenomenon in neurosurgery might lead to a progressive inaccuracy of the neuronavigation system and can reach up to 2.4 cm (Georg Widhalm et al., 2010). Thus, precise localization of brain structures as well as the tumor margin, especially at the end of surgery, is frequently not possible since the neuronavigation is based on preoperatively acquired imaging data.

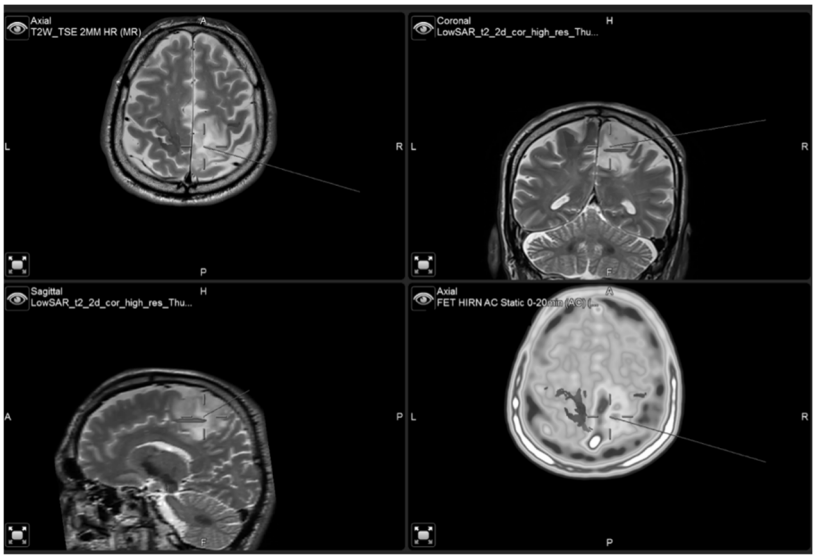


Figure 2: Intraoperative application of neuronavigation with multiple image data. Navigation-guided resection of a left parietal/postcentral glioma with non-significant contrast-enhancement with multiple image data including T2-weighted sequences, fiber tracking/diffusion tensor imaging and positron emission tomography (*right below*).

## *2.2 Intraoperative imaging*

Generally, the extent of resection after brain tumor surgery is investigated by postoperative MRI performed in most centers within the first 72 hours to detect a potential residual tumor (Albert et al., 1994). In the case of a large and unexpected residual tumor, a second surgery has to be taken into consideration. Thus, the acquisition of image data during surgical resection of brain tumors would be the ideal way to detect and subsequently remove residual tumor tissue in the same procedure. In this sense, in 1999 Black et al. first described the use of intraoperative MRI

during surgery of brain tumors (Black et al., 1999). In 2011, Senft et al. demonstrated in a randomized, controlled trial that significantly more patients in the intraoperative MRI group had a complete glioma resection compared to the control group (96% vs 68%) (Senft et al., 2011). In this sense, intraoperative MRI provides the advantage of an immediate intraoperative update of imaging information. The new MRI sequences on the one hand can be used to evaluate the extent of resection during surgery and on the other hand can be uploaded into the neuronavigation system. This very useful feature provides the neurosurgeon with regenerated imaging information intraoperatively. In the case of residual tumor tissue being visible on the intraoperative MRI images, surgery can be continued safely, based on the advantage of a compensated brain-shift. Consequently, this innovative method is useful at increasing the rate of complete resections of brain tumors. Due to the disadvantages of this technique, such as prolonged operation time and high expense, intraoperative MRI is not widely available.

### *2.3 Functional imaging*

Furthermore, diffusion tensor imaging (DTI), functional MRI (fMRI) and transcranial magnetic stimulation (TMS) are powerful techniques to visualize brain function during the preoperative investigation of tumors in eloquent brain regions. First of all, DTI data is capable of visualizing relevant white matter tracts such as the corticospinal tract or arcuate fascicle in the proximity of a brain tumor (Nimsky et al., 2006). Secondly, fMRI investigates brain activity and is capable of detecting changes associated with blood flow. As a result, eloquent brain regions especially relevant for motor and speech function can be identified with the assistance of fMRI (Hall et al., 2005). Finally, TMS represents a new and promising method for preoperative mapping of functional brain areas similar to direct intraoperative cortical electrical stimulation (Picht et al., 2016). Primarily, TMS has been demonstrated to be a reliable method for preoperative mapping of the motor cortex of brain tumors localized in, or in the proximity of, the precentral gyrus with a high accuracy. In recent years, TMS has also increasingly been investigated for precise preoperative mapping of brain areas relevant for speech function.

