Gross Total Resection Rates in Contemporary Glioblastoma Surgery: Results of an Institutional Protocol Combining 5-Aminolevulinic Acid Intraoperative Fluorescence Imaging and Brain Mapping

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BACKGROUND: Complete resection of contrast-enhancing tumor has been recognized as an important prognostic factor in patients with glioblastoma and is a primary goal of surgery. Various intraoperative technologies have recently been introduced to improve glioma surgery.

OBJECTIVE: To evaluate the impact of using 5-aminolevulinic acid and intraoperative mapping and monitoring on the rate of complete resection of enhancing tumor (CRET), gross total resection (GTR), and new neurological deficits as part of an institutional protocol.

METHODS: One hundred three consecutive patients underwent resection of glioblastoma from August 2008 to November 2010. Eligibility for CRET was based on the initial magnetic resonance imaging assessed by 2 reviewers. The primary end point was the number of patients with CRET and GTR. Secondary end points were volume of residual contrast-enhancing tissue and new postoperative neurological deficits.

RESULTS: Fifty-three patients were eligible for GTR/CRET (n = 43 newly diagnosed glioblastoma, n = 10 recurrent); 13 additional patients received surgery for GTR/CRET-ineligible glioblastoma. GTR was achieved in 96% of patients (n = 51, no residual enhancement > 0.175 cm^3); CRET was achieved in 89% (n = 47, no residual enhancement). Postoperatively, 2 patients experienced worsening of preoperative hemianopia, 1 patient had a new mild hemiparesis, and another patient sustained sensory deficits.

CONCLUSION: Using 5-aminolevulinic acid imaging and intraoperative mapping/monitoring together leads to a high rate of CRET and an increased rate of GTR compared with the literature without increasing the rate of permanent morbidity. The combination of safety and resection-enhancing intraoperative technologies was likely to be the major drivers for this high rate of CRET/GTR.

KEY WORDS: Complete resection of the contrast-enhancing tumor, 5-ALA, Glioblastoma, Gross total resection, Intraoperative mapping, Neuronavigation

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Glioblastoma is a malignant, locally invasive brain tumor with a grim prognosis despite various and intense treatment modalities.[1] Recent studies have found a positive influence of gross total resection (GTR) on overall survival[2-5]; consequently, achieving GTR should be an important goal in glioblastoma surgery. In recent years, various new intraoperative techniques have been introduced into the operating room to improve resection rates and the safety of surgery. They have different merits and range from tools that assist in the planning of surgery (navigation, functional magnetic resonance imaging [MRI], fiber tracking) or resection of the tumor

ABBREVIATIONS: CRET, complete resection of enhancing tumor; **5-ALA,** 5-aminolevulinic acid; **GTR,** gross total resection; **IOM,** intraoperative monitoring; **MEP,** motor evoked potential; **SSEP,** somatosensory evoked potential

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(intraoperative MRI, ultrasound, 5-aminolevulinic acid [5-ALA]) to techniques that improve patient safety by electrophysiological monitoring of function to avoid neurological deficits (motor and sensory evoked potential monitoring, mapping, awake craniotomy). These techniques are increasingly being used, but it remains difficult to quantify their clinical value.

The objective of our study was to evaluate the influence of a multimodal approach combining resection- and safety-enhancing techniques on the rate of GTR and complete resection of enhancing tumor (CRET) in glioblastoma surgery as a surrogate marker of their clinical value. Our institutional protocol included the use of 5-ALA for intraoperative fluorescence imaging and navigation as surgical standard in all patients and the use of cortical and subcortical mapping, including awake surgery, in those patients with tumors close to motor and language eloquent areas. We specifically investigated residual tumor volume on the postoperative contrast-enhanced MRI and the rate of new neurological deficits.

PATIENTS AND METHODS

Study Design and Patient Population

We conducted a retrospective analysis of the results from a glioblastoma surgical-protocol introduced as a standard procedure in our department on August 1, 2008. Eligible patients were > 18 years of age and surgically treated (other than biopsy) for glioblastoma from August 1, 2008, to November 30, 2010, at the Department of Neurosurgery, Bern University Hospital, Bern, Switzerland. Inclusion criteria were the availability of a preoperative MRI (T1 weighted with and without gadolinium enhancement plus T2-weighted images) no older than 14 days and a protocol-specified postoperative MRI within 72 hours.

Two senior neurosurgeons (A.R. and J.B.) assessed preoperative MRIs for eligibility for complete resection of the contrast-enhancing part of the tumor of all patients who were diagnosed with glioblastoma. A tumor was defined as contrast-enhancing tissue with a centrally necrotic core on gadolinium-enhanced T1 sequences. Patients were eligible for the study if the glioblastoma was unilateral and not multifocal and if no enhancement was detected within presumed eloquent localization. In the case of enhancing tumor in presumed eloquent localization, eligibility was considered if the clinical history suggested that the tumor was shifting or compressing rather than infiltrating the eloquent structure (no or minor deficit).

