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Resection of Malignant Brain Tumors in Eloquent Cortical Areas: A New Multimodal Approach Combining 5-ALA and Intraoperative Monitoring

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1. Introduction

1.1. Primary Malignant Brain Tumors (PMBTs)

Depending on the age group, anaplastic astrocytomas and glioblastomas are the most common PMBTs comprising about 60 - 90% of all brain tumors.[27, 45] These tumors have been described to have a male predilection and typically occur between the ages 40 – 60 years (anaplastic astrocytoma) and 60 – 70 years (glioblastoma) (Figure1.1). Despite intense research over the past four decades the mean survival of patients has not improved significantly. [41] One year survival rates still range between only 60 – 70% for patients with anaplastic astrocytomas and 30 - 40% for patients with glioblastomas.[27]

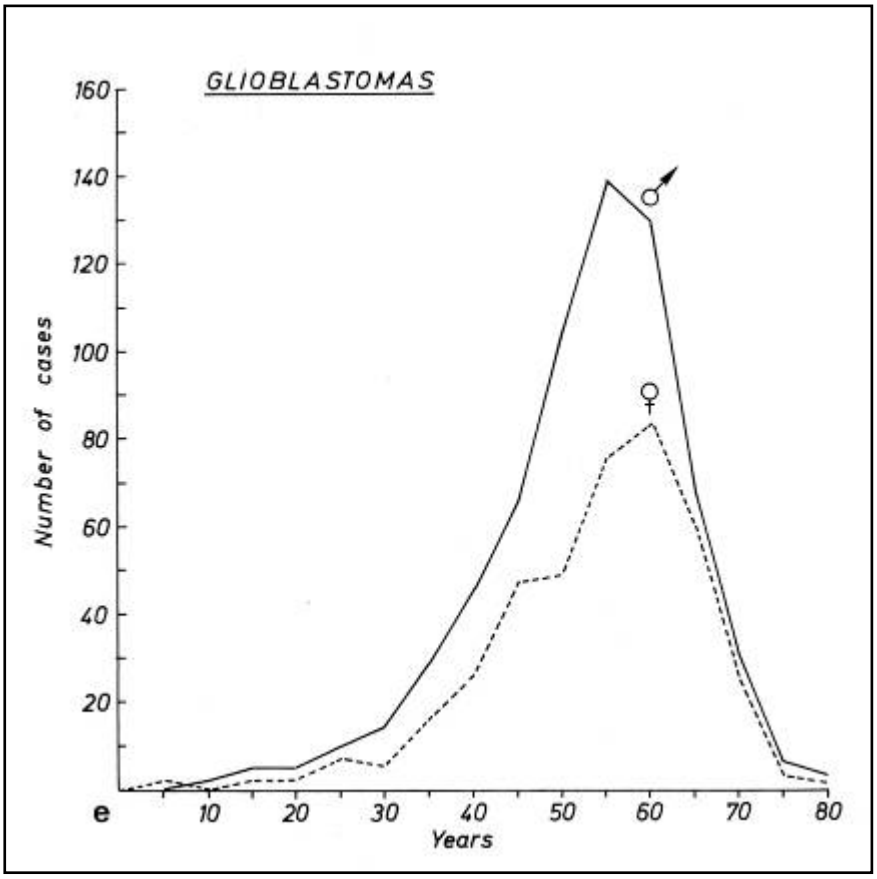

Figure 1.1: Age distribution of patients with glioblastomas. (graph 9e, page 88 from Zülch KJ: Brain Tumors: Their Biology and Pathology. 3. Edition; Springer-Verlag, 2004).

Infiltrative growth patterns and tumor recurrences are typical for PMBTs making them so far incurable and very difficult to treat.

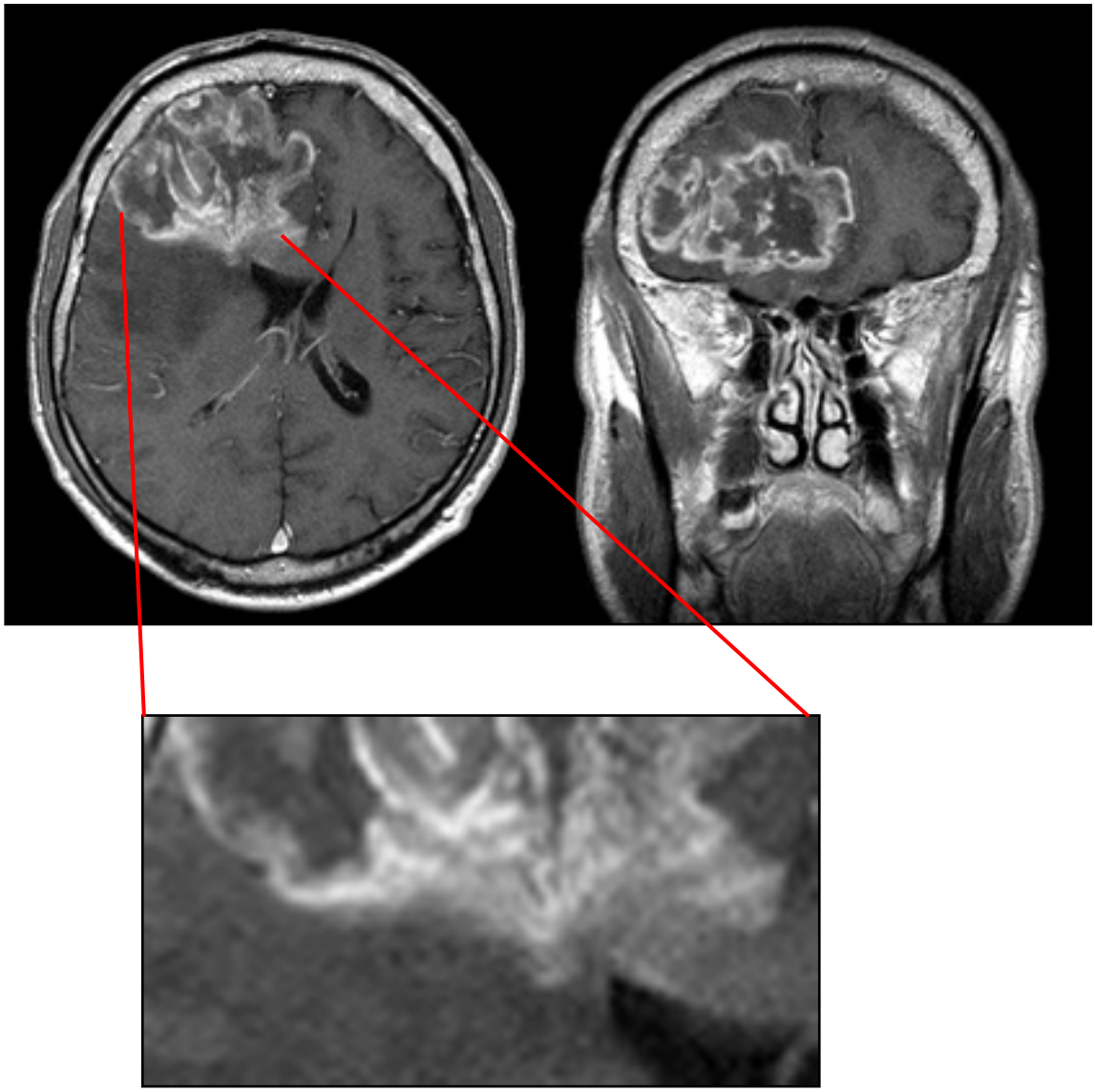

Figure 1.2: MRI with contrast enhancement showing the infiltration zone of a glioblastomas.

These facts at hand it is comprehensible that intense research has been and still is going on in order to find better treatment modalities to prolong progression free survival of these patients.[19] PMBTs require an interdisciplinary and multimodal treatment strategy including a maximal surgical tumor resection

followed by adjuvant chemo and/or radiotherapy. Research is being performed to advance every single step of these treatment modalities. In an effort to improve adjuvant treatment of PMBTs several protocols have been developed combining various chemotherapies and also substances inhibiting angioneogenesis with radiotherapy. All these protocols were and still are being evaluated in international prospective studies.[5, 38, 44] Tumor recurrences have been shown to usually occur directly or close to the resection cavity[2] and a gross total resection (GTR) is therefore essential.[34] Furthermore, several studies have shown that GTR of these tumors has a direct effect on overall survival of these patients.[1, 23, 34, 43] However, resection of invasively growing tumors using a standard white light microscope with a halogen or xenon light source frequently results in an unintended incomplete tumor resection. The reason for that is the invasive growth pattern (Figure 1.2). In infiltration zones borders between healthy brain and tumor tissue are blurred with infiltration zones being not clearly visible as pathologic intraoperatively. In certain "non eloquent" areas of the brain it is possible to resect a "safety zone" around the tumor in order to ensure a total tumor resection, however, this is not possible in or near functional areas of the brain. Therefore, precise intraoperative localization of functional areas is absolutely essential in order to avoid causing deficits during microsurgical tumor removal. Even though there are well known landmarks to localize functional areas on the cortical surface, they are no longer applicable if functional areas and cerebral tracts are displaced by a space occupying lesion (Figure 1.3).

1.2. Functional Imaging Techniques

Technological advances in imaging techniques over the past two decades have made it possible to non-invasively localize functional cortical areas such as speech centers and motor areas as well as cortical tracts preoperatively. Available techniques are functional MRI (fMRI), which is a blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) method allowing localization of speech and motor areas.[4, 17, 29, 30]

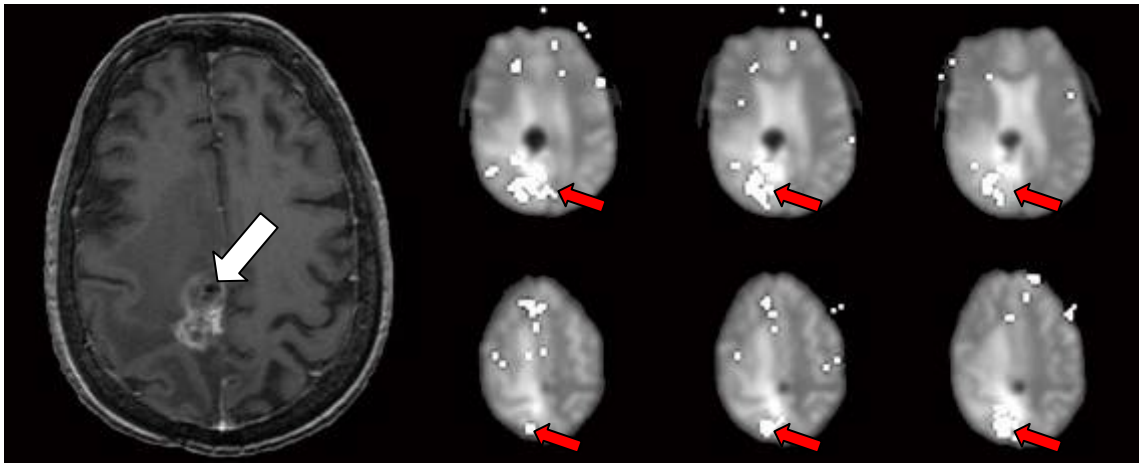

Figure 1.3: MRI with contrast enhancement showing a tumor (white arrow) in the right motorcortex (large image on the left) and the posterior displacement of the functional area of the left foot (red arrows) visualized in t-maps of BOLD images (six images on the right).

Another method to localize motor and speech function non-invasively is transcranial magnetic stimulation (TMS). This method uses a magnetic stimulus which is aimed at the region of interest of the brain. The magnetic impulse triggers a motor response which can then be recorded.

Since functional areas are all connected it is essential to also localize cortical tracts which can be visualized by using diffusion tensor imaging (DTI) based MRI. The principle theory of DTI is to exploit the anisotropic diffusion of water molecules in the brain which is assumed to be the strongest within the boundaries along cortical tracts. Several algorithms have been developed over the past few years making noninvasive visualization of the main connecting fiber tracts of the brain possible. Fiber tracts, however, are not visualized based on anatomical but rather on calculated images using different algorithms to visualize the direction of water molecule diffusion during post-processing of these images.[3, 9, 10] Calculated data is then projected on anatomical images for better orientation (Figure 1.4). Being able to see the displacement of functional

areas and cortical tracts preoperatively allows to better plan surgical approaches and prevents injury of functional areas during the approach.