All these above-mentioned functional imaging data can be integrated into the neuronavigation and intraoperatively applied to limit the resection of brain tumors in or adjacent to eloquent brain regions. Consequently, navigation with functional imaging data is a useful tool to minimize the risk of a new postoperative neurological deficit, which is again limited by

the decrease of accuracy due to brain-shift.

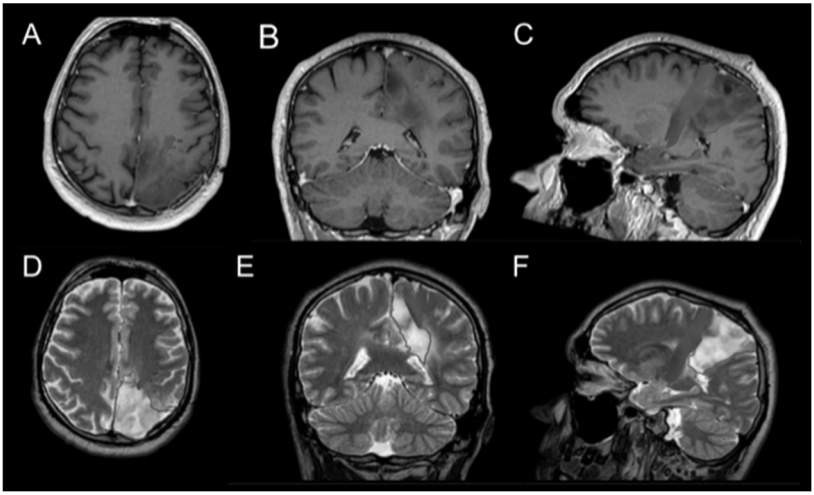


Figure 3: Intraoperative use of navigation with fiber tracking data to increase the safety of brain tumor surgery. Navigation with fiber tracking data using (A, D) axial, (B, E) coronal and (C, F) sagittal contrast-enhanced T1-weighted images (*above*) and T2-weighted images (*below*) to limit resection of brain tumors in and near the central motor region and minimize the risk of postoperative neurological deficits.

### *2.4 Intraoperative monitoring and brain mapping*

To localize and monitor the brain function in eloquent brain tumors, intraoperative monitoring and brain mapping/stimulation represent powerful techniques to prevent injuring sites of motor, language and sensory function. Intraoperative monitoring refers to the constant reassessment of neurological function by using direct excitation of neural pathways during the brain tumor resection while the patient is anesthetized. The two most frequently applied methods during neurosurgical procedures are motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs). By direct stimulation of brain regions involved in the motor- and/or sensory pathways, it is possible to monitor the functional integrity in “real-time” in order to reduce postoperative neurological deficits by avoiding damage to those eloquent areas.

Current limitations of intraoperative monitoring alone revolve around eloquent areas, such as language regions, that are not solely integrated in either the motor and/or the sensory system. In such cases, the so-called “brain mapping/stimulation” during awake surgery is a powerful method to precisely identify functional language areas not involved in the sensory and/or motor system after dura opening and prior to the tumor resection. During the different steps of tumor resection, the neurosurgeon repeatedly stimulates suspected language areas to examine the patient’s language performance in an awakened state. In case of a significant deterioration of language function, the tumor resection should thus be terminated to avoid a permanent postoperative neurological deficit. Recently, a meta-analysis found that the intraoperative use of brain mapping/stimulation results in fewer postoperative late severe neurological deficits as well as more complete tumor resections compared to surgeries without brain mapping/stimulation (De Witt Hamer et al., 2012).