All MRIs were performed on a 1.5- or a 3-T scanner with a head coil. Unenhanced and enhanced (magnetization-prepared rapid-acquisition gradient echo sequences with 0.1 mmol/kg body weight gadolinium-DTPA given intravenously) T1 sequences without gap were obtained (256 [times] 256 matrix, rectangular field of view, 1-mm slice thickness). Information on patient demographics and presenting symptoms was retrieved from standardized assessments documented in the operative and hospital records. All patients were assessed neurologically on the day before surgery, 24 and 48 hours after surgery and before discharge, and in the outpatient clinic 3 months after surgery. Neurological assessment was based on National Institutes of Health Stroke Scale and performed by the treating neurosurgeon. Motor strength was graded according the House-Brackmann and Medical Research Council scales. New postoperative neurological deficits were regarded as temporary if patients showed complete recovery before the follow-up visit after 3 months and as permanent if persisting. The Karnofsky Performance Scale was used to assess the patient's performance before surgery and at the time of the postoperative follow-up visit.

Treatment Strategy

Tumor location was analyzed on contrast-enhanced T1 sequences, and the proximity to eloquent structures was assessed. Eloquence of tumor localization was determined by the grading system proposed by Sawaya et al[6] and modified by Lacroix et al.[3] The primary motor and sensory cortex, basal ganglia, thalamus, hypothalamus, cerebral peduncles, brainstem, dentate nucleus, presumed language areas (identified by fMRI), and primary visual cortex were considered eloquent structures. We modified the grading system by adding essential white matter tracts linked to these eloquent regions. The pyramidal tract, the posterior part of the optic radiation, and the arcuate fascicule were therefore also regarded as eloquent. We used iPlan 3.0.2 software (VectorVision, Brainlab, Heimstetten, Germany) to determine the exact volumetry of the contrast-enhancing tumor.

Surgical Procedure

All patients received 4 mg dexamethasone 3 times a day for at least 2 days before surgery. A functional MRI (fMRI) was performed in case of tumor localization close to presumed language, motor, and visual areas. We believe fMRI to be helpful in planning the surgical approach, but we do not rely on fMRI for intraoperative decision making about the eloquence of a structure. Diffusion tensor imaging was obtained and used for tractography to visualize the spatial relationship between selected fiber tracts and the tumor. Magnetization-prepared rapid-acquisition gradient echo sequences were introduced into an image navigation unit and used for pointer and microscope neuronavigation in all patients. 5-ALA was administered (20 mg/kg body weight; Medac, Wedel, Germany) 3 hours before the induction of anesthesia (range, 2-4 hours). Surgery was performed through a neurosurgical microscope (Zeiss, Oberkochen, Germany) with a fluorescence kit enabling repetitive switching from xenon illumination to violet-blue excitation light.

5-ALA–induced fluorescence was used repeatedly during the tumor tissue resection. The surgeons regularly changed between white light and blue light, especially at the resection border. Resection was continued with the Cavitron Ultrasonic Surgical Aspirator temporarily under the blue light to remove all red or pink enhancing tissue, except for pink staining of the ventricular wall. Resection was continued until all fluorescence had been removed unless the surgeon thought that further resection to be unsafe because of either anatomic or navigation landmarks or because of changes in intraoperative monitoring (IOM) signals. At the end of surgery, the resection cavity was again checked with blue light to ensure completeness of tumor removal.

Intraoperative Neurophysiology

Electrophysiological monitoring was performed by a dedicated team in all cases of presumed motor or speech eloquent tumor localization. In tumors close to the primary motor cortex or the corticospinal tract, intraoperative neuromonitoring for motor evoked potentials (MEPs) was carried out either by transcranial electrical stimulation with electrodes using a 24-channel electroencephalographic system[7-9] or by direct cortical stimulation via a cortical strip electrode placed on the precentral gyrus.[10] For a constant current with anodal stimulation, train-of-5 stimuli with an interstimulus interval of 4.0 ms and an individual impulse width of 500 microseconds were used.[7-9] Cortical and subcortical mapping was performed with a probe delivering a monopolar current[11] and the

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above-mentioned parameters under total intravenous anesthesia.[8] Motor responses were monitored by needle electrodes placed in standardized target muscles. In awake surgery, a 50-Hz bipolar stimulation with a maximal duration of 4 seconds was used.[12-14] Additionally, somatosensory evoked potentials (SSEPs) of all 4 extremities were monitored. Localization of the central sulcus was done with the help of median nerve phase-reversal technique.[15]

Intraoperative neuromonitoring criteria that led to a pause in resection or aborting the surgery were the following: MEP loss in target muscles, sudden unilateral increment of motor threshold unexplained by anesthetic confounders, and loss of > 60% of SSEP amplitude.[7,10,16] During 50-Hz cortical and subcortical stimulation, a positive response led to stopping tumor removal at this site.[12-14] During monopolar mapping, resection was continued until a stimulation motor threshold of 5 to 3 mA was reached if direct cortical stimulation MEP remained stable. Stepwise tumor resection was initially executed not only at positions of higher mapping thresholds but also during subsequent surgery at positions where MEP was elicited by monopolar high-frequency train-of-5 at lower thresholds (<10 mA). By applying a distance-to-current relationship (1 mm = 1 mA) that we have observed during previous surgeries, we intended to map those tumors with very low current (3-6 mA) to avoid the false-positive MEP response resulting from current spread of higher stimulation intensities. This would allow us to get as close as possible to motor structures while still sparing them from incision and resection. At a threshold level of 3 mA, ie, when 3 mA elicited a motor response, resection was stopped to avoid postoperative motor neurological deficits.