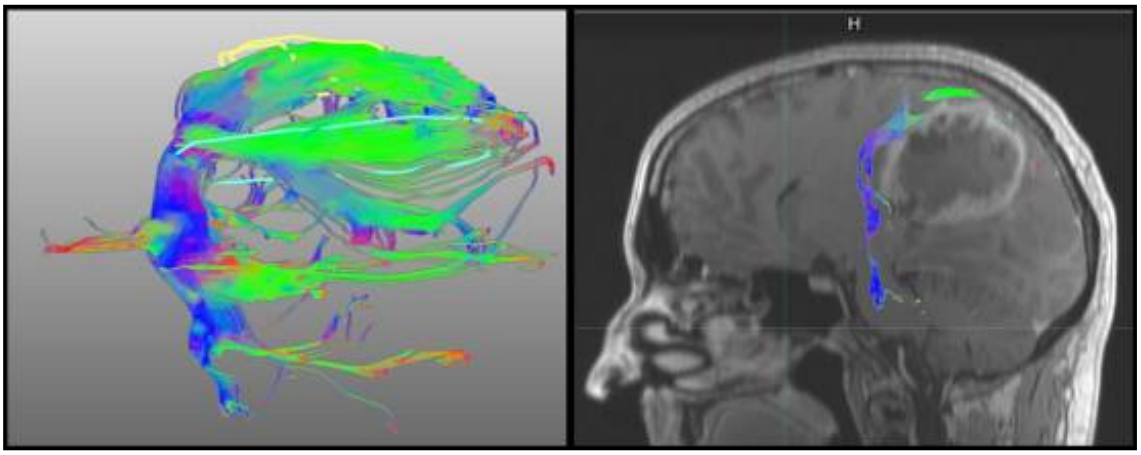

Figure 1.4 The left image shows DTI based fibertracking with a 3D reconstruction of an anteriorely displaced pyramidal tract. In the image on the right the calculated fiber tracts are shown after image fusion with anatomical data (T1 weighted contrast enhanced MRI). Here the anterior displacement of the pyramidal tract by the glioblastoma can be clearly recognized. Blue lines in the image represent fibers in cranial to caudal direction, green lines left to right and red lines fibers in anterior to posterior direction NeuroQLab 2.7 (Institute for Medical Image Computing, Fraunhofer MEVIS, Bremen)

However, since fMRI data is accurate approximately in only 60 – 70%[11, 14, 22] and since DTI based fiber tracts are based only on calculated data, locations of non-invasively localized functional areas and fiber tracts have to be verified intraoperatively with direct cortical and subcortical stimulation.

Parallel to technological advances in brain imaging, neuronavigation systems were developed in the past two decades allowing localization of brain tumors more precisely before opening the skull. Based on preoperatively acquired MRI data with special markers (feducials) on the patients head, the patient is registered in the system using a pointer by localizing the markers. Neuronavigation enables the neurosurgeon to make minimally invasive approaches, precisely tailored to the size of the lesion. Additionally, it is also possible to insert functional and DTI data into the neuronavigation system making it a very useful tool to localize eloquent areas of the brain.

A weakness of neuronavigation systems is that accuracy is lost during course of a surgery due to the so called “brain shift” which occurs after opening the dura and releasing cerebrospinal fluid and even more so after removal of brain tissue.[28] After the brain has shifted all the preoperatively acquired functional and anatomical data as displayed on the neuronavigation is not valid any longer and the neurosurgeon has to relay again on anatomical landmarks.

1.3. Intraoperative Tumor Visualization

In the past decade intraoperative MRI systems (Figure 1.5) were developed largely solving this problem of inaccuracies in neuronavigation due to brain shift by making it possible to acquire new images during surgery.[21] The new intraoperative images are used to update the neuronavigation compensating the brain shift. Furthermore, intraoperative MRI systems have the big advantage that a resection control can be performed intraoperatively using contrasted enhanced and flair MRI.[16] However, these systems require considerable financial investments and are therefore not readily available.

Figure 1.5: Intraoperative MRI system (IMRISneuro) with a mobile magnet.

Ultrasonography, on the other hand, is considerably less expensive and therefore readily available. Using modern high resolution ultrasound machines it is possible to visualize tumor borders and perform an intraoperative resection control.[42] However, so far the resolution of available machines is still inferior to images from an MRI.

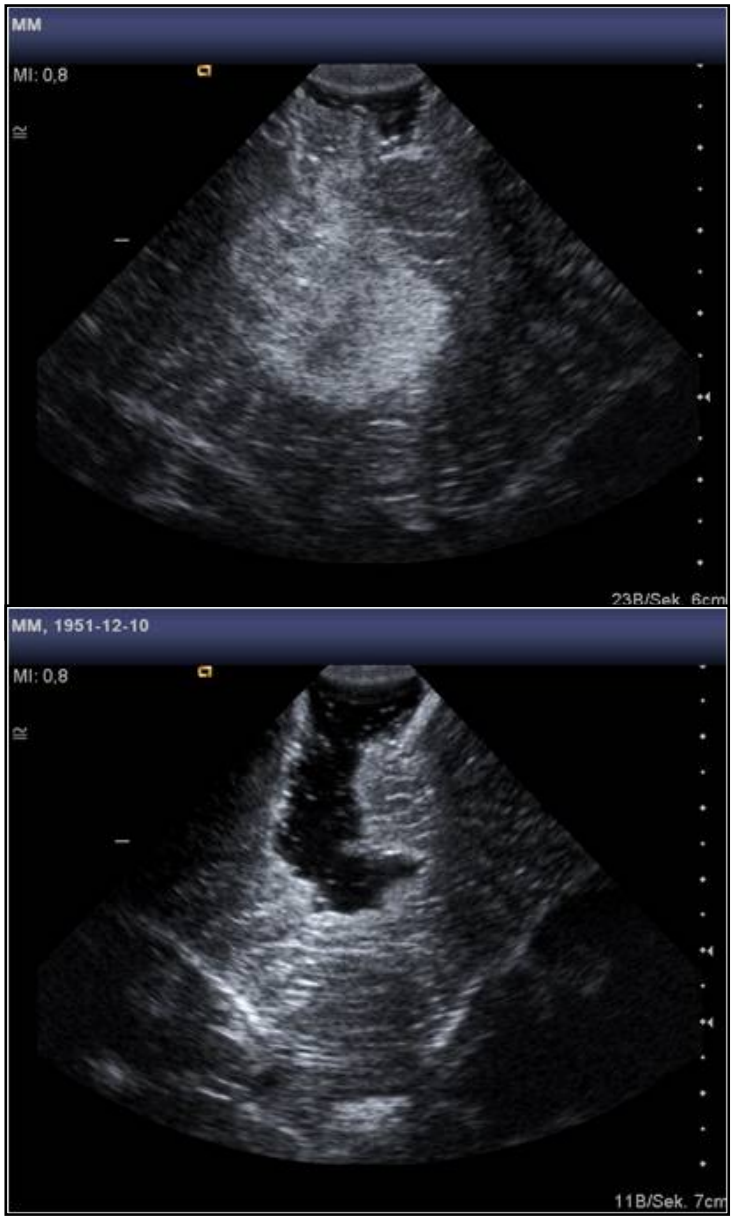

Figure 1.6: Intraoperative sonography images at the beginning of the resection (top image) and and at the end of resection bottom image);
(Siemens ACUSON Antares System 5.0)

All of the above imaging techniques have their merits but also some limitations which is, that they are all “off line”. This means that resection has to be interrupted in order to acquire new images. Furthermore, contrast enhanced MRI shows only a disturbance of the blood brain barrier and not the actual tumor tissue since the contrast agent does not enter tumor cells. Hence, the actual tumor size is always larger then seen with the contrast enhancement on MRI.

1.4. 5-Aminolevulinic Acid (5-ALA)

Introduction of fluorescence-guided tumor resection for PMBTs by Stummer et al. in 1998 revolutionized intraoperative tumor visualization.[37] This method is based on 5-aminolevulinic acid (5-ALA) which is a non-fluorescent prodrug leading to intracellular accumulation of fluorescent protoporphyrin IX (Figure 1. 7) in PMBTs.[36]

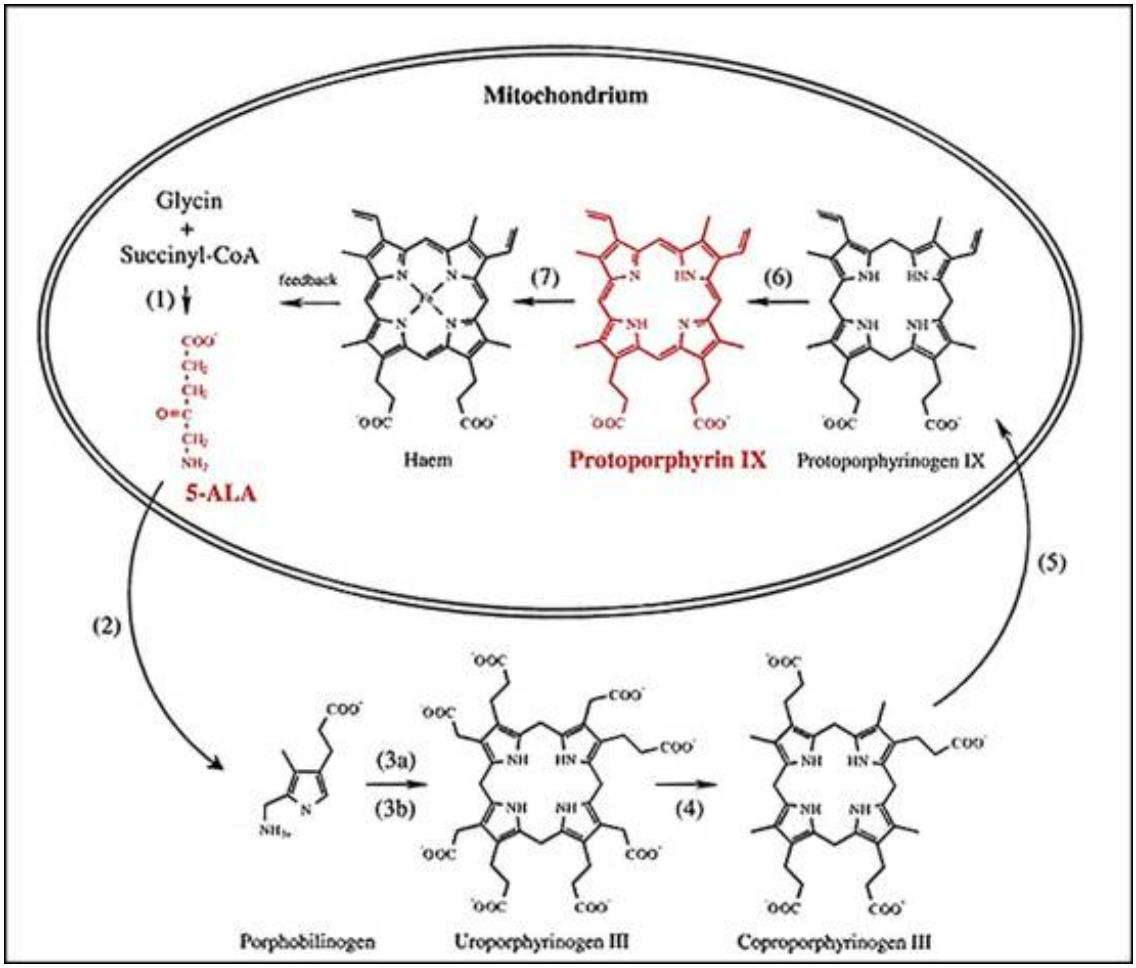

Figure 1.7: Biochemical cycle of 5-aminolevulinic acid leading to accumulation of protoporphyrin IX in mitochondria of tumor cells (graph from: Klinische Fluoreszenzdiagnostik und Photodynamische Therapie; Kapitel 1.2 Photosensibilisatoren S. 29-38; Blackwell Verlag, 2003)

A special violet-blue excitation light source and filter on the surgical microscope is used in order to make tumor cells visible as fluorescent cells intraoperatively. The major advantage of fluorescence-guided tumor resection is that the neurosurgeon can clearly differentiate between healthy brain and tumor tissue also in infiltration zones (Figure 1.7) during resection.[33, 35]