### 2.4.1 Intraoperative occurrence of epileptic seizures

Intraoperative monitoring and brain mapping/stimulation during surgery of brain tumors localized in eloquent areas might lead to epileptic seizures/abnormalities on EEG monitoring. With regard to awake craniotomies, these possible consequences for the patient have to be considered by the neurosurgeon. Dineen et al. reviewed in a recent study the most important consequences of epileptic seizures during awake craniotomies (Dineen et al., 2019). According to their data, the authors observed a high risk of aspiration and breathing problems based on pharmacologically caused respiratory depression due to the absence of airway protection in awake patients. As a result, the postictal and/or post-therapeutic status of the patient (somnolence, confusion, dysphasia) can impede the intraoperative mapping after medical seizure treatment during awake surgery. Further studies also described a possible increase in the essential mapping thresholds due to postictal cortical depression with possible false localization of eloquent brain areas (Blume et al., 2004; Karakis et al., 2015). Dineen et al. further investigated in their study in 544 consecutive functional mapping cases relevant factors for the appearance of epileptic seizures during surgery and found that the risk of intraoperative seizures can be markedly reduced by preoperative administration of an AED loading dose (Dineen et al., 2019).

## 3. Toxicity of Perioperatively and Locally applied substances

In recent decades, specific substances were introduced in the neurosurgical field to support the neurosurgeon during resection of brain tumors. Furthermore, new approaches with the local application of specific substances in brain tumors were also developed that bypass the limited permeability of the blood–brain barrier (BBB) in order to increase the therapeutic agent concentrations in brain tumors.

### *3.1 5-Aminolevulinic Acid (5-ALA)*

Intraoperative visualization of tumors with the assistance of fluorescence represents an innovative technique for improved visualization of tumor tissue during surgery. Since 1992, 5-aminolevulinic-acid (5-ALA) has been increasingly applied as a fluorescent dye for such fluorescence-guided procedures in different surgical disciplines. After oral administration of primarily non-fluorescing 5-ALA, this dye leads to intratumoral accumulation of fluorescing protoporphyrin IX (PpIX) in specific tumors. With the assistance of a modified neurosurgical microscope including a xenon light source and longpass filter, specific brain tumors can be visualized during surgery independent of brain-shift by their characteristic red fluorescence under violet-blue excitation light. As a consequence, this innovative technique supports the neurosurgeon, especially to improve the definition of the margin in brain tumors. In 2000, Stummer et al. described that 5-ALA fluorescence-guided surgery of HGG resulted in an increased rate of complete resections of the contrast-enhancing tumor area compared to historic data with conventional white-light procedures (Stummer et al., 2000). In 2006, Stummer et al. described a randomized multicenter phase III trial that found a significantly higher rate of complete resections (65% and 36%, respectively) and prolonged six months progression-free survival (41% and 21%, respectively) in HGG surgically treated with 5-ALA fluorescence-guided surgery compared to conventional white-light resections (Stummer et al., 2006). Based on these convincing data, the use of 5-ALA was approved in the European Union for resection of HGG in 2007. Ten years later, 5-ALA was also approved by the Food and Drug Administration (FDA) in the United States. Nowadays, 5-ALA fluorescence-guided surgery is widely used at many neurosurgical centers worldwide for improved resection of HGG. In recent years, the 5-ALA fluorescence technique has also been increasingly used in brain tumors other than HGG for improved intraoperative visualization of

anaplastic foci in radiologically suspected LGG, meningiomas, metastases and lymphomas (Kiesel et al., 2018; Marhold et al., 2019; Millesi et al., 2016; Georg Widhalm et al., 2010, 2013).