Postoperative Imaging Evaluation

An early (within 72 hours) postoperative MRI was obtained in all nonbiopsy patients. Two members of the Department of Neuroradiology (Bern University Hospital, Bern, Switzerland) who were blinded to the preoperative judgment of GTR eligibility assessed the extent of resection. In case of pathological enhancement suspicious for tumor remnant, volumetric analysis through manual segmentation of the contrast-enhancing tumor remnant was performed across all slices (VectorVision; Brainlab, Heimstetten, Germany).[17] Patients with resectable tumor remnant > 0.175 cm^3[18] were scheduled for a second intervention within 6 days.

Statistical Analysis

Descriptive statistics were used to summarize clinical characteristics using standard methods (mean, range, percentages). Comparison of Karnofsky Performance Status and preoperative tumor volume in the complete resection-eligible and complete resection-ineligible subgroups was done with the Mann-Whitney test.

The primary end points were the numbers of patients with CRET and GTR on MRI. We used the definition of GTR from the 5-ALA Study Group (< 0.175 cm^3 residual contrast enhancement on postoperative MRI)[18] in addition to the stricter definition CRET as suggested by the Response Assessment in Neuro-Oncology Working Group.[19] Secondary end points were volume of residual contrast-enhancing tissue, complication rate, and permanent postoperative neurological deficits. Any contrast enhancement on the postoperative MRI qualified the resection as a partial resection.

To address the issue of a selection bias when preoperatively predicting CRET, we calculated the rates of complete and partial resections for 2 groups: complete resection-eligible patients and all consecutive patients operated for glioblastoma.

RESULTS

Fifty-three of the 103 cases (51%) were deemed eligible for CRET, 17 (17%) were planned for partial resection, and 33 (32%) were planned for biopsy only. The mean age was similar in patients eligible and ineligible for complete resections (60 and 58 years, respectively), but tended to be higher in the biopsy group (67 years). The preoperative Karnofsky score of complete resection-eligible patients was higher compared with resection-ineligible patients (85 and 76, respectively, $P = .05$). The complete resection-ineligible and -eligible groups had similar mean Karnofsky scores before and after surgery (76-77, and 85-86, respectively). There was a trend for greater tumor volume in the complete resection-ineligible patients compared with complete resection-eligible patients (43.4 and 27.4 cm^3, respectively; $P = .05$; Table 1). Of the 53 complete resection–eligible cases, 19 tumors (36%) were located in presumed eloquent brain areas.

Primary End Point

In complete resection-eligible patients, the surgical goal of CRET was achieved in 89% (47 of 53 patients), 97% (33 of 34) of those with preoperatively presumed noneloquent tumor location, and 74% (14 of 19) of those with preoperatively presumed eloquent tumor location. In 3 cases, a small enhancing tumor remnant (mean volume, 1.805 cm^3; range, 0.22-4.916 cm^3) was seen on the postoperative MRI and resected within 6 days after

TABLE 1. Patient Characteristics[a]

Characteristic	GTR/CRET Eligible	GTR/CRET Ineligible	Biopsy	Overall
Cases, n (%)	53 (51)	16 (16)	34 (33)	103 (100)
Mean age (range), y	60 (39-80)	58 (38-76)	67 (37-87)	62 (37-87)
Female/male, n/n (%/%)	22/31 (41/59)	5/10 (33/67)	13/21 (38/62)	40/62 (39/61)
Karnofsky score, n				
Preoperative	85	76	NA	83
Postoperative (3 mo)	86	77	NA	84
Mean tumor volume (range), cm^3	27.4 (0.43-92.8)	43.4 (15.7-81.39)	NA	31.3 (0.43-92.8)

[a]CRET, complete resection of enhancing tumor; GTR, gross total resection.

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the initial surgery, leading to the overall CRET rate of 89%. All 3 patients had initial noneloquent tumor localization and received 5-ALA as the only auxiliary technique during early redo surgery. In 4 patients, a nodular enhancement of 0.037 to 0.1 cm^3 (mean volume, 0.0805 cm^3) suspicious for a small tumor remnant in a noneloquent location was observed on early postoperative MRI. When other definitions of GTR are applied to our study that also included a small tumor remnant, (resection of $>$ 98%[20] or $>$ 90%[21] of enhancing tumor), the rates of GTR are 96% and 98%, respectively (Table 2).