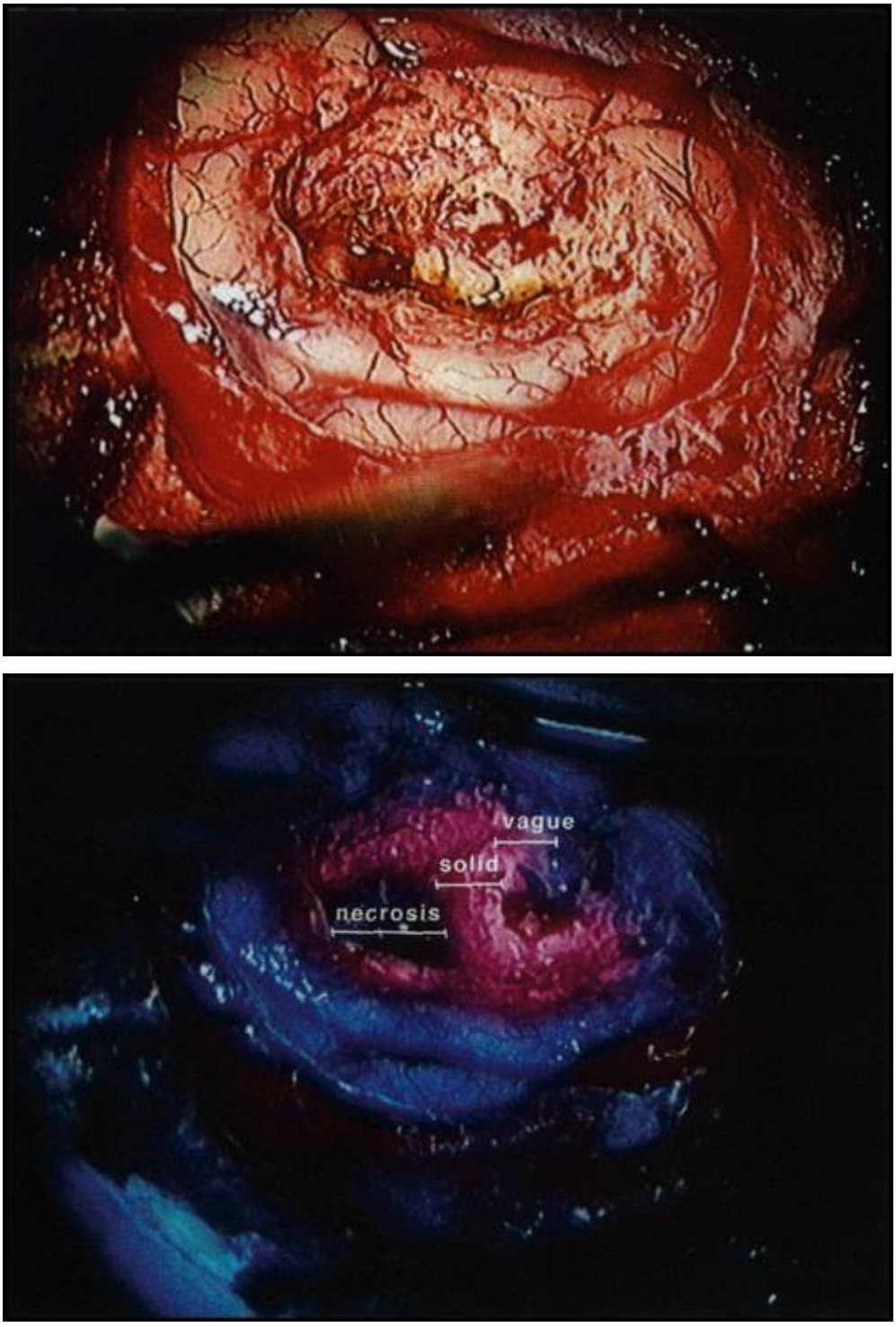

Figure 1.8: Top figure shows brain tissue and tumor tissue under white light. Bottom figure shows the same area under blue light with fluorescent tumor tissue in different intensities marking different zones of the tumor visible. (images from: Stummer et al., J Neurosurg 93:1003-1013, 2000)

Several studies are available showing that by using fluorescence-guided tumor resection a GTR can be achieved in a higher percentage (Figure 1.8) compared to resections performed with only a white light source.[24, 31, 32, 37]

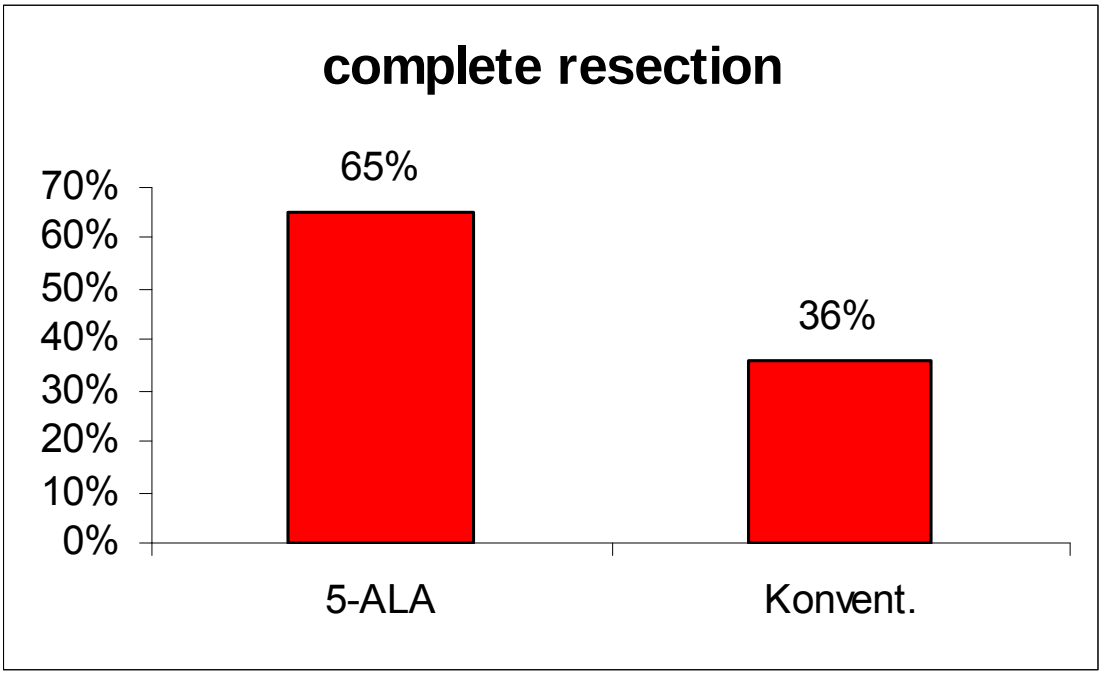

Figure 1.9: Graph showing the percentage of gross total resection reached with 5-ALA and blue light versus resection under conventional white light as published by Stummer et al. (graph adapted from: Lancet Oncol 7:392-401, 2006)

However, in eloquent cortical areas fluorescent-guided resection with its improved radicality might bear an increased risk of causing neurological deficits if functional cortical areas and fiber tracts are injured while resecting all fluorescent tumor cells. Whereas several publications are available highlighting the positive aspects of this revolutionary method so far there are no publications available on methods how to preserve functional areas and fiber tracts during fluorescent-guided tumor resection.

1.5. Brain Mapping and Neuromonitoring

Several invasive and non-invasive techniques are available to localize functional areas of the brain which are routinely used for intraoperative monitoring. The oldest technique is direct cortical stimulation. Brain mapping with direct electric cortical stimulation has been introduced to neurosurgery by Foerster[15] in the nineteen thirties. Brain mapping is based on applying electrical current via a bipolar or monopolar stimulator directly on the exposed brain which triggers a response i.e. a motor evoked potential in a selected target muscle. The time delay between stimulation and response as well as the amplitude of the potential are recorded and compared during the course of a surgery. Cortical stimulation can also be used for speech mapping but in this case the patient has to be awake. Motor or sensory function of speech is temporarily disturbed by the current applied to the brain resulting in speech arrest or dysphasia revealing the exact location of Broca's or Wernicke's area. Today brain mapping is still the gold standard for intraoperative localization of functional areas and fiber tracts.[7] A drawback of this method is that it is invasive and requires the brain to be exposed so it can only be used intraoperatively.

A less invasive intraoperative monitoring technique is the transcranial electric stimulation (TES) where high voltage impulses of up to 600V are applied for a few milliseconds via stimulation needles directly on the skull.[40] The current triggers a motor potential in the target muscles of the stimulated area of the motor cortex. The potentials are recorded and are continuously compared to baseline values, acquired before resection, during the course of a surgery making a deterioration of motor evoked or sensory evoked potentials obvious.

2. Study Objective

The goal of this study was to find a way to maximize resection of PMBT in eloquent cortical areas using fluorescent-guided tumor resection under preservation of functional areas and fiber tracts. A new multimodal approach combining intraoperative monitoring with fluorescent-guided tumor resection which has previously not been described in literature was designed in order to reach this goal. An evaluation of this new approach should show if fluorescent-guided tumor resection in eloquent areas of the brain bears an increased risk of causing neurological deficits. Furthermore, in what percentage of cases fluorescent cells are visible in functional areas or fiber tracts localized by direct cortical or subcortical stimulation.

3. Patients and Methods

3.1. Study Design and Patients

A study was performed between May 2007 and March 2009. Using a prospective study design consecutive patients who fulfilled the inclusion criteria entered the study.

Inclusion criteria were a PMBT (atypical astrocytoma WHO grade III / glioblastoma) in an eloquent cortical area. Patients on first diagnosis or with a tumor recurrence, regardless of adjuvant therapies were included. The Karnofsky Performance Scale had to be 70% or higher. Exclusion criteria were medical conditions prohibiting a general anesthesia or the application of 5-ALA either due to insufficient renal or hepatic function.

Thorough neurological examinations were performed before and within one week after surgery and before discharge in order to determine neurological deficits. After surgery all patients underwent adjuvant chemo- and radiotherapy according to the Stupp protocol.[38]

3.2. Pre- and Postoperative MRI

All patients received MR imaging in a 1,5T scanner (Siemens Vision / Sonata / Avanto Erlangen, Germany). Pre- and postoperative imaging included a morphological T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) MRI with 1mm slices before and after administration of contrast medium. T2-weighted sequences were acquired to visualize edema. A quantitative volumetric tumor analysis was performed pre- and postoperatively based on 3D MPRAGE data with contrast enhancement. Images were loaded into the CBYON neuronavigation system (Med-Surgical Services, Inc.) where the tumor was outlined manually in each image in which a tumor was identified based on its contrast enhancement. Using the surface areas of a tumor on each individual image and the thickness of each image slice (1mm) a quantitative tumor volume calculation was performed. A tumor volume reduction of 98% and more was defined as a GTR. All preoperative MRI sequences were acquired using standard fiducials on the patients' heads as reference points for the neuronavigation system.

Preoperatively all patients underwent blood oxygen level dependent (BOLD) fMRI and DTI examinations in order to localize motor function, speech function as well as fibers tracts and visualize their displacement by the tumor. All fMRI tasks were performed on the ipsilateral side and on the contralateral side of the cerebral lesion to account for inter-hemispheric differences in brain activation patterns. The motor tasks to locate the motorcortex consisted of active finger-to-thumb oppositions, repetitive flexion and extension of the toes (while avoiding movement of the lower extremity proximal to the foot) with a frequency of about 1Hz. Functional images were postprocessed using the Siemens "Neuro-3D" module. Evaluated BOLD images were projected onto anatomical MRI images for better orientation. Data was then loaded into a CBYON neuronavigation system (Med-Surgical Services, Inc.) and marked as a volume of interest on the T1 3D MPRAGE images with contrast enhancement.

DTI sequences were acquired in 12 directions using 2mm slices. NeuroQLab 2.7 (Institute for Medical Image Computing, Fraunhofer MEVIS, Bremen) was used for postprocessing of DTI images and fiber tracking. After fusion of DTI data with 3D MPRAGE images the “volume of interest” was outlined on the T1 images with contrast enhancement. The volume of interest from which the fiber tracking was started, was selected in the area surrounding the tumor in order to visualize displacement. Postprocessed T1 data with selected fiber tracts was exported and then loaded into the neuronavigation system for preoperative planning and intraoperative navigation.

3.3. Preoperative Planning and Intraoperative Navigation

A CBYON neuronavigation system (Med-Surgical Services, Inc.) with 2D image rendering and 3D volume-rendering capabilities for preoperative planning and intraoperative navigation was used (Figure 3.2). The system has the capability to modulate the opacity of tissue layers allowing the neurosurgeon “to see through surfaces” onto deeper structures. The volumes of the lesion, and fiber tracts as well as important arteries and veins were segmented manually and colored using the integrated “volume of interest” planning feature (Figure 3.1).

