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Abstract: BACKGROUND: Glioblastoma resection guided by 5-aminolevulinic acid (5-ALA) fluorescence and intraoperative magnetic resonance imaging (iMRI) may improve surgical results and prolong survival. OBJECTIVE: To evaluate 5-ALA fluorescence combined with subsequent low-field iMRI for resection control in glioblastoma surgery. METHODS: Fourteen patients with suspected glioblastoma suitable for complete resection of contrast-enhancing portions were enrolled. The surgery was carried out using 5-ALA-induced fluorescence and frameless navigation. Areas suspicious for tumor underwent biopsy. After complete resection of fluorescent tissue, low-field iMRI was performed. Areas suspicious for tumor remnant underwent biopsy under navigation guidance and were resected. The histological analysis was blinded. RESULTS: In 13 of 14 cases, the diagnosis was glioblastoma multiforme. One lymphoma and 1 case without fluorescence were excluded. In 11 of 12 operations, residual contrast enhancement on iMRI was found after complete resection of 5-ALA fluorescent tissue. In 1 case, the iMRI enhancement was in an eloquent area and did not undergo a biopsy. The 28 biopsies of areas suspicious for tumor on iMRI in the remaining 10 cases showed tumor in 39.3%, infiltration zone in 25%, reactive central nervous system tissue in 32.1%, and normal brain in 3.6%. CONCLUSION: 5-ALA fluorescence-guided resection may leave some glioblastoma tissue undetected. MRI might detect areas suspicious for tumor even after complete resection of all fluorescent tissue; however, due to the limited accuracy of iMRI in predicting tumor remnant (64.3%), resection of this tissue has to be considered with caution in eloquent regions. ABBREVIATIONS: 5-ALA, 5-aminolevulinic acidCRET, complete resection of contrast-enhancing tumorEOR, extent of resectioniMRI, intraoperative magnetic resonance imaging.

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Combining 5-ALA Fluorescence and Intraoperative MRI in Glioblastoma Surgery: A Histology-Based Evaluation

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KEY WORDS: 5-ALA fluorescence, Glioblastoma, Intraoperative magnetic resonance imaging, Resection control

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Prolongation of survival in glioblastoma patients is related to the degree of resection.[1-5] Gross total resection (98% of tumor mass) improves outcome, and even tumor reduction of 78% has been shown to increase survival and the success of adjuvant therapy.[6-9] The degree of resection is thus of the greatest importance, but tumor heterogeneity and the infiltrative nature of glioma cells can make it difficult to achieve radical resection without inducing neurological deficits.[10,11]

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **CRET,** complete resection of contrast-enhancing tumor; **EOR,** extent of resection; **iMRI,** intraoperative magnetic resonance imaging

Different imaging modalities have been investigated with respect to their accuracy in tumor visualization. 5-Aminolevulinic acid (5-ALA)–derived fluorescence as an intraoperative visual marker has proved to be especially helpful and has already become the standard of care in some institutions.[5,12-15] The evidence that the use of 5-ALA leads to a significantly higher rate of complete resection of contrast-enhancing tumor (CRET) and increased progression-free survival at 6 months was demonstrated in a randomized, controlled multicenter trial in 2006.[13] Intraoperative MRI (iMRI) for glioblastoma resection

control has been investigated by several groups since 1996[16,17] and has facilitated increased resection rates in low- and high-grade gliomas.[18-20] iMRI provides information about the intraoperative structural anatomy and guides navigation toward suspected areas of remnant tumor independent of surgery-related brain shift.[21-25] Both 5-ALA fluorescence and iMRI have their own set of limitations. Common to both is the problem of clearly delineating the boundary between the infiltration zone and healthy tissue.

In this study, we combined the 2 techniques in a series of operations in order to optimize the degree of resection. Using histological samples as a reference, we first assessed the accuracy of 5-ALA fluorescence in detecting tumor tissue during fluorescence-guided resection. On complete resection of all 5-ALA fluorescent tumor tissue, we performed iMRI and assessed its accuracy in detecting remnant tumor.

METHODS

We included patients operated on at the University Hospital Zurich, Switzerland, between August 2009 and June 2011 with a primary diagnosis of glioblastoma (no other tumor entity, metastases, recurrent glioblastoma, or malignant transformation of a previously known lower grade glioma). Patients were only enrolled if the T1 contrast-enhancing areas on preoperative MRI were considered completely resectable, taking into account the anatomic location of the tumor. Tumors extending into the primary motor cortex, language- and speech-processing cortex, the internal capsule, basal ganglia, thalamus, skull base, and brainstem were excluded.