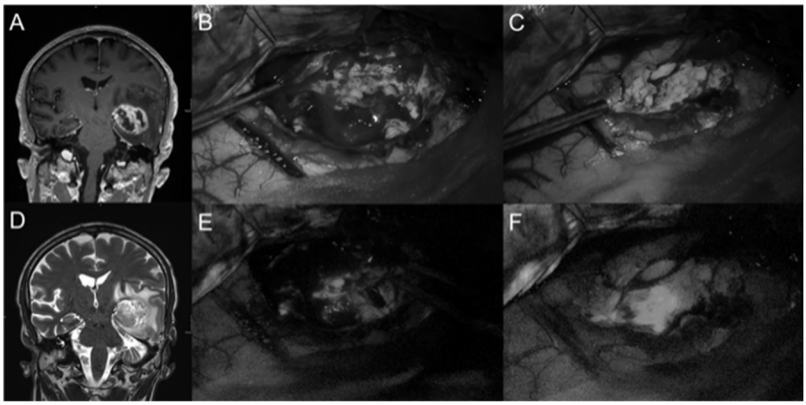


Figure 4: Fluorescence-guided surgery using 5-ALA in a patient suffering from a glioblastoma. Coronal T1-weighted image shows a contrast-enhancing lesion in the left temporal lobe (D) with a hyperintense “infiltration zone” on T2-weighted sequences. (B) Conventional white-light microscopy demonstrates tumor tissue with distinct macroscopic abnormalities (E) that can be visualized by strong 5-ALA fluorescence under violet-blue excitation light. (C) The region near the tumor border reveals no clear macroscopic abnormalities under white-light microscopy, (F) but tumor tissue can still be detected with visible 5-ALA fluorescence.

### *3.2 Neurotoxicity of 5-ALA*

In general, 5-ALA is a well-tolerated fluorescent dye and adverse effects are rare in routine clinical practice. However, some potential side effects of 5-ALA must be considered. First of all, 5-ALA results in activation of its fluorescing metabolite PpIX, not only in the brain but in the skin as well. Thus, 5-ALA is a potential phototoxic substance that might lead to skin and subcutaneous tissue disorders such as photosensitivity or photodermatosis. However, 5-ALA and its metabolites are eliminated quickly from the body (t½ = 50 minutes), therefore, the risk of skin photosensitivity is limited to one or two days (Regula et al., 1995). Consequently, patients should avoid contact with sunlight and should remain ~~are kept~~ in a darkened room for at least 24h after 5-ALA administration.

Furthermore, 5-ALA might lead to an increase in liver function parameters/enzymes or an elevation of blood bilirubin and hepatobiliary disorders. Moreover, in patients suffering from renal or hepatic dysfunction, 5-ALA metabolism is slower and the risk of phototoxicity may be increased due to the fact that 5-ALA is usually excreted within 24 hours by the kidneys and sometimes by the liver (Utsuki et al., n.d.). Therefore, patients with risk factors with regard to hepatobiliary conditions or preoperatively elevated hepatic enzyme levels require closer monitoring after surgery until physiological levels are established. Furthermore, in patients suffering from porphyria the administration of 5-ALA is contraindicated.

By administering the standard dose of 5-ALA (20 mg per kg bodyweight) no further severe side effects usually occur. Rarely, hypotension or gastrointestinal disorders such as nausea, vomiting and diarrhea might occur in patients after 5-ALA administration. However, in many patients suffering from hypotension, this condition was already present before oral 5-ALA intake (Chung and Eljamel, 2013). Furthermore, gastrointestinal disorders after 5-ALA administration might also be caused by other drugs applied during the perioperative course or general anesthesia, which are known to cause postoperative side effects such as nausea and vomiting.

### 3.2.1 5-ALA based photodynamic therapy (PDT)

In recent decades, local photodynamic therapy (PDT) showed promising results in the treatment of primarily recurrent HGG and has been performed with various substances. However, this innovative treatment approach was limited for a long time by its considerable risk of treatment related adverse effects due to the restricted selectivity in tumor cells. PDT based on 5-ALA relies on the principle of the preferential accumulation in the mitochondria of HGG cells (Castano et al., 2005). In short, activated by irradiation at a specific wavelength, this photosensitizer inducts reactive oxygen species (ROS)-mediated apoptosis, which is a programmed cell death mechanism in tumor cells (Bonnet et al., 2007; Michelakis et al., 2008).