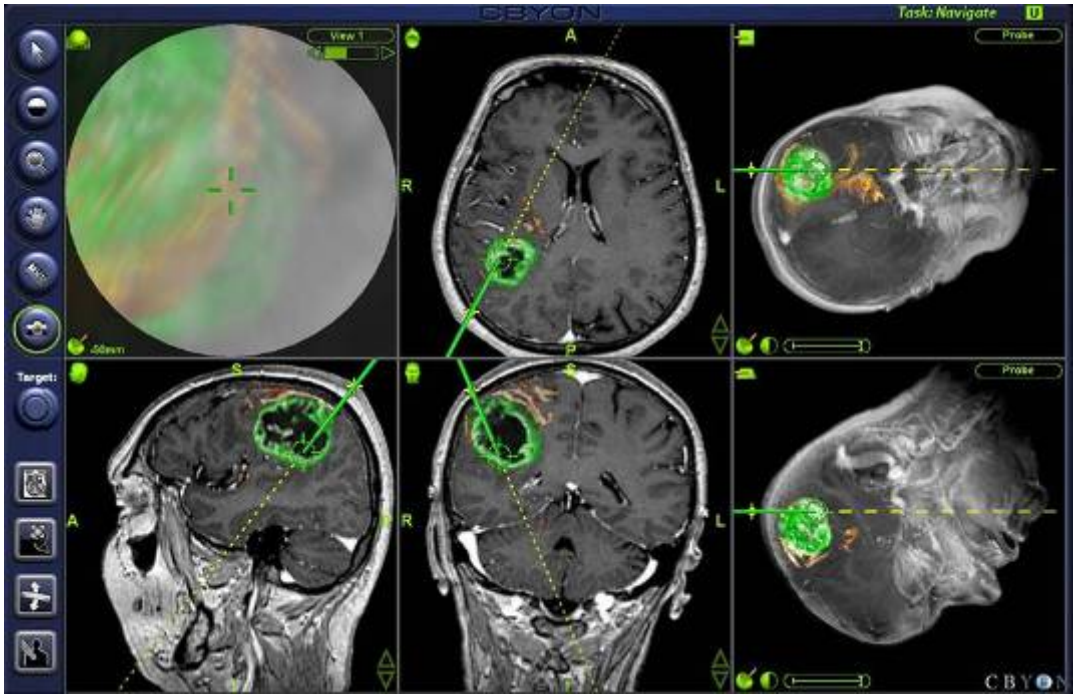

Figure 3.1: Intraoperative screenshot from CBYON neuronavigation system showing a segmented tumor in green and fiber tracts in orange color. The top left image shows the tumor and a displaced fiber tract in the “virtual endoscopic view”.

Intraoperatively the head of the patient was fixed in a Mayfield head clamp and the patient was then registered in the navigation system with a pointer using the fiducials on the patients’ head as reference points (Figure 3.2).

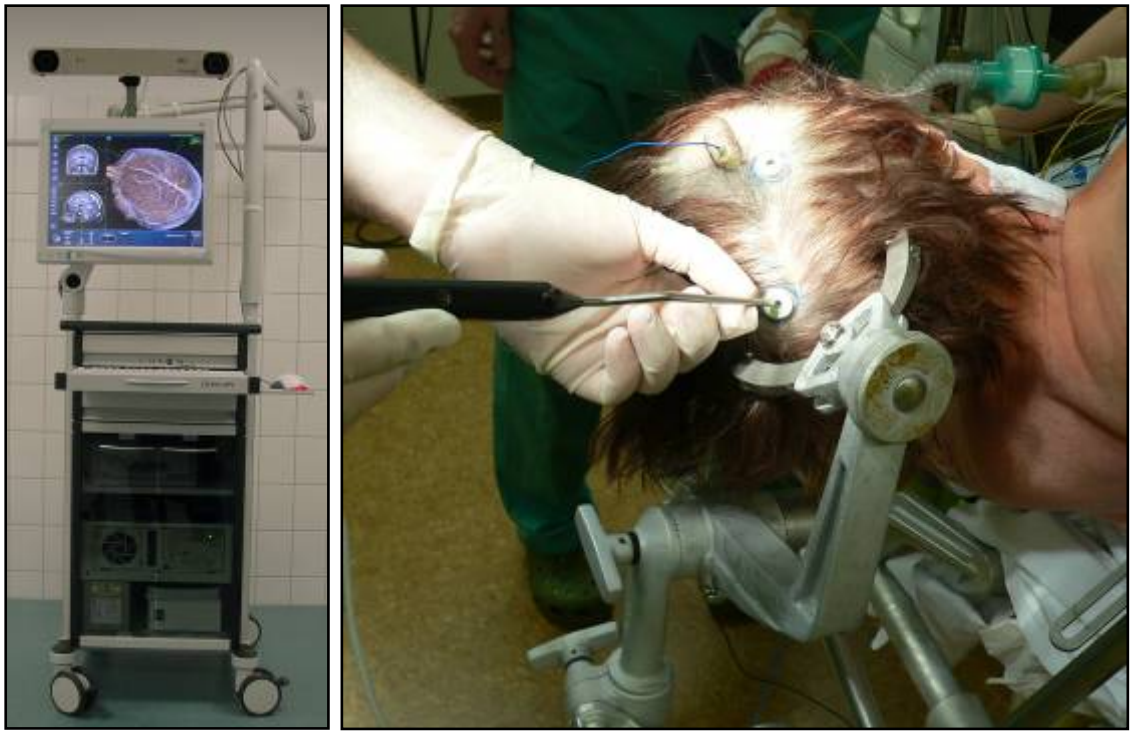

Figure 3.2: The left image shows the CBYON neuronavigation system which is an optical system using an infrared camera. The right image shows the intraoperative registration of a patient the head fixed in a Mayfield head clamp using feducials as reference points and a pointer of the navigation.

In order to faster localize functional areas the stimulator probe was registered in the neuronavigation system by mounting a reference frame on it (see image 3.3). In this way the stimulator acted as a navigation pointer. Functional areas and fiber tracts could be localized faster based on the preoperative functional and DTI data and stimulated to verify their location.

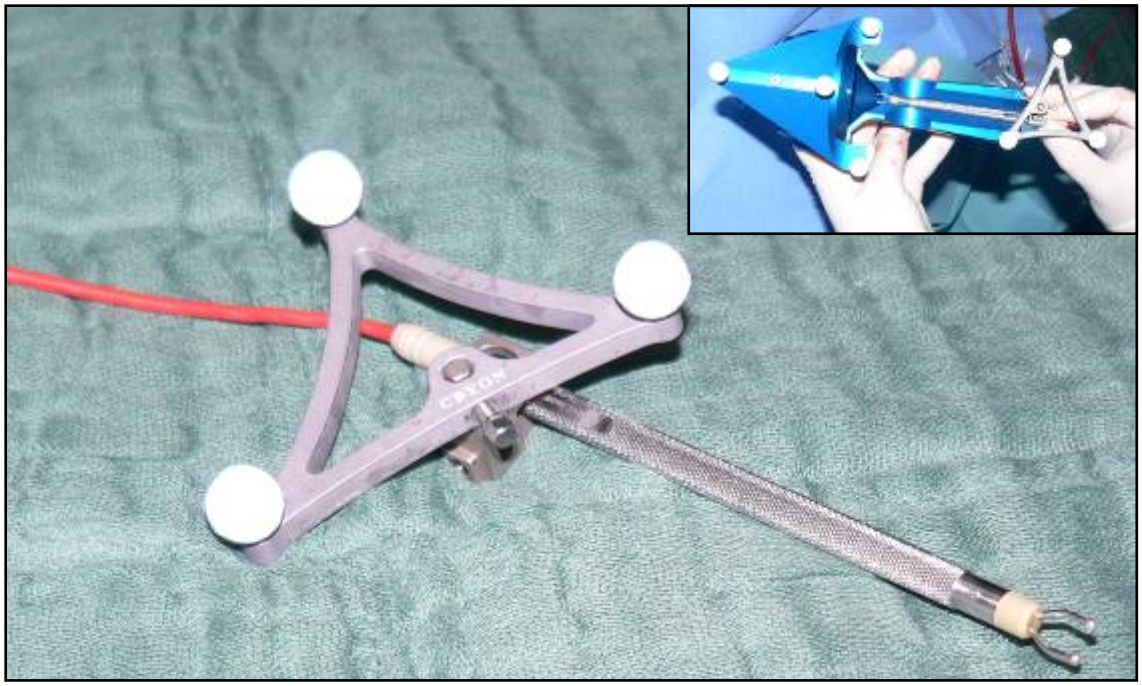

Figure 3.3: Bipolar stimulator and reference frame with three reflective spheres mounted on it (small image on top left shows the stimulator in the navigation registration mount)

3.4. Tumor Resection

Patients received 5-ALA (Gliolan / medac GmbH; Hamburg, Germany) 6 hours before surgery. The substance was dissolved in tap water in a dosage of 20mg/kg - bodyweight.

Intraoperatively the tumor was visualized using an OPMI Pentero (Carl Zeiss, Germany) surgical microscope equipped with a special fluorescence kit including a 440nm short-pass filter for the xenon light source to produce a violet-blue excitation light and a 440nm long-pass filter on the microscope eyepieces. Microsurgical resection was started using the xenon white light source. During resection especially in tumor border zones and infiltration zones the violet-blue excitation light was turned on to visualize tumor tissue. The operating room was dimmed as much as possible to improve visibility of fluorescent tissue. Surgeries were performed under permanent electrophysiological monitoring. In tumor border zones direct cortical and

subcortical stimulation was performed especially in areas with fluorescent tissue (see image 3.4), before resection was continued. The goal was always to achieve a total resection of fluorescent tissue.

3.5. Intraoperative (Neurophysiological) Monitoring (IOM)

Before applying the Mayfield head clamp on the patient's head, needles were placed in the patients scalp for intraoperative monitoring of motor evoked potentials (MEP) and sensory evoked potentials (SEP).
Corkscrew electrodes were placed at C-1 and C-3 or C-3 and C-4 for stimulation with high-frequency trains of 5 to 7 pulses at 2-millisecond intervals corresponding to 500 Hz. Stimulations were always applied contralaterally to the affected side using 350–600 V with 50 µsecs between stimuli typically ~1 to 2 times/minute. Motor evoked potentials were recorded from needles placed in the affected target muscles. Baseline values for SEPs and MEPs were acquired before craniotomy. Cortical and subcortical stimulations were performed using a bipolar probe. Rectangular pulses and a biphasic current with a frequency of 60 Hz were used for cortical and subcortical stimulations. Intensities of the current ranged from 1 to 6 mA, with every stimulation lasting 2 seconds.

Resection was stopped when stimulation positively localized a functional area or fiber tract also in areas with fluorescent tissue indicating tumor tissue. Furthermore, if a permanent decrease in MEP amplitudes acquired from transcranial electric stimulation of > 50% compared to the baseline value occurred, resection was stopped as well.

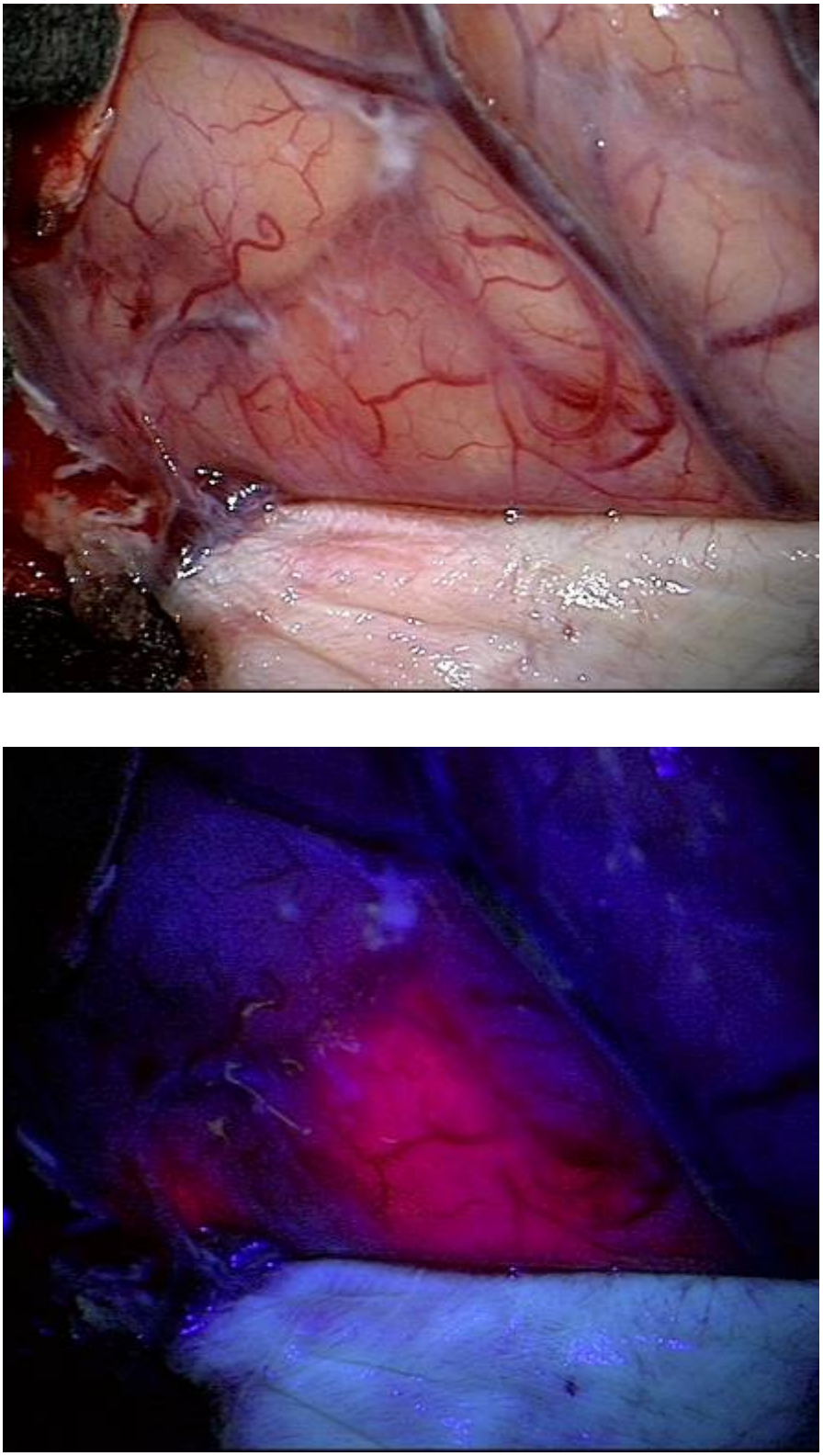

Figure 3.4: Intraoperative screen shot showing cortical surface through the surgical microscope with white light (image on top) and blue light (image on bottom) visualizing cortical tumor infiltration.