In the entire surgical cohort, including cases in which the surgeon preoperatively judged the glioblastoma as ineligible for complete resection, CRET (no residual enhancing tumor visible on postoperative MRI) was achieved in 77% (51 of 66 patients).

Intraoperative Neurophysiology and Its Consequence for Extent of Resection

IOM was applied in 15 patients for a tumor within or adjacent to a presumed eloquent area. Changes in SSEP and MEP led to early termination of resection in 3 patients. Despite residual 5-ALA fluorescence, 2 of these 3 patients had CRET and 1 patient had a small tumor remnant on postoperative MRI ($<$ 0.175 cm^3, GTR). IOM was stable throughout surgery in 12 patients, thus allowing the surgeon to resect the 5-ALA–positive tissue safely (Table 3). One resection was terminated early because of fluorescence in the primary motor cortex (the postoperative MRI showed no residual enhancement; CRET). In another case, the surgeon considered further resection to be unsafe because of obvious infiltration of the corticospinal tract (partial resection according to MRI).

Neurological Deficits

The rate of new permanent motor and speech deficits was 3.8%. One patient (1.9%) had a permanent mild hemiparesis resulting from vascular injury during a nonmonitored surgery, and another patient (1.9%) developed a predicted permanent impairment of fine motor skills of his nondominant hand after CRET of a glioblastoma that infiltrated the primary sensory cortex (This patient had been advised of the risk and chose to sacrifice the sensory loss to obtain a CRET against our advice). In another 2 patients, preoperative partial hemianopia worsened into complete hemianopia resulting from impairment of the posterior part of the optic radiation with sparing of the primary visual cortex (3.8%). Thus, the combined rate of motor, speech, and visual deficits was 7.5% for complete resection–eligible patients and 10% for all patients who underwent surgery (Table 4).

TABLE 2. Achieved Rate of Resection in the Gross Total Resection/Complete Resection of the Enhancing Tumor-Eligible Group[a]

Different Definitions of GTR	GTR/CRET-Eligible Patients (n = 53), n (%)
$>$ 90% Contrast-enhancing remnant[21]	52 (98)
$>$ 98% Contrast-enhancing remnant[20]	51 (96)
$>$ 0.175-cm^3 Tumor remnant volume[18]	51 (96)
No contrast enhancement (CRET)[19]	47 (89)

[a]CRET, complete resection of enhancing tumor; GTR: gross total resection. Analysis using different definitions of GTR as described by Butowski et al,[21] Feigl et al,[20] Stummer et al,[18] and Vogelbaum et al.[19]

Auxiliary Techniques

Neuronavigation based on magnetization-prepared rapid-acquisition gradient echo sequences was used in all cases. An fMRI was performed for presumed language, motor, and visual areas in 12 (18%), 15 (22%), and 2 (3%) patients, respectively. For planning the surgical approach to the tumor, diffusion tensor imaging was obtained in 34 of the 53 patients (64%) to visualize the spatial relationship between selected fiber tracts (corticospinal tract, optic radiation, fasciculus arcuatus) and tumor. Neuronavigation was used in all patients. Intraoperative fluorescence tumor imaging (5-ALA) was administered to 48 of the 53 resection-eligible patients (91%). Five patients did not receive 5-ALA because of either a medical condition prohibiting drug administration or breach of protocol.

Direct cortical or transcranial MEP monitoring and cortical or subcortical mapping for motor and speech function were applied in 22 patients (32%) in whom the tumor was close to eloquent cortex or tracts that were eligible for transcranial electrical stimulation/direct cortical stimulation/SSEPs and mapping. SSEPs of all 4 extremities were monitored in 20 patients (29%).

DISCUSSION

GRT as the Goal of Glioblastoma Surgery

Various studies have suggested an association between the extent of resection and overall survival.[3-5,22-24] Although this was not the primary end point, the recent multicenter prospective randomized study of 5-ALA fluorescence-guided surgery confirmed these findings and revealed an improved median survival (16.7 vs 11.8 months) for patients with achieved GTR compared with those with a postoperative tumor remnant.[18] This analysis provided Level 2b evidence that survival depends on CRET in glioblastoma. Consequently, GTR with preservation of neurological functions—maximum safe resection-—has become the surgical target in the treatment of glioblastoma. However, without intraoperative imaging, this target is often missed.