A previous study investigated the impact of 5-ALA and its ability to induce ROS-mediated apoptosis of tumor cells (Sugiyama et al., 2014). The findings demonstrated the potential of 5-ALA as a selective antitumor photosensitizer for PDT (Ueta et al., 2017). Nowadays, two main applications of 5-ALA based PDT are used. On the one hand, irradiation is executed with a balloon diffuser in the resection cavity immediately after

5-ALA fluorescence-guided resections. By this approach, no additional 5-ALA administration is required. On the other hand, stereotactic interstitial PDT (iPDT) is performed preferentially with cylindrical diffusers, which deliver light irradiation directly inside the tumor tissue.

### 3.2.2 Neurotoxicity of PDT

Due to its high tumor selectivity, 5-ALA in PDT evokes only minor adverse effects, such as short-lasting phototoxicity, therefore displaying relatively safe therapeutic properties as a photosensitizer. The major advantage of 5-ALA for safe PDT is the quick photobleaching effect of the active metabolite PpIX (Stepp and Stummer, 2018). Thus, especially in tumor cells containing only a little photosensitizer, even prolonged irradiation and extremely high doses of light cannot induce phototoxic effects as long as the intensity is low enough to avoid thermal damage. Since cells of the normal brain parenchyma accumulate none or only minimal amounts of PpIX, there is no risk of phototoxic damage to the normal brain. Nevertheless, there exists evidence that 5-ALA based PDT directly interferes with endothelial cells within the brain, thus leading to a mediated opening of the BBB (Semyachkina-Glushkovskaya et al., 2017). The amount of these endothelial cells is only small (<1%), but the effects of 5-ALA based PDT on the BBB might lead to induction of local, transient edema in the surrounding normal brain tissue (Ito et al., 2005; Stepp and Stummer, 2018). This adverse effect must be considered during treatment planning and management in the context of steroid administration to minimize the 5-ALA PDT induced edema.

## *3.3 BCNU Wafers*

Another interesting and locally applied approach is the implantation of biodegradable polymers impregnated with carmustine (bis-chloroethyl nitrosourea, BCNU) in the tumor resection cavity of HGG. BCNU wafers (Gliadel®; Eisai, Tokyo, Japan) are usually used in addition to the standard therapy of surgery, radiation and chemotherapy for treatment of HGG. One of the advantages of the therapy with BCNU wafers is the supply of high doses of local chemotherapy at the tumor cavity, bypassing the BBB (Shibahara et al., 2018). In 1995, Brem et al. initially studied the applicability and safety of BCNU wafers for patients with a GBM (H Brem, Ewend, et al., 1995; H Brem, Piantadosi, et al., 1995; Henry Brem et al., 1991). In 2003 Westphal et al. published a phase 3 trial of local chemotherapy with BCNU wafers in patients with primary HGG and

found that the median survival rate for the BCNU wafer plus radiation group was 13.9 months, whereas 11.6 months was reported for the placebo wafer plus radiation group (Westphal et al., 2003). In the following years, subsequent studies analyzed the therapy with BCNU wafers especially in combination with temozolomide (TMZ) and radiation therapy. In these studies, the median survival rate showed an extension of up to 21 months (Affronti et al., 2009; Bock et al., 2010; McGirt et al., 2009; Noël et al., 2012; Pallud et al., 2015; Sonoda et al., 2017). In 1997, Gliadel® gained FDA approval for the treatment of recurrent GBM and in 2003 for newly diagnosed HGG.

### 3.3.1 Neurotoxicity of BCNU Wafers

In 2016, Ashby et al. published a literature review analyzing patients with a newly diagnosed HGG after implantation of BCNU wafers combined with standard radiotherapy and adjuvant TMZ and also reported the occurrence of side effects (Ashby et al., 2016). According to this review, the most frequent adverse events were myelosuppression (10.2%), neurological deficits (7.8%) and healing abnormalities (4.3%). Furthermore, epileptic seizures, fatigue and gastrointestinal disorders were also reported. However, systemic carmustine levels usually showed only low amounts and thus these adverse events might also be based on the systemic toxicity of standard adjuvant therapy.