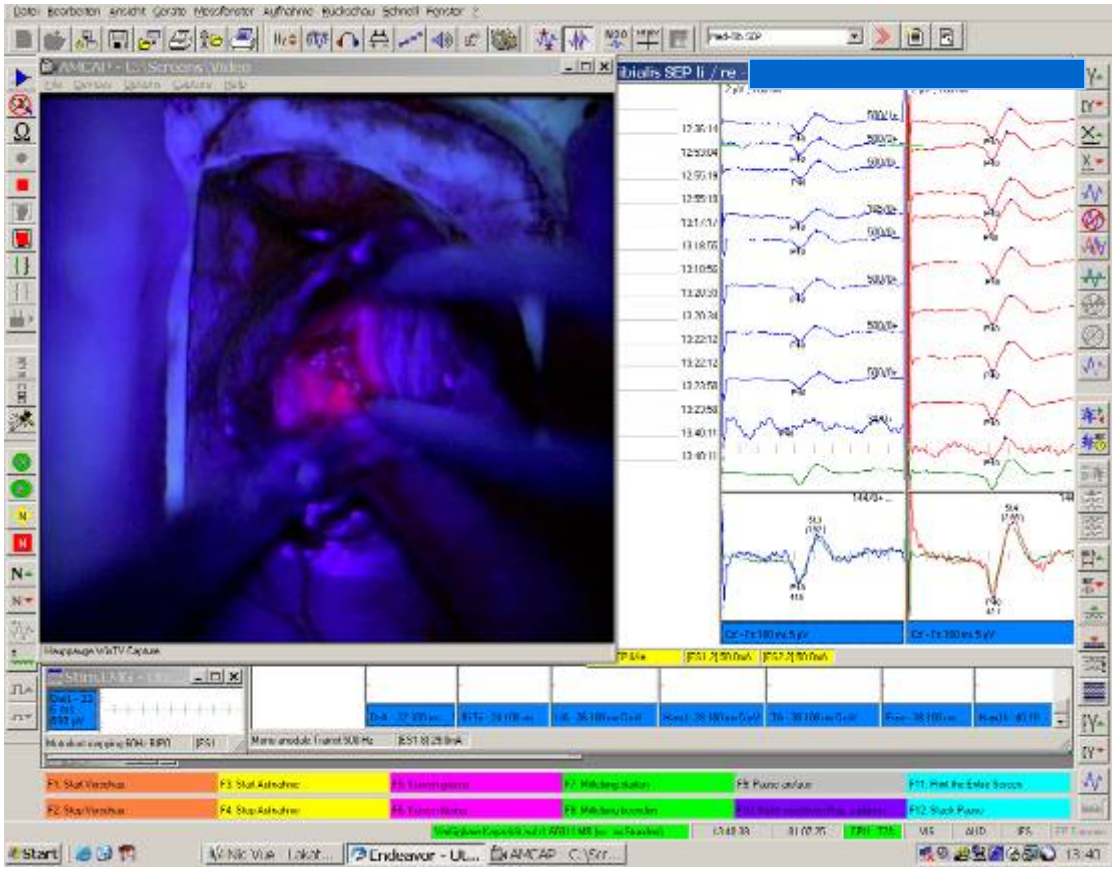

Figure 3.5: Intraoperative screen shot from the neuromonitoring machine showing the view of the surgical microscope in the blue light mode with fluorescent tumor tissue on the left and SEP potentials on the right side of the screen.

3.6. Data Management

MeDigS-Archive V1.1.2 (FMS, Graz, Austria) was used to store and manage all patient data and digital images. Microsoft Excel 2003 spread sheets were used to enter patient data i.e. neurological symptoms, tumor locations and volumes.

4. Result

Twenty-five procedures were performed in 18 consecutive patients (12 men and 6 women) with a mean age of 55 years (range 27–76 years). Four patients underwent between 2 and 4 surgeries within a median follow-up period of 11 months because of tumor recurrences while on adjuvant therapies. A progression-free survival > 6 months was observed after GTR in 83% of the patients, and 1 patient died because of tumor progression after 10 months of follow-up. The mean tumor volume before surgery was 30.5 cm^3 (range 0.5–84 cm3). Gross-total resection was achieved in 16 (64%) of the surgeries. Volumetric tumor analyses in patients in whom GTR was not achieved showed a mean remnant tumor of 3.9 cm3 (range 0.3–8.7 cm3). In 6 surgeries (24%) resection was stopped because a functional area or cortical tract was identified or because MEP amplitudes were reduced in an area where fluorescent tumor cells were still visible. In 2 patients preexisting hemiparesis became accentuated after surgery, and 1 of these patients suffered from a new homonymous hemianopia after a second resection due to tumor recurrence (Table 1). The mean Karnofsky Performance Scale score was 90% before and 89% after surgery. No postoperative complications, such as bleeding or a CSF fistula, were observed in any of the patients. The 5-ALA was well tolerated, caused no adverse effects, and intraoperatively showed fluorescent tumor tissue in all cases as well as in patients with tumor recurrences. Functional cortical areas and cortical tracts were successfully located using cortical and subcortical stimulations. None of the patients suffered an intraoperative seizure because of stimulation. Histopathological results showed that 15 patients harbored GBMs, and 1 of these patients had a recurrence of a WHO Grade III anaplastic astrocytoma. Three patients suffered from WHO Grade III anaplastic oligodendrogliomas. Tables 2 and 3 list details on tumor locations as well as pre- and postoperative symptoms and neurological deficits. After surgery all patients underwent adjuvant chemo- and radiotherapy according to the Stupp protocol.[39]

symptoms	seizures	headaches	aphasia	hemiparesis
preoperatively	4	6	8	(discrete) 5
post-operatively	1	4	8 (3 significantly improved)	5 (2 accentuated)

Table 4.1: Pre- and postoperative symptoms and neurological deficits

# of patients / procedures	18	25
tumors	15 glioblastomas	3 anaplastic Oligodendrogliomas WHO III
tumor volumes / range	30.5cm^3	0.5 to 84cm^3
# of gross total resections / percentage	16	64%
pre-/ postoperative Karnofsky scores	mean 90	mean 89

Table 4.2: Patient data and treatment outcome

Tumor locations /#
pre- or central region / 10
left parieto-occipital region / 1
left parietal / 3
cerebellar peduncle / 1
left fronto lateral / 2
left insular region / 1

Table 4.3: Tumor locations

5. Discussion

Primary malignant brain tumors have been subject to a variety of innovative treatment modalities over the past 4 decades. Each method has demonstrated specific merits and limitations. Nevertheless, it is fair to say that so far no treatment has shown significantly better results with respect to patient survival. However, the degree of volume reduction in these tumors has been shown to play a major role in overall survival[8, 31, 34] most likely because a reduced tumor load enhances the effects of adjuvant therapies. Based on this finding, the value of tools that increase the possibility of achieving a GTR becomes obvious. Thus, fluorescence-guided tumor resection represents a breakthrough in the microsurgical treatment of primary malignant brain tumors. The suitability of this method is highlighted by several studies reporting a greater number of GTRs by using 5-ALA as compared with conventional microsurgical tumor removals under white xenon light.[18, 31] Even though the number of patients in our study was relatively small, the percentage of successful GTRs (64%) in our patients corresponds to rates published in the literature.[31] Moreover, the low rate of reported side effects in patients who receive 5-ALA is confirmed by our experience; that is, no adverse side effects were observed in our study. Fluorescence-guided tumor resection was at its introduction and still is accompanied by a certain degree of euphoria because no other method can visually guide the neurosurgeon to the actual tumor borders, which are not usually recognized by the naked eye. Comparable methods involving ultrasonography and intraoperative MR imaging have the disadvantages of requiring more or less expensive technical equipment, and resection must be stopped to check for remnant tumor tissue. Furthermore, contrast-enhanced MR imaging visualizes only areas where the blood-brain barrier is disturbed rather than tumor tissue per se. On reviewing the literature, one can see that the main focus of studies evaluating 5-ALA lay in the emphasis on the radicality of resection that can be achieved. Even robotic laser resection of fluorescence-enhanced tumor tissue has been shown to achieve GTR.[20, 25] Thus far, however, there is one aspect that seems to be neglected in studies published on this subject; that is, greater radicality carries a significant risk of neurological

deficits especially when excising tumors in eloquent cortical areas. In our opinion, QOL, like the degree of tumor resection, plays an important role in patients with primary malignant brain tumors since their life expectancy is very limited. In searching the available literature, we found no authors describing the technique of fluorescence-guided brain tumor resection in combination with the well-established method of cortical and subcortical stimulation. Naturally, this finding begs the question, What happened to all the pioneering work published by Ojemann, Berger, and others?[6, 7, 12, 13, 26] Why have no authors evaluating 5-ALA mentioned this combined technique? Perhaps refinements in applying the technique have yet to be made by routinely combining it with other established methods used to preserve neurological function. Because we routinely perform cortical stimulations in cases in which tumors are in the vicinity of eloquent cortical areas or cerebral tracts, we initiated this prospective study and decided to publish our first results. Of course, one could argue that the use of intraoperative monitoring would, to a certain degree, diminish the advantages of fluorescence-guided tumor resection by keeping the neurosurgeon from resecting tumor tissue from where it is positively indicated by fluorescent tumor cells. However, we did not find this to be a limitation, and our results compare favorably with data from other reports. In only 24% of our surgeries was resection stopped in areas where fluorescent tissue could still be positively identified. If we had continued resection in these patients, the percentage of postoperative neurological deficits would have been drastically increased and we would have reduced the QOL in one-third of our patients. As for many other brain tumors but especially in cases of primary malignant brain tumors a multimodal approach offers the best results with respect to the radicality of tumor resection and simultaneous preservation of neurological function. We found that the preoperative visualization of functional cortical areas and cortical tracts is a very useful diagnostic addition (Figures 6.1 and 6.2). During preoperative planning of the surgical approach as well as during the navigation-guided resection, it was very helpful to see the displacement of eloquent cortical areas. Fluorescence and intraoperative monitoring, however, represented the most important tools with respect to resection radicality and functional

preservation, and this is shown by our results after surgery, with only 1 patient suffering a new neurological deficit and 2 having an accentuation of preexisting hemiparesis. In using this multimodal approach, it is realistic to expect very low morbidity.