The study was approved for 14 patients (Table 1) by the Zurich State Ethics Committee (reference no. E−29/2009).

Equipment

The equipment used for all 14 operations included an OMPI Pentero microscope with a blue-light setting at 400 to 410 nm (Carl Zeiss, Oberkochen Germany), a PoleStar N30 iMRI system (0.15 T) with a StealthStation S7 integrated navigational system (Medtronic Inc, Minneapolis, Minnesota), and a CUSA NXT ultrasonic tissue ablation system (Integra Lifesciences, Plainsboro Township, New Jersey).

Preoperative Management

Four hours before induction of anesthesia, 5-ALA (Gliolan; Medac GmbH, Hamburg, Germany) was administered orally under supervision (20 mg/kg body weight).

Surgical Procedure

All interventions followed a strict protocol for surgery and tissue sampling (Figure 1). Operations were performed by 3 staff neurosurgeons with advanced training in the use of 5-ALA. After registration of the navigation system, the first iMRI was performed: T1-weighted and contrast-enhanced with Dotarem (gadolinium-DOTA) (Guerbet) 20 mL/75 kg intravenously.

Tumor resection was performed by alternately operating under white and blue light. Continuous biopsy specimens were taken and classified according to the level of visible tissue fluorescence (0 = nonexistent, 1 = weak, 2 = moderate, and 3 = strong). In the absence of visible fluorescence (category 0), samples were only taken if the area clearly appeared to be involved in the tumor despite the absence of fluorescence. Samples for frozen section analysis were obtained at the beginning of tumor resection. Surgery was carried out until no fluorescent tissue remained. At this point, the second contrast-enhanced iMRI scan was performed. In case of the absence of an enhancing signal, complete resection was assumed, and the surgery was terminated. When contrast enhancement was seen, that specific area was localized with the help of the navigation system, and a detailed reinvestigation carried out in order to reassess the absence of fluorescence. Tissue samples were taken, and the area enhancing on iMRI was resected under navigation guidance.

Histological Analysis

Histopathological evaluation was carried out according to the World Health Organization 2007 diagnostic consensus criteria.[26] The neuropathologists were blinded to all parameters of tissue sampling, including intraoperative location, time of sampling (before or after iMRI), and degree of fluorescence and contrast enhancement. For each sample, nuclear MIB-1 antibody (anti–Ki-67) staining was assessed to measure cellular activity and determine an individual proliferation index.[27] The tissue samples were divided into 4 groups according to histological features:

1. Tumor tissue: increased polymorphism, multinuclear cells, atypical mitotic figures, focal or extensive necrosis, pseudopallisading, blood vessel proliferation, bleeding.
2. Infiltration zone: markedly increased cell density and/or satellitosis, vascular endothelial proliferation, reactive astrocytes, tumor components.
3. Reactive central nervous system (CNS) tissue: minor increased cell density, changes in blood vessel endothelia.
4. Unaltered brain tissue: no pathological changes.

48-Hour Postoperative MRI

All patients underwent 48-hour postoperative MRI in a 3-T MRI scanner. Residual tumor was defined as detectable contrast enhancement on T1-weighted series with a volume of more than 0.175 cm^3. These criteria were applied previously by other groups.[13,19]

Follow-up

We conducted a retrospective follow-up analysis at 40 months. Points of interests were 6-month progression-free survival and overall survival time.

RESULTS

Patients and Samples

Fourteen patients were operated on in total; in 13 of them, the diagnosis of glioblastoma was confirmed (Figure 2). In 1 patient, the frozen section and definite histological analysis revealed a diagnosis of CNS lymphoma, and the patient was excluded from the study. One patient who did not exhibit any 5-ALA fluorescence was also excluded. In this latter patient, 5 tissue samples were taken from visibly abnormal regions, all of which were identified histologically as solid glioblastoma tissue.

TABLE 1. Patient Series[a]

Patient No.	Age, y	Tumor Location	Contrast-Enhancing Tumor Remnant on iMRI	Result on 48-h Postoperative MRI	6-Month Progression-Free Survival	