Definitions for GTR and CRET

In descriptions of the amount of resected tumor volume after glioblastoma surgery, the term total removal is avoided to acknowledge the diffuse, infiltrating nature of these tumors. Instead, the term GTR is used to describe a close to total or total removal of all contrast-enhancing tumor on gadolinium-enhanced T1-weighted MRI. Various authors have defined GTR differently, allowing contrast-enhancing remnants of $<$ 2%,[20] $<$ 5%,[25] and $<$ 10%[21] of the initial tumor or volumes[18] of up to 0.175 cm^3 to be considered

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TABLE 3. Use of Intraoperative Monitoring and 5-Aminolevulinic Acid Fluorescence for Tumors Within or in the Vicinity of Eloquent Areas[a]

Patient	Proximity to Eloquent Area[b]	Modality of IOM	Influence of IOM and 5-ALA on Completeness of Resection	Completeness of Resection According Postoperative MRI	Postoperative Neurological Deficits[c]
1	Within optic Tract	No IOM applied	Resection of all fluorescence	CRET/GTR	None
2	Within optic tract	No IOM applied	Macroscopic total resection (no 5-ALA used[d])	GTR only[e]	None
3	Within optic tract	No IOM applied	Resection of all fluorescence	CRET/GTR	None
4	Within optic tract, in vicinity to the basal ganglia	SSEP, TES MEP, DCS MEP, mapping	Resection of all fluorescence owing to stable IOM	CRET/GTR	None
5	Within sensory cortex	SSEP, TES MEP, phase reversal	Macroscopic total resection SEP changes (no 5-ALA used[d])	CRET/GTR	None
6	In vicinity to the motor cortex	SSEP, TES MEP, DCS MEP, mapping	Resection of all fluorescence owing to stable motor monitoring (mapping showed close vicinity to CST)	CRET/GTR	None
7	Within sensory cortex	No IOM applied	Incomplete resection of fluorescence owing to fluorescence within the primary motor cortex	CRET/GTR	Permanent impairment of manual dexterity
8	Within optic tract, in vicinity to CST	SSEP, speech mapping, visual mapping	Incomplete resection of fluorescence owing to identification of eloquent fiber tracts through mapping	CRET/GTR	Permanent hemianopia
9	Within optic tract	No IOM applied	Macroscopic total resection (no 5-ALA used[d])	GTR only[e]	None
10	In vicinity to the sensory cortex	SSEP, TES MEP, phase reversal	Resection of all fluorescence owing to stable IOM	CRET/GTR	None
11	Within basal ganglia	No IOM applied	Resection of all fluorescence	CRET/GTR	Transient motor deficit of the left side
12	Within speech areas	DCS MEP, phase reversal, speech and motor mapping	Resection of all fluorescence owing to stable IOM and identification of eloquent speech areas (awake speech mapping)	CRET/GTR	None
13	Within optic tract	No IOM applied	Macroscopic total resection (no 5-ALA used[d])	GTR only[e]	None
14	Within optic tract	No IOM applied	Resection of all fluorescence	CRET/GTR	None
15	Within sensory cortex	No IOM applied	Incomplete resection of fluorescence owing to the surgeon's intraoperative judgment that the CST was infiltrated	Partial	None
16	Within basal ganglia	No IOM applied	Resection of all fluorescence	CRET/GTR	None
17	Within sensory cortex	SSEP, TES MEP	Incomplete resection of fluorescence owing to irreversible alterations in MEP monitoring despite persisting 5-ALA fluorescence	GTR only[e]	None
18	Within CST	SSEP, TES MEP	Resection of all fluorescence owing to stable IOM	CRET/GTR	None
19	Within Optic Tract	SSEP, TES MEP, DCS MEP, phase reverse, mapping	Resection of all fluorescence owing to stable IOM	CRET/GTR	None
20	Within speech areas	SSEP, TES MEP, DCS MEP, mapping	Macroscopic total resection owing to stable IOM (no 5-ALA used[d])	CRET/GTR	None
21	Within basal ganglia	No IOM applied	Resection of all fluorescence	CRET/GTR	None
22	In vicinity to the sensory cortex	SSEP, DCS MEP, TES MEP, phase reversal	Resection of all fluorescence despite SEP changes (reversible)	CRET/GTR	None

(Continues)

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TABLE 3. *Continued*

Patient	Proximity to Eloquent Area[b]	Modality of IOM	Influence of IOM and 5-ALA on Completeness of Resection	Completeness of Resection According Postoperative MRI	Postoperative Neurological Deficits[c]
23	In vicinity to the sensory cortex	SSEP, TES MEP, mapping	Resection of all fluorescence owing to stable motor monitoring (mapping showed close vicinity to CST)	CRET/GTR	None
24	In vicinity to the CST	SSEP, TES MEP	Resection of all fluorescence owing to stable IOM	CRET/GTR	None
25	In vicinity to the CST	SSEP, TES MEP	Incomplete resection of fluorescence owing to SEP changes	CRET/GTR	None
26	In vicinity to the sensory cortex	SSEP, TES MEP, phase reversal, mapping	Incomplete resection owing to irreversible changes in DCS MEP (mapping showed close vicinity to CST)	CRET/GTR	None

[a]CRET, complete resection of enhancing tumor; CST, corticospinal tract; DCS, direct cortical stimulation; 5-ALA, aminolevulinic acid; GTR, gross total resection; IOM, intraoperative monitoring; MEP, motor evoked potentials; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potentials; TES, transcranial electrical stimulation.
[b]According to preoperative MRI. "In vicinity" describes tumor tissue within 7 mm from an eloquent area.
[c]Postoperative neurological deficits were collected 3 months after surgery.
[d]These patients received no 5-ALA because of either contraindications for 5-ALA (mainly elevated liver enzymes) or breach of protocol.
[e]Postoperative MRI of these patients showed small enhancing remnants of < 0.175 cm^3. Resections were thus GTR but not CRET.