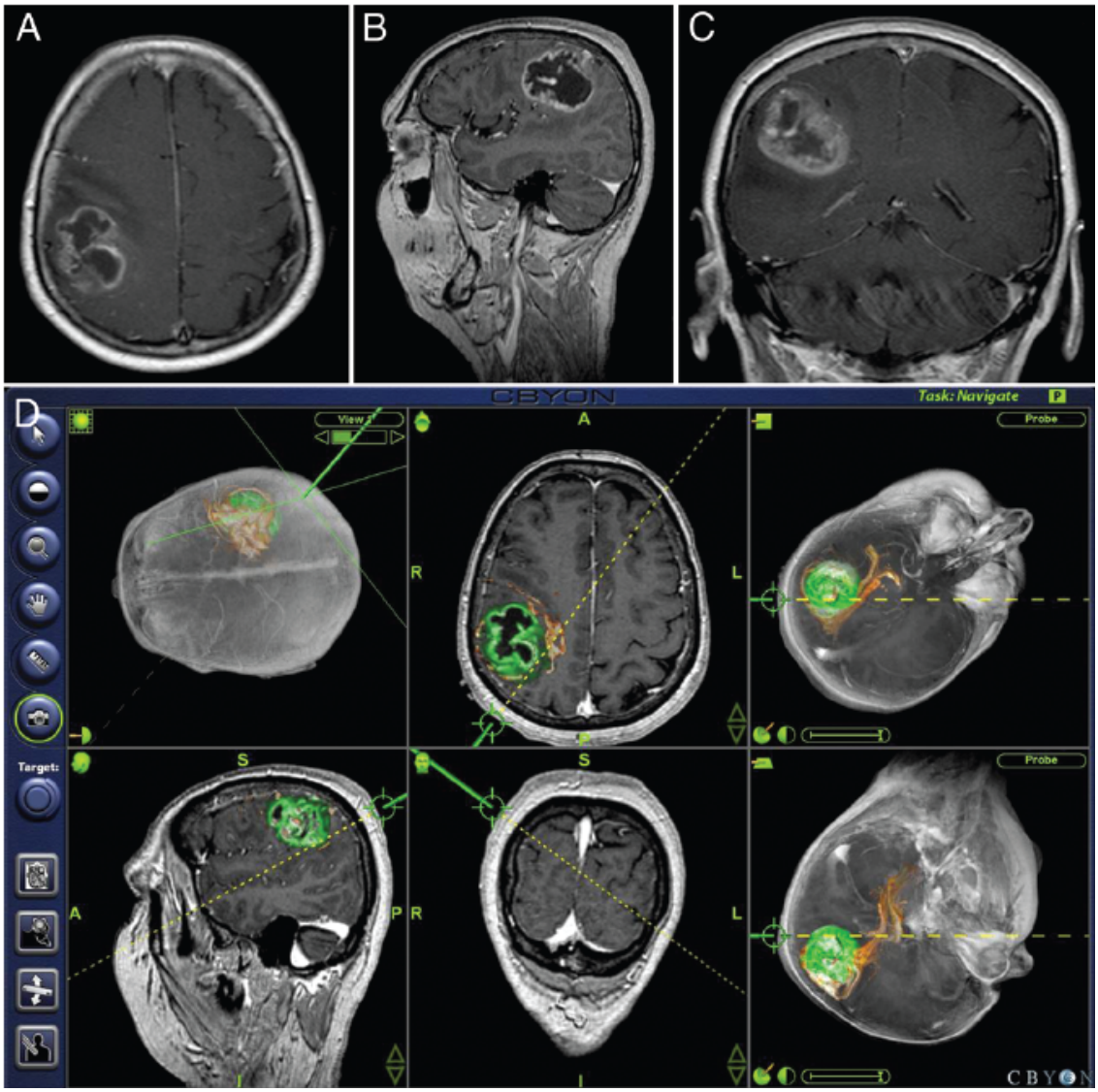

Figure 5.1: Preoperative (A–C) and intraoperative neuronavigation (D) MR images obtained in a 67-year-old woman by using the CBYON neuronavigation system (Med-Surgical Services, Inc.), showing segmented tumor tissue (green) and motor fiber tracts (orange). These images show a right postcentral glioblastoma (32.2 cm^3) displacing the central gyrus and pyramidal tracts anteriorly. Presenting symptoms on admission were weakness of the left arm and disturbed fine motor skills of the left hand.

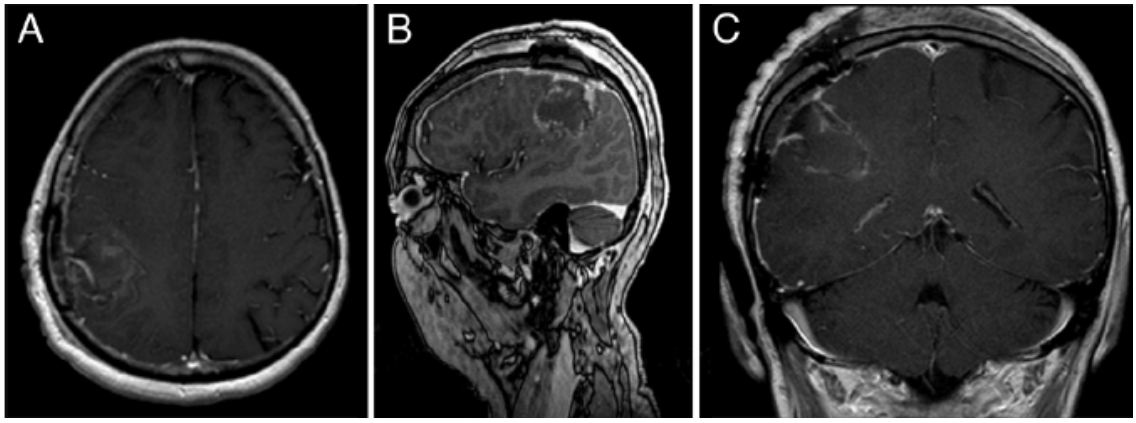

Figure 5.2: Postoperative axial (A), sagittal (B), and coronal (C) contrast-enhanced MR images obtained 24 hours after surgery, showing a 93% reduction in tumor volume. Resection had to be stopped in an area with fluorescent tumor tissue still visible near the pyramidal tracts because of positive subcortical stimulation. Postoperatively, the patient showed no new neurological deficits.

Importantly, we must emphasize that this method represents no new attempt to cure primary malignant brain tumors but instead shows the synergy that can be achieved by combining 2 established methods. Despite all the obvious advantages of fluorescence-guided tumor resection and even though we encountered no problems with respect to tumor detection, we should mention that there are potential limitations in terms of lesion detection. In cases in which tumor parts are not continuous with the main lesion, layers of healthy tissue could hide fluorescent tumor cells, resulting in an unwanted incomplete tumor removal not detectable on MR imaging.

6. Conclusions

Improving treatment outcomes in patients with primary malignant gliomas remains a formidable challenge, but the possibilities of performing a GTR in eloquent areas of the brain without causing neurological deficits is a realistic goal that can be achieved by using a multimodal approach. The advantages of fluorescence-guided tumor resection are enhanced by combining it with both intraoperative monitoring and the well-established procedure of cortical and subcortical stimulation. More patients must be treated and additional studies performed to further evaluate the benefits of this multimodal approach in the surgical treatment of primary malignant brain tumors.

7. Summary

Anaplastic astrocytomas WHO grade III and glioblastomas are the most common PMBTs comprising about 60 - 90% of all brain tumors depending on age groups. Treatment of these malignant tumors requires a multimodal strategy with microsurgical resection followed by adjuvant chemo and/or radiotherapy. Several studies have revealed that a GTR has a direct effect on overall survival of these patients. However, frequently a GTR cannot be achieved because the borders between healthy brain and diseased tissue are blurred in the infiltration zones of malignant brain tumors. Especially in eloquent cortical areas, resection is frequently stopped before a total removal is achieved in order to avoid causing neurological deficits. Even though there are well known landmarks to localize functional areas on the cortical surface they are no longer applicable if functional areas and cerebral tracts are displaced by a space occupying lesion.

Several techniques including fMRI, DTI tractography and transcranial magnetic stimulation are available to localize and visualize functional regions and fiber tracts of the brain preoperatively. Furthermore, this data can also be used in combination with a neuronavigation system in order to easier localize functional areas intraoperatively. However, despite of obvious merits of these imaging techniques, there are also downsides making them not 100% reliable. Therefore, brain mapping with direct cortical stimulation and transcranial electric stimulation is still the gold standard to localize functional areas, fiber tracts and to monitor motor functions intraoperatively.

The recently introduced fluorescent-guided tumor resection of PMBTs with 5-ALA represents a breakthrough in intraoperative visualization of tumor cells. Studies have shown that with this new technique GTRs of PMBTs are achieved more frequently. But, in eloquent cortical areas an increased radicality potentially bears the risk of causing neurological deficits. In current literature, however, this problem is not being addressed. It has been described that when performing a fluorescent-guided microsurgical resection of a PMBT the

neurosurgeon should perform the resection only as far as he considers it safe. This shows that especially when performing fluorescent-guided tumor resections, precise intraoperative localization of functional areas and cortical tracts is absolutely essential in order to avoid causing deficits.

Due to these vague descriptions on how to avoid causing neurological deficits during fluorescent-guided tumor resection in literature, it was the goal of this study to find a way to safely maximize resections of PMBTs in eloquent cortical areas. It was planned to perform GTRs under preservation of functional areas and fiber tracts using fluorescent-guided tumor resections. A new multimodal approach combining intraoperative monitoring with fluorescent-guided tumor resection which has previously not been described in literature was designed in order to reach this goal.

In a prospective study 25 procedures were performed in 18 consecutive patients (12 men and 6 women) with a mean age of 55 years (range 27–76 years). 5-ALA was well tolerated, caused no adverse effects, and intraoperatively showed fluorescent tumor tissue in all cases. Functional cortical areas and cortical tracts were successfully located using cortical and subcortical stimulations. Histopathological results showed that 15 patients harbored GBMs, 1 of these patients had a recurrence of a WHO Grade III anaplastic astrocytoma. Three patients suffered from WHO Grade III anaplastic oligodendrogliomas.

Despite of the fact that all tumors were located in eloquent cortical areas we achieved a GTR in 64% of our patients. This result corresponds to rates published in literature, however, in studies not focusing on resections in eloquent areas of the brain. In 24% of our surgeries resection had to be stopped because a functional area or cortical tract was identified or because MEP amplitudes were reduced in an area where fluorescent tumor tissue could still be positively identified. If we had continued resection in these patients, the percentage of postoperative neurological deficits would have been drastically

increased and we would have reduced the quality of life in one-fourth of our patients. This result clearly highlights the benefit of our new method that combines fluorescent-guided tumor resection with intraoperative monitoring. Only 1 of our patients suffered from a new neurological deficit after a GTR and only 2 had an accentuation of a pre-existing hemiparesis. Taking into consideration that all tumors were located in eloquent cortical areas this is an excellent surgical and functional outcome which could not have been achieved with fluorescent-guided resection alone.

During preoperative planning of the surgical approach as well as during navigation-guided resection, it was very helpful to see displacement of eloquent cortical areas as visualized by imaging techniques including fMRI and DTI fiber tracking. Nevertheless, 5-ALA based tumor fluorescence and intraoperative monitoring represented the most important methods with respect to radicality of resection and functional preservation.

Our results clearly show that combining fluorescence-guided tumor resection with the gold standard of cortical and subcortical stimulation represents a necessary refinement to fluorescent-guided tumor resection. In applying our new multimodal method, it is realistic to expect a very low morbidity while achieving a GTR in patients with PMBTs.

8. Zusammenfassung

Anaplastische Astozytome und Glioblastome sind die häufigsten primären Hirntumoren und machen abhängig von der Altersgruppe 60 bis 90 % aller Hirntumoren aus. Die Behandlung dieser malignen Tumoren erfolgt in der Regel multimodal mit mikrochirurgischer Resektion und adjuvanter Chemo- und/oder Radiotherapie. In mehreren Studien wurde nachgewiesen, dass eine Komplettresektion des Tumors eine direkte Auswirkung auf die Überlebenszeit dieser Patienten hat. In vielen Fällen kann jedoch keine Totalresektion erreicht werden, da die Grenzen zwischen gesundem Hirngewebe und Tumorgewebe, besonders in Infiltrationszonen, nicht eindeutig sind. Vor allem bei der Resektion von Hirntumoren in eloquenten Hirnarealen wird die Resektion häufig zu früh abgebrochen, um neurologische Defizite durch Verletzung von Funktionsarealen und Hirnbahnen zu vermeiden. Obwohl es eindeutige anatomische Landmarken an der Oberfläche des Kortex gibt, verlieren diese ihre Gültigkeit, wenn eine Raumforderung eine Verlagerung dieser Landmarken verursacht.

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Es gibt mehrere bildgebende Verfahren wie fMRI, DTI und tanskranielle Magnetstimulation mit denen Funktionsareale und Faserbahnen präoperativ dargestellt werden können. Die Daten dieser bildgebenden Verfahren können auch in ein Neuronavigationssystem importiert werden um die intraoperative Lokalisation von Funktionsarealen und Faserbahnen zu erleichtern. Obwohl diese Methoden für die OP-Planung sehr hilfreich sind, sind sie nicht immer hundertprozentig verlässlich. Aus diesem Grund ist das Brainmaping mit Hilfe der direkten kortikalen Stimulation und der transkraniellen Elektrostimulation noch immer der Goldstandard um intraoperativ Funktionsareale und Faserbahnen zu lokalisieren und zu monitoren.