## *3.4 Convection-Enhanced Delivery (CED)*

In recent decades, convention-enhanced delivery (CED) was introduced as another promising local treatment approach. In the 1990s a group of researchers led by Edward Oldfield of the National Institute of Health was the first to describe and develop CED (Bobo et al., 1994; Lonser et al., 2002; Nguyen et al., 2003). CED allows local delivery of targeted agents in the brain bypassing the BBB. In this sense, one or more catheters are inserted through a standard burr hole into the brain/tumor area with navigational guidance. Subsequently, an infusion pump is connected to the catheter and specific drugs are delivered via infusion directly into the targeted area. The advantages of this innovative technique are to provide high local drug concentrations inside the tumor. Still, the most frequently applied agents are those which cannot be transported easily through the BBB. However, further studies and developments, e.g., regarding catheter technology and prolonged delivery are warranted to

benefit from such a promising and innovative technique and take advantage of its full therapeutic capability.

### 3.4.1 Neurotoxicity of CED

A previous review analyzed clinical trials of the last two decades with regard to the safety and tolerability of various agents for CED including antibodies, targeted toxins, interleukins, chemotherapeutic drugs, targeted radioisotopes, and vaccines (Shi and Sanche, 2019). In this review, the authors classified CED related toxicities as immediate (within hours of the placement of catheters), early (hours to days after CED) and late (days to weeks after infusion) side effects. In detail, immediate side effects are induced by physical damage to the brain tissue as well as cerebral hemorrhage through catheter placement and might cause symptoms such as headache, epileptic seizures and neurological deterioration. Early side effects are usually caused by mechanical stress through the infusion of fluids and the most common symptoms include headache, epileptic seizures, worsening of neurological symptoms, shivering, and mild fever. Late side effects include mainly neurological symptoms due to toxicity from the delivered drugs.

Furthermore, the authors of the aforementioned review article also distinguished between local and systemic toxicities. (1) Local toxicities (common and severe) include “neurotoxicity” that is mainly based on inflammatory reactions, tissue necrosis and perifocal edema. Depending on the tumor size and localization, patients with “neurotoxicity” show symptoms of headache, seizures, nausea, pyrexia, sensory disturbance, upper motor neuron lesion, aphasia/speech disorder, and memory impairment. However, tumor debulking or craniotomy was necessary in only a few cases to treat cerebral edema and intracranial hypertension (Rand et al., 2000). Mostly, edema can be well controlled by the use of corticosteroids. Certainly, the severity of local toxicity is dependent on the type of the infused substance. Further studies also described local infections after catheter placement that were usually, however, well controllable by antibiotics (Carpentier et al., 2010; Pöpperl et al., n.d.; Tanner et al., 2007). Systemic toxicities (rare and transitory) include general toxicity with symptoms such as fever, fatigue and erythema as well as gastrointestinal symptoms. Other studies also observed hematological changes and liver enzyme perturbations (H Brem, Ewend, et al., 1995; Carpentier et al., 2006, 2010; Laske et al., 1997; Souweidane et al., 2018).

## 4. Tumor Treating Fields (TTF)

The application of "tumor treating fields" (TTF) constitutes a new adjuvant therapeutic modality in the treatment of GBM that exposes the tumor to localized low-intensity alternating electric fields at a frequency of 100-300 kHz (200 kHz used in GBM). The exact mechanism of action is not completely understood; however, preclinical in vitro data suggest growth inhibition by mitotic arrest at metaphase/anaphase due to microtubule subunit misalignment (Fonkem and Wong, 2012; Stupp et al., 2012; Wick, 2016). In addition to cell cycle interruption leading to caspase-independent autophagy and necroptosis, recent preclinical analyses also showed a reduced potential of glioma cells for migration and invasion that might contribute to growth control. To apply the electrical field to the tumor, four transducer arrays with a total of thirty-six electrodes are placed directly to the scalp. Prior to transducer placement, the head needs to be shaved and transducer arrays are changed once or twice a week to provide optimal electric field transmission. Transducers are connected to a control unit with integrated exchangeable batteries that last for two to three hours each. The currently available (second commercially available) TTF unit (Optune® NovoTTF-200-A System, Novocure, Israel) weighs approximately six pounds (2.7 kg) and is designed to be carried by the patient in a shoulder bag (Kinzel et al., 2019; Stupp et al., 2017). Ideally, continuous application of the field over twenty-four hours a day should be obtained and study protocols required patients to wear the device for at least eighteen to twenty-two hours daily.