GTR. Increasing evidence indicating that differences in the amount of resected tumor (in the range of 90%-100%) have an influence on overall survival necessitates clarification of the term GTR. The Response Assessment in Neuro-Oncology Working Group has recently discussed the need for strict definitions of extent of resection analysis and proposed the term CRET for comparison of retrospective analysis of completeness of surgical resection in glioblastoma surgery.[19] We used the Response Assessment in Neuro-Oncology definition of CRET accordingly but also applied GTR as defined by the 5-ALA Study Group for comparison of resection rates.

The Role of Intraoperative Imaging

The rather low rates of GTR in conventional glioblastoma surgery were often explained by the difficulties in differentiating tumor tissue from brain parenchyma during surgery.[26] The advent of intraoperative imaging in glioblastoma surgery—5-ALA and intraoperative MRI—has led to a better identification of the size and location of tumor remnants and an increased rate of GTR.[18,27-29] This was confirmed in 2 prospective randomized studies. Stummer et al[18] randomized selected, GTR-eligible patients to the use of 5-ALA and fluorescence microscopy, in addition to conventional white light microscopy. There was an increased rate of achieved GTR (defined as postoperative remnant tumor volume < 0.175 cm^3) of 65% in the 5-ALA group compared with 36% in the white light group. Senft et al[29] randomized patients for the use of intraoperative MRI. Using the same GTR definition, they showed that more patients in the intraoperative MRI group had a GTR (96%) than in the control group (68%). The high rate of GTR in our study (96%) confirms the impact of intraoperative imaging during surgery of glioblastoma, but we believe that imaging alone is not sufficient. It will detect residual tumor but will fail to provide the neurosurgeon any information on whether tumor tissue close to motor or speech eloquent areas can eventually be removed safely. Thus, when imaging is used alone, it is likely that the surgeon will deliberately perform more subtotal resections in cases with imaging-presumed eloquence of the glioblastoma. A recent series of patients who underwent glioblastoma removal with intraoperative 1.5-T MRI primarily used integration of functional data (fMRI, magnetoencephalography, fiber tracking) into neuronavigation to assess eloquent tumor location without electrophysiology and reported an overall GTR rate of 42%.[30]

The Role of Intraoperative Mapping and IOM

One of the challenges in glioblastoma surgery is the complete removal of the contrast-enhancing tumor while preserving neurological functions.[4,20] New-onset motor deficits and aphasia after surgery are associated with decreased overall survival,[24] in addition to the obvious decrease in quality of life. However, 2 aspects should be considered. On one hand, increasing resection toward the tumor border in the vicinity of eloquent areas may lead to a higher risk of neurological deficits resulting

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TABLE 4. Overall Permanent Neurological Deficits Stratified According to Gross Total Resection/Complete Resection of Enhancing Tumor Status[a]

Type of Deficit	Resection Group	Deficit Unchanged by Surgery, n (%)	Improvement of Preoperative Deficit, n (%)	New or Worsened Deficit, n (%)
Motor	GTR/CRET eligible	5 (9.4)	3 (5.7)	2 (3.8)
	GTR/CRET ineligible	1 (6.3)	0	3 (18.7)
Sensor	GTR/CRET eligible	1 (1.9)	1 (1.9)	0
	GTR/CRET ineligible	0	0	0
Aphasia	GTR/CRET eligible	2 (3.8)	1 (1.9)	0
	GTR/CRET ineligible	1 (6.3)	0	0
Hemianopia	GTR/CRET eligible	2 (3.8)	0	2 (3.8)
	GTR/CRET ineligible	3 (18.9)	0	0

[a]CRET, complete resection of enhancing tumor; GTR, gross total resection. For all categories, n = 53 GTR/CRET eligible; n = 16 GTR/CRET ineligible.

from direct damage to brain tissue or vascular injury. The 5-ALA study showed an increased rate of initial neurological deficits (at 48 hours after surgery) such as hemiparesis and aphasia in patients operated on with 5-ALA, whereas patients operated on without 5-ALA had a higher risk of developing neurological deficits within the next 6 months.[31] On the other hand, intraoperative motor and speech mapping and monitoring may indirectly increase the rate of complete resections by clarifying whether a preoperatively presumed eloquence is intraoperatively "true" eloquence or "false" eloquence. Cases in which the neurosurgeon uses mapping and does not find true eloquence may end as complete resections instead of partial resections owing to tumor remnants in the area of presumed eloquence. This concept of presumed eloquence as a modifiable risk factor predicting disease progression and death can be used by applying IOM and mapping, including awake craniotomy.[32] It may thus help in both avoiding deficits and achieving GTR/CRET. The clinical value of combining resection- and safety-enhancing technologies has recently been analyzed in eighteen patients who underwent resection of high-grade glioma in eloquent locations.[20] According to the authors, the reported GTR rate of 64% suggests that selected cases of presumed eloquent "high-risk"[32] situated tumors may be resected as long as adequate safety-enhancing measures are taken to keep the risk of neurological deficits low. However, deficits can still occur in areas where monitoring and mapping are not yet in routine use, ie, primarily the visual system or areas ineligible for monitoring or mapping.