Die erst vor einigen Jahren in die Neurochirurgie eingeführte fluoreszenzgestützte Tumorresektion von primär malignen Hirntumoren mit 5-ALA stellte einen Quantensprung in der intraoperativen Tumorvisualisierung dar. Es konnte in einigen Studien eindeutig nachgewiesen werden, dass mit

Hilfe dieser neuen Methode der Prozentsatz der Komplettresektion des Tumors bei primär malignen Hirntumoren höher ist als mit konventionellen Methoden (65% vs. 36% Stummer et al.)[33]. In eloquenten Hirnarealen besteht jedoch die Gefahr, dass durch eine höhere Radikalität der Resektion die Wahrscheinlichkeit steigt neurologische Defizite zu verursachen. Dieses Problem wird in der wissenschaftlichen Literatur jedoch nicht angesprochen. Man findet lediglich die Beschreibung, dass die fluoreszenzgestützte Tumorresektion nur soweit durchgeführt werden soll, wie es als „sicher" eingeschätzt wird. Aber gerade während fluoreszenzgestützter Tumorresektionen in eloquenten Hirnarealen ist die genaue intraoperative Lokalisation von Funktionsarealen essentiell um neurologische Defizite zu vermeiden.

Es stellt sich daher die Frage wie man mit der fluoreszenzgestützten Tumorresektion eine Tumortotalresektion erreichen kann ohne dabei neurologische Defizite zu verursachen. Um dieses Ziel zu erreichen wurde eine neue multimodale Methode entwickelt, in der die fluoreszenzgestützte Tumorresektion unter permanentem intraoperativen Neuromonitoring durchgeführt wird.

In einer prospektiven Studie wurden an 18 konsekutiven Patienten mit primär malignen Hirntumoren in eloquenten Hirnarealen insgesamt 25 operative Eingriffe durchgeführt. Die Patientengruppe setzte sich aus 12 Männern und 6 Frauen mit einem mittleren Alter von 55 Jahren (27 bis 76 Jahren) zusammen. 5-ALA wurde für die fluoreszenzgestützte Tumorresektion eingesetzt und wurde von allen Patienten sehr gut vertragen. Während aller Operationen konnten Funktionsareale und Hirnbahnen mit Hilfe der kortikalen und subkortikalen Stimulation eindeutig lokalisiert werden. Die histopathologische Auswertung zeigte, dass in dieser Studie insgesamt 15 Patienten mit einem Glioblastom und drei mit einem anaplastischen Oligodendrogliom WHO Grad III eingeschlossen wurden. Postoperativ wurden alle Patienten mit einer adjuvanten Chemo- und Radiotherapie nach dem Stupp-Schema behandelt.

Obwohl alle Tumoren in eloquenten Hirnarealen lokalisiert waren konnte im Rahmen dieser Studie bei 64 % aller Eingriffe eine Tumortotalresektion erreicht werden. Dieses Ergebnis ist konkordant mit Ergebnissen von Studien in der wissenschaftlichen Literatur welche sich aber nicht nur auf Tumoren in eloquenten Hirnarealen beziehen ist. In insgesamt 24% der Operationen musste die Resektion aufgrund eines eindeutig lokalisierten Funktionsareals oder einer Hirnfaserbahn beziehungsweise wegen einer Latenzerhöhung oder Amplitudenminderung eines MEPs abgebrochen werden. Wäre in diesen Fällen die Resektion nur nach der Fluoreszenz weitergeführt worden, hätte dies bei einem Drittel unserer Patienten neurologische Defizite verursacht und somit die Lebensqualität dieser Patienten erheblich eingeschränkt. Dies unterstreicht den großen Vorteil unserer neuen Methode.

Nur ein Patient in dieser Studie hatte nach der Operation ein neues neurologisches Defizit und zwei weitere eine Akzentuierung eines bereits präoperativ bestandenen Defizits.

Unsere Ergebnisse zeigen eindeutig, dass die Kombination der fluoreszenzgestützten Tumorresektion mit dem intraoperativen Monitoring eine notwendige Ergänzung fluoreszenzgestützten Tumorresektion darstellt. Durch den Einsatz der neuen Methode kann man auch bei Tumortotalresektionen in eloquenten Hirnarealen bessere funktionelle Ergebnisse erreichen.

9. List of Illustrations

10. List of Tables

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12. Original Paper

Resection of malignant brain tumors in eloquent cortical areas: a new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring

Clinical article

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Object. Several studies have revealed that the gross-total resection (GTR) of malignant brain tumors has a significant influence on patient survival. Frequently, however, GTR cannot be achieved because the borders between healthy brain and diseased tissue are blurred in the infiltration zones of malignant brain tumors. Especially in eloquent cortical areas, resection is frequently stopped before total removal is achieved to avoid causing neurological deficits. Interestingly, 5-aminolevulinic acid (5-ALA) has been shown to help visualize tumor tissue intraoperatively and, thus, can significantly improve the possibility of achieving GTR of primary malignant brain tumors. The aim of this study was to go one step further and evaluate the utility and limitations of fluorescence-guided resections of primary malignant brain tumors in eloquent cortical areas in combination with intraoperative monitoring based on multimodal functional imaging data.

Methods. Eighteen patients with primary malignant brain tumors in eloquent areas were included in this prospective study. Preoperative neuroradiological examinations included MR imaging with magnetization-prepared rapid gradient echo (MPRAGE), functional MR, and diffusion tensor imaging sequences to visualize functional areas and fiber tracts. Imaging data were analyzed offline, loaded into a neuronavigational system, and used intraoperatively during resections. All patients received 5-ALA 6 hours before surgery. Fluorescence-guided tumor resections were combined with intraoperative monitoring and cortical as well as subcortical stimulation to localize functional areas and fiber tracts during surgery.

Results. Twenty-five procedures were performed in 18 consecutive patients. In 24% of all surgeries, resection was stopped because a functional area or cortical tract was identified in the resection area or because motor evoked potential amplitudes were reduced in an area where fluorescent tumor cells were still seen intraoperatively. Gross-total resection could be achieved in 16 (64%) of the surgeries with preservation of all functional areas and fiber tracts. In 2 patients presurgical hemiparesis became accentuated postoperatively, and 1 of these patients also suffered from a new homonymous hemianopia following a second resection.

Conclusions. The authors' first results show that tumor resections with 5-ALA in combination with intraoperative cortical stimulation have the advantages of both methods and, thus, provide additional safety for the neurosurgeon during resections of primary malignant brain tumors in eloquent areas. Nonetheless, more cases and additional studies are necessary to further prove the advantages of this multimodal strategy. *(DOI: 10.3171/2009.10.JNS09447)*

Key Words • **fluorescence-guided tumor resection** • **cortical stimulation** • **primary malignant brain tumor** • **neuronavigation** • **fiber tracking**

Despite intense research over the past 4 decades, GBM remains the most common primary brain tumor.[23] Several adjuvant therapies have been developed to improve progression-free survival in patients with these lesions.[10] Nevertheless, the first and most important step in any treatment of primary malignant brain tumors is GTR.[7,8,12] In 1928 Walter Dandy went to extremes and used hemispherectomies in an attempt to cure patients with GBMs, but even these patients suffered recurrences in the opposite brain hemisphere. Although there is still no cure for GBMs, GTR has been shown to play an important role in the overall survival of patients

Abbreviations used in this paper: GBM = glioblastoma multiforme; GTR = gross-total resection; MEP = motor evoked potential; QOL = quality of life; SEP = sensory evoked potential; 5-ALA = 5-aminolevulinic acid.

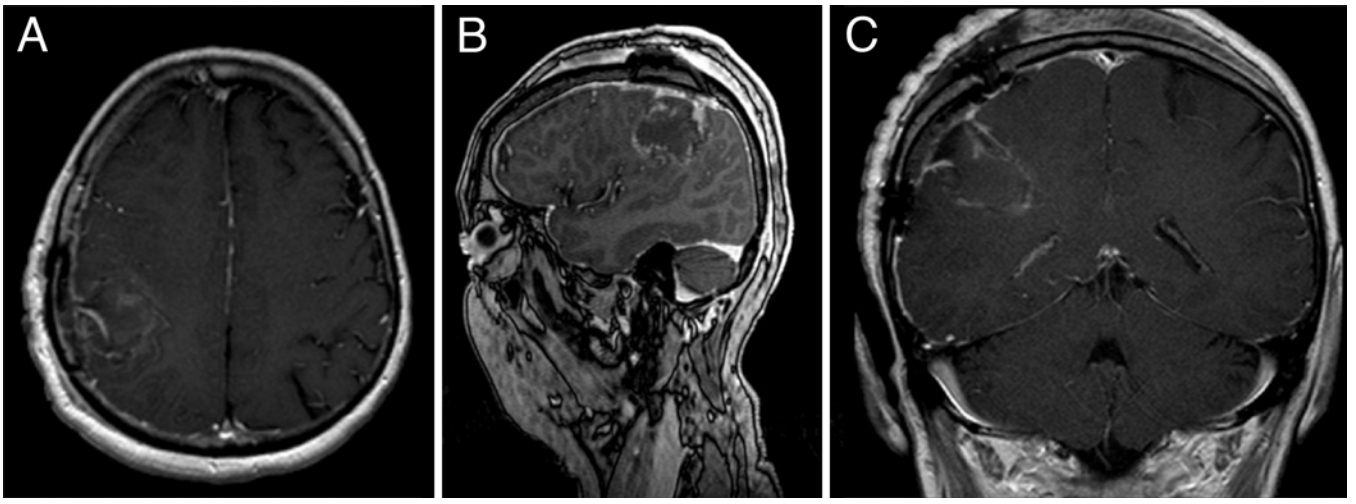

Fig. 2. Postoperative axial **(A)**, sagittal **(B)**, and coronal **(C)** contrast-enhanced MR images obtained 24 hours after surgery, showing a 93% reduction in tumor volume. Resection had to be stopped in an area with fluorescent tumor tissue still visible near the pyramidal tracts because of positive subcortical stimulation. Postoperatively, the patient showed no new neurological deficits.

fied. If we had continued resection in these patients, the percentage of postoperative neurological deficits would have been drastically increased and we would have reduced the QOL in one-third of our patients.

As for many other brain tumors—but especially in cases of primary malignant brain tumors—a multimodal approach offers the best results with respect to the radicality of tumor resection and simultaneous preservation of neurological function. We found that the preoperative visualization of functional cortical areas and cortical tracts is a very useful diagnostic addition (Figs. 1 and 2). During preoperative planning of the surgical approach as well as during the navigation-guided resection, it was very helpful to see the displacement of eloquent cortical areas. Fluorescence and intraoperative monitoring, however, represented the most important tools with respect to resection radicality and functional preservation, and this is shown by our results after surgery, with only 1 patient suffering a new neurological deficit and 2 having an accentuation of preexisting hemiparesis. In using this multimodal approach, it is realistic to expect very low morbidity. Importantly, we must emphasize that this method represents no new attempt to cure primary malignant brain tumors but instead shows the synergy that can be achieved by combining 2 established methods.

Despite all the obvious advantages of fluorescence-guided tumor resection and even though we encountered no problems with respect to tumor detection, we should mention that there are potential limitations in terms of lesion detection. In cases in which tumor parts are not continuous with the main lesion, layers of healthy tissue could hide fluorescent tumor cells, resulting in an unwanted incomplete tumor removal not detectable on MR imaging.