Results of randomized phase III trials are currently available for the use of TTF in recurrent GBM and as maintenance therapy in newly diagnosed GBM. In the initial examination of TTF against chemotherapy according to physicians' choice in recurrent GBM, no benefit in overall survival (primary endpoint) was observed (Stupp et al., 2012). However, in a subsequent trial comparing TMZ + TTF to TMZ alone after completed adjuvant concomitant radiochemotherapy in newly diagnosed GBM, the addition of TTF demonstrated a marked improvement in median overall survival (20.9 months vs. 16.0 months) at the interim analysis, resulting in the trial's premature closure (Stupp et al., 2017; Wick, 2016).

FDA approval for the Optune® device was granted in 2011 for the treatment of recurrent GBM and extended to newly diagnosed GBM in 2015 (Mehta et al., 2017). Contraindications of Optune treatment include implanted active medical devices such as pacemakers, brain stimulators and CSF shunts, unreplaced skull defects or bullet fragments as well as known sensitivity/allergy to the hydrogels used in the transducer array

placement. Further trials in other tumor entities are currently being performed, including other CNS neoplasms such as brain metastases, meningioma and oligodendroglioma (Wang et al., 2019).

Despite the promising results with regard to prognosis and safety, application of TTF currently remains subject to controversial discussions. Concerns regarding TTF arise from insufficiently understood mechanisms of action and methodological concerns, especially the lack of a placebo-control (i.e. sham device) and a higher level of care in the intervention group (Wick, 2016). Furthermore, the considerable therapy costs of approximately €21.000 per month were repeatedly mentioned as a major drawback of TTF treatment and a recent analysis deemed the technique not cost-effective by conventional thresholds at the current price (Bernard-Arnoux et al., 2016; Weller, 2018; Wick, 2016). However, a future decline in treatment costs may lead to improved cost-effectiveness as well as the availability of TTF.

### *4.1 Neurotoxicity of TTF*

The toxicity profiles observed in the clinical trials showed no increased risk of systemic adverse effects with a lower rate of typical therapy-associated events (i.e. infectious, gastrointestinal, hematologic) as compared to active chemotherapy control. The most common and relevant side effects associated with TTF are skin reactions of varying severity at the transducer sites. Total rates of dermatologic adverse events in clinical trials were 19% (3% severe) and 54% (2% severe) respectively, while smaller series reported incidences of up to 90% (Kirson et al., 2007, 2009; Mrugala et al., 2017; Stupp et al., 2012, 2017). Treatment recommendations for the typically observed dermatological adverse events (dAE) such as dermatitis, erosions and ulcerations are provided by the device manufacturer. While recommended treatment of mild dAE (Grade 1) is based on topical steroids and antibiotics, moderate dAE (Grade 2) reactions mostly require systemic treatment and adapted array placement. In the case of severe dAE (Grade 3) reactions treatment interruption should be considered.

Further symptoms initially more frequently reported in the TTF treatment arm as compared to chemotherapy alone in the interim analysis included mostly transient unspecific neurological signs such as mild anxiety, headaches, insomnia and confusion (Stupp et al., 2015). However, no increased incidence of these neurological symptoms was observed in the final trial results.

Altogether, TTF is a promising treatment modality in GBM treatment that should be further investigated to answer the questions currently leading to its low acceptance as a standard of care (Weller, 2018; Wick, 2016). It is of note, however, that all concerns currently raised address primarily the effectiveness of TTF, while no evidence suggests a significant risk of severe (neuro-) toxicity (Stupp et al., 2012, 2017; Weller, 2018; Wick, 2016).

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