Early Second Surgery for Tumor Remnants

Our strategy of early reoperation was adapted in light of the 5-ALA Study Group assessment of the effect of GTR on survival. As mentioned, the 5-ALA Study Group reported a survival benefit of 4.9 months in patients with achieved GTR compared with subtotal resections.[2] Thus, achieving a CRET or GTR should be the goal of glioblastoma surgery. There is no reason why an early second surgery should not be offered to the patient when the early (72 hours) postoperative MRI shows residual tumor and the resection was not stopped because of detection of eloquent tissue. For those centers not having intraoperative MRI, why should early postoperative MRI have only diagnostic value? Our protocol thus states that reoperation should be considered in cases of tumor remnants > 0.175 cm^3 to provide the patient with the optimal surgical result (GTR) according to the literature. The additional burden of a second surgery within a few days needs to be weighed against a potential survival benefit, but we found no additional neurological deficits in the 3 patients who underwent reoperation. Although small tumor remnants with a volume of > 0.175 cm^3 were subjected to a second surgery within 6 days to obtain a complete resection, 4 patients with remnants of a volume < 0.175 cm^3 were not considered for a second surgery because we thought that the additional burden of a second surgery was disproportionate to the small volume of tumor remnant. The strategy of early second surgery, which was not part of the treatment protocol in the randomized trial of the 5-ALA Study Group, may have contributed to our high GTR rate of 96% compared with 65% in the 5-ALA randomized trial. Our small number of patients who underwent early second surgery does not allow any further conclusion regarding the value of this strategy.

How Many Glioblastomas Are Eligible for Complete Resection?

There is always a concern of a possible bias in reported GTR rates that occurs when a very conservative selection in favor of the "true" GTR-eligible patients is performed. This bias may also exist in randomized trials and must be kept in mind when the rates of GTR in these studies are compared with the rates of GTR achieved in a consecutive series of patients, ie, in routine clinical management.

The rate of GTR documented by early postoperative MRI may serve as a marker of resection success. It would help to determine the impact of new technologies on a consecutive series of patients. Unfortunately, studies rarely report the number of excluded patients (not GTR eligible) who were primarily planned for partial resection.

A recent prospective randomized trial investigating the impact of intraoperative low-field MRI on the GTR rate in glioblastoma

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patients assessed 57% of glioblastoma patients to be eligible for GTR.[29] Of the 103 consecutive patients in our series, 51% were assessed as eligible for complete resection, 17% of all glioblastomas were planned for partial resection, and 32% had stereotactic biopsy, a number that was similar to the biopsy rate (30%) of the Glioma Outcomes Project, a large multicenter glioma database.[33]

Even when all surgical cases planned for complete or partial resection are included in our calculation of the rate of complete resection, CRET was achieved in 77% (47 patients in the complete resection–eligible group and 4 patients in the partial resection group had an MRI-confirmed CRET). The high CRET rate of 77% in all surgical cases speaks against an overly conservative attitude in the assessment of preoperative GTR eligibility in our cohort.

Comparison of GTR Rate and the 5-ALA Randomized Trial

It was our intention to demonstrate that in contemporary glioblastoma surgery, a GTR rate of 65% as achieved in the randomized controlled trial of Stummer et al[18] should not be seen as the "gold standard rate." Indeed, 5-ALA is a much more powerful technology for detection of residual glioblastoma tissue and thus for achieving complete resection (GTR/CRET). Several contributing factors may have influenced the rate in the Stummer et al study: The majority of study centers had no experience with the new technology of 5-ALA–induced fluorescence before the start of the study; several centers recruited only a few patients to the study; and navigation, mapping, or monitoring was not routinely used (W. Stummer, MD, unpublished data, May 2007). In a recent analysis of the 5-ALA study results, the authors showed that in up to two-thirds of cases with subtotal resection, the surgeon aborted the removal of the tumor for various reasons but knew that the resection was incomplete.[2] Thus, contemporary experience with safety-enhancing technologies should result in a GTR rate $>$ 65% in GTR-eligible patients.