Conclusions

Improving treatment outcomes in patients with primary malignant gliomas remains a formidable challenge, but the possibilities of performing a GTR in eloquent areas of the brain without causing neurological deficits is a realistic goal that can be achieved by using a multimodal approach. The advantages of fluorescence-guided tumor resection are enhanced by combining it with both intraoperative monitoring and the well-established procedure of cortical and subcortical stimulation. More patients must be treated and additional studies performed to further evaluate the benefits of this multimodal approach in the surgical treatment of primary malignant brain tumors.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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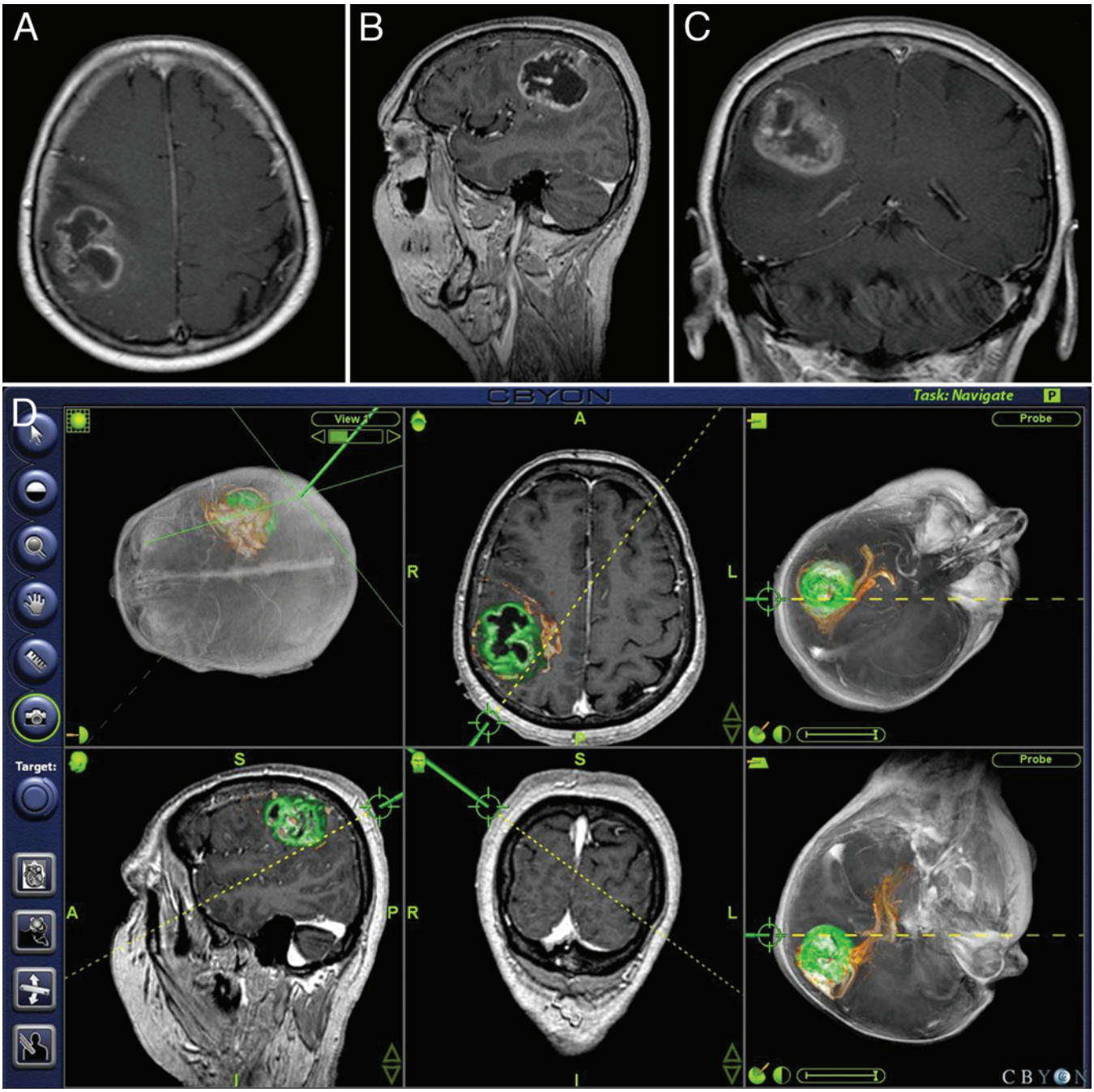

Fig. 1. Preoperative **(A–C)** and intraoperative neuronavigation **(D)** MR images obtained in a 67-year-old woman by using the CBYON neuronavigation system (Med-Surgical Services, Inc.), showing segmented tumor tissue *(green)* and motor fiber tracts *(orange)*. These images show a right postcentral GBM (32.2 cm^3) displacing the central gyrus and pyramidal tracts anteriorly. Presenting symptoms on admission were weakness of the left arm and disturbed fine motor skills of the left hand.

ers?[1,2,4,5,15] Why have no authors evaluating 5-ALA mentioned this combined technique? Perhaps refinements in applying the technique have yet to be made by routinely combining it with other established methods used to preserve neurological function.

Because we routinely perform cortical stimulations in cases in which tumors are in the vicinity of eloquent cortical areas or cerebral tracts, we initiated this prospective study and decided to publish our first results. Of course, one could argue that the use of intraoperative monitoring would, to a certain degree, diminish the advantages of fluorescence-guided tumor resection by keeping the neurosurgeon from resecting tumor tissue from where it is positively indicated by fluorescent tumor cells. However, we did not find this to be a limitation, and our results compare favorably with data from other reports. In only 24% of our surgeries was resection stopped in areas where fluorescent tissue could still be positively identi-

TABLE 1: Summary of pre- and postoperative symptoms and neurological deficits

Time	No.			
	Seizure	Headache	Aphasia	Hemiparesis
preop	4	6	8	5*
postop	1	4	8†	5‡

* Discrete.
† Three cases significantly improved.
‡ Two preoperative cases became accentuated after surgery.

resis became accentuated after surgery, and 1 of these patients suffered from a new homonymous hemianopia after a second resection due to tumor recurrence (Table 1).

The mean Karnofsky Performance Scale score was 90% before and 89% after surgery. No postoperative complications, such as bleeding or a CSF fistula, were observed in any of the patients.

The 5-ALA was well tolerated, caused no adverse effects, and intraoperatively showed fluorescent tumor tissue in all cases as well as in patients with tumor recurrences. Functional cortical areas and cortical tracts were successfully located using cortical and subcortical stimulations. None of the patients suffered an intraoperative seizure because of stimulation.

Histopathological results showed that 15 patients harbored GBMs, and 1 of these patients had a recurrence of a WHO Grade III anaplastic astrocytoma. Three patients suffered from WHO Grade III anaplastic oligodendrogliomas. Tables 2 and 3 list details on tumor locations as well as pre- and postoperative symptoms and neurological deficits. After surgery all patients underwent adjuvant chemo- and radiotherapy according to the Stupp protocol.[22]

Discussion

Primary malignant brain tumors have been subject to a variety of innovative treatment modalities over the past 4 decades. Each method has demonstrated specific merits and limitations. Nevertheless, it is fair to say that so far no treatment has shown significantly better results with respect to patient survival. However, the degree of volume reduction in these tumors has been shown to play a major role in overall survival,[3,16,19] most likely because a reduced tumor load enhances the effects of adjuvant therapies. Based on this finding, the value of tools that increase the possibility of achieving a GTR becomes obvious. Thus, fluorescence-guided tumor resection represents a breakthrough in the microsurgical treatment of primary malignant brain tumors. The suitability of this method is highlighted by several studies reporting a greater number of GTRs by using 5-ALA as compared with conventional microsurgical tumor removals under white xenon light.[9,16] Even though the number of patients in our study was relatively small, the percentage of successful GTRs (64%) in our patients corresponds to rates published in the literature.[16] Moreover, the low rate of reported side effects in patients who receive 5-ALA is confirmed by our

TABLE 2: Patient data and treatment outcome

Parameter	Value
no. of patients	18
no. of procedures	25
tumor type	
GBM	15
WHO Grade III anaplastic oligodendrogliomas	3
tumor vol in cm^3 (range)	30.5 (0.5–84)
no. of GTRs (%)	16 (64)
mean KPS score	
preop	90
postop	89

experience; that is, no adverse side effects were observed in our study.

Fluorescence-guided tumor resection was at its introduction and still is accompanied by a certain degree of euphoria because no other method can visually guide the neurosurgeon to the actual tumor borders, which are not usually recognized by the naked eye. Comparable methods involving ultrasonography and intraoperative MR imaging have the disadvantages of requiring more or less expensive technical equipment, and resection must be stopped to check for remnant tumor tissue. Furthermore, contrast-enhanced MR imaging visualizes only areas where the blood-brain barrier is disturbed rather than tumor tissue per se.

On reviewing the literature, one can see that the main focus of studies evaluating 5-ALA lay in the emphasis on the radicality of resection that can be achieved. Even robotic laser resection of fluorescence-enhanced tumor tissue has been shown to achieve GTR.[11,14] Thus far, however, there is one aspect that seems to be neglected in studies published on this subject; that is, greater radicality carries a significant risk of neurological deficits especially when excising tumors in eloquent cortical areas. In our opinion, QOL, like the degree of tumor resection, plays an important role in patients with primary malignant brain tumors since their life expectancy is very limited. In searching the available literature, we found no authors describing the technique of fluorescence-guided brain tumor resection in combination with the well-established method of cortical and subcortical stimulation. Naturally, this finding begs the question, What happened to all the pioneering work published by Ojemann, Berger, and oth-

TABLE 3: Tumor locations

Tumor Location/No.
pre- or central region/10
lt parietooccipital region/1
lt parietal/3
cerebellar peduncle/1
lt fronterolat/2
lt insular region/1

with these lesions.[18,20] Especially in the infiltration zones of malignant brain tumors, the borders between healthy brain and tumor tissue are blurred, making complete tumor removal very challenging. For this reason, high-resolution ultrasonography—and in a few centers, MR imaging—is used to intraoperatively confirm that total tumor removal has been achieved. However, both are "offline" methods requiring the resection to be stopped to see the results. With the introduction of fluorescence-guided tumor resections using 5-ALA came a method that allows a neurosurgeon to see tumor tissue during resection, helping to reveal diseased tissue when it is not visible to the naked eye.[17] Several studies have shown the usefulness of 5-ALA in the resection of malignant brain tumors;[13,16,21] however, radical resection always carries the danger of causing neurological deficits especially when removing tumors in eloquent areas of the brain. But preserving function to maintain or even improve the QOL for these patients is equally, if not more, important because of their very limited life expectancy.

We designed a prospective study to evaluate the utility and limitations of combining fluorescence-guided resections of primary malignant brain tumors in eloquent cortical areas and intraoperative neurophysiological monitoring with cortical and subcortical stimulation.

Methods

A prospective study performed between May 2007 and March 2009 included consecutive patients harboring malignant primary brain tumors in eloquent areas. Informed consent was obtained from all patients. Neurological examinations before and within 1 week after surgery were performed to evaluate existing and new deficits, respectively. Only patients with a Karnofsky Performance Scale score of at least 70% underwent fluorescence-guided tumor resection and were included in this study. Follow-up examinations were performed on the 1st postoperative day, 4 weeks after surgery, and every 3 months thereafter. Progression-free survival was defined as the time to tumor progression after surgery as diagnosed on follow-up MR imaging.

Magnetic Resonance Imaging

Preoperative and postoperative imaging included T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) MR imaging with and without contrast enhancement as well as T2-weighted sequences to visualize edema. Diffusion tensor and functional MR imaging were performed to visualize functional cortical areas and cerebral fiber tracts. Volumetric tumor analyses were performed as described in a previous publication[6] before and after surgery to accurately determine tumor size and the extent of tumor resection. Imaging data were analyzed offline, loaded into a neuronavigational system, and used intraoperatively. A GTR was defined as a reduction > 98% of the tumor volume based on volumetric measurements.

Tumor Resection and Intraoperative Monitoring

Patients orally received 5-ALA (20 mg/kg bodyweight), which had been diluted in tap water 6 hours before surgery. All surgeries were performed microsurgically and under neuronavigational guidance using minimally invasive craniotomies. We used an OPMI Pentero microscope (Carl Zeiss) equipped with a fluorescence kit, including a violet-blue excitation light during the fluorescence-guided tumor resections. Microsurgical removal was started using a standard white xenon light and switched to the violet-blue excitation light whenever tumor borders were difficult to differentiate from healthy brain tissue. Especially at the end of a resection, the cavity was systematically inspected in the violet-blue light mode to identify any residual tumor.

Intraoperative monitoring included tracking of MEPs and SEPs. Motor evoked potentials were continuously recorded using transcranial electrostimulation via corkscrew electrodes positioned at C-1 and C-3 or C-3 and C-4 for stimulation with high-frequency trains of 5 to 7 pulses at 2-millisecond intervals corresponding to 500 Hz. Stimulations were always contralaterally applied to the affected side using 350–600 V with 50 μsecs between stimuli. In most cases stimulation was applied ~ 1 to 2 times/minute. Motor evoked potentials were recorded from needles placed in the affected target muscles. Baseline values for SEPs and MEPs were acquired before craniotomy. Cortical and subcortical stimulations were performed to localize functional areas and cortical tracts surrounding the lesions. These stimulations were applied using a bipolar probe with the tips 5 mm apart. Pulses for cortical and subcortical stimulations were rectangular, and the current was biphasic with a frequency of 60 Hz. The intensity of the current ranged from 1 to 6 mA, with every stimulation lasting 2 seconds. Using stimulation, the key criterion to stop a resection was the positive localization of either a functional area or a cortical tract in the resection area even if fluorescent tissue was still visible in that area. Moreover, in cases of a permanent decrease in MEP amplitudes acquired from transcranial electrostimulation of > 50% compared with the baseline resection was stopped.

Results

Twenty-five procedures were performed in 18 consecutive patients (12 men and 6 women) with a mean age of 55 years (range 27–76 years). Four patients underwent between 2 and 4 surgeries within a median follow-up period of 11 months because of tumor recurrences while on adjuvant therapies. A progression-free survival > 6 months was observed after GTR in 83% of the patients, and 1 patient died because of tumor progression after 10 months of follow-up.

The mean tumor volume before surgery was 30.5 cm^3 (range 0.5–84 cm^3). Gross-total resection was achieved in 16 (64%) of the surgeries. Volumetric tumor analyses in patients in whom GTR was not achieved showed a mean remnant tumor of 3.9 cm^3 (range 0.3–8.7 cm^3). In 6 surgeries (24%) resection was stopped because a functional area or cortical tract was identified or because MEP amplitudes were reduced in an area where fluorescent tumor cells were still visible. In 2 patients preexisting hemipa-

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