CONCLUSION

Our consecutive series demonstrates that it is possible to increase the rate of surgical success in cases eligible for CRET beyond the rates published by the 5-ALA Study Group (GTR rates of 96% in our study vs 65% in the 5-ALA randomized trial). The devoted use of different available surgical adjuncts, especially 5-ALA fluorescence, cortical and subcortical mapping, MEP monitoring, speech monitoring in awake settings, and early second surgeries for tumor remnants, contributed to the goal of maximizing tumor resection while keeping postoperative deficits at an acceptable level. Complete resection of enhancing tumor was achieved in 89% of complete resection-eligible patients and in 77% of all surgical cases. Compared with published studies, such a multimodal approach leads to an increased rate of GTR/CRET without increasing the rate of permanent and functionally relevant neurological morbidity. Additional studies on progression-free survival and overall survival, as well as on the clinical significance of very small tumor remnants ($<$ 0.175 cm^3), are warranted.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Maximal safe resection of the contrast-enhancing component of glioblastoma multiforme tumors has recently been shown to provide a patient survival benefit when combined with standard of care chemoradiation in a prospective study.[1] Tumors located within or adjacent to eloquent areas of the brain pose a challenge to neurosurgeons who require intraoperative mapping techniques to define motor, speech, and visual pathways during surgical resection to avoid neurologic deficits in patients. The use of 5-aminolevulinic acid (5-ALA) and fluorescence-guided microsurgical resection of glioblastoma multiforme tumors has provided the neurosurgeon direct intraoperative visualization of the tumor, especially the tumor margin that correlates with the area of tumor contrast enhancement.[2]

The authors describe their initial experience with the combined use of 5-ALA fluorescence-guided surgery and intraoperative mapping/monitoring for gross total resection (GTR) and complete resection of enhancing tumor (CRET) in newly diagnosed and recurrent glioblastoma multiforme patients. In those patients eligible for CRET, the authors hypothesize that a larger number of patients can undergo GTR of their tumor when fluorescence-guided surgery and intraoperative cortical mapping are performed by the neurosurgeon. The primary end points of the study were the number of patients with GTR and CRET on magnetic resonance imaging (MRI). The authors hold rigid criteria for GTR in this series as defined as no residual contrast enhancement or no residual contrast enhancement $>$ 0.175 cm^3 by volumetric measurements. The latter definition of GTR is based on the phase 3 randomized study by Stummer et al[3] and fluorescence-guided surgery in malignant gliomas. Patients underwent various intraoperative mapping techniques, including cortical/subcortical motor mapping and awake craniotomies for those patients with tumors close to motor and language eloquent areas. CRET was achieved in 89% (47 of 53) patients, 97% (33 of 34) for those with preoperatively presumed noneloquent tumor location, and 74% (14 of 19) for those with preoperatively presumed eloquent tumor location. In 3 cases, a small enhancing tumor remnant (mean volume, 1.805 cm^3) was seen on the postoperative MRI and resected within 6 days after the initial surgery, leading to the overall CRET rate of MRI complete resection of 89%.

The authors are able to show a higher rate of complete resection of enhancing tumor beyond the rates published by Stummer et al in the 5-ALA phase 3 randomized trial (96% vs 65%) with the addition of intraoperative mapping and monitoring techniques. They are able to achieve this without increasing neurological morbidity. The authors' results are promising in their small group of patients and provide the basis for the further study of combining intraoperative mapping techniques to fluorescence-guided surgery in patients with tumors in or near eloquent areas in the brain.

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Contemporary management of patients with glioblastoma (GBM) includes surgical resection of the bulk tumor, when feasible. The term "maximal safe resection" has been used to describe the balancing act neurosurgical oncologists must perform to both provide clinical benefit, in the form of bulk tumor resection, and avoid harm, in the form of new neurological deficits or avoidable medical morbidities. Various tools have been developed to help accomplish the completeness of resection goal, including image guided navigation systems, intraoperative imaging (ultrasound, CT, MRI), and most recently the use of 5-ALA for the production of intraoperative tumor fluorescence. Other tools allow us to reduce the risk of permanent neurological morbidity, including preoperative functional evaluation with fMRI, DTI tractography, MEG and navigated transcranial magnetic stimulation, and intraoperative functional evaluation with electrocorticography, cortical stimulation and awake neurological monitoring. The authors have described their experience with the use of a combined strategy of 5-ALA guided

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resection with direct cortical stimulation in a series of patients who were judged, based upon pre-operative imaging, to be eligible for a complete resection of enhancing tumor (CRET). In this highly selected group of patients, they found that they could achieve their goal of CRET in a greater percentage of patients than described in other series, without producing an increase in neurological morbidity. An important question not raised in this study is how best to manage patients in whom the goal of a CRET is uncertain based upon pre-operative imaging. Will use of 5-ALA push the surgeon to resect more tumor than they should, and will DCS alone be adequate to reduce the temptation to remove that "last bit of tumor" that is, in reality, too close to a functional pathway?

An additional interesting point is raised by the authors' practice of returning to the OR to remove unresected enhancing tumor in 3 patients. Although return to OR for further resection is a validated strategy in the management of some pediatric tumors, this has not been a conventional practice in the management of GBM. Resection of residual tumor is a relatively straightforward practice at sites that have intraoperative MRI at their disposal, and in that setting there is little added risk to continuing the procedure that is already underway. Whether it will be justified to have patients undergo all of the events associated with a new surgery (including anesthesia, re-opening of the incision, and the extension of the hospital stay) remains to be demonstrated in a larger cohort of patients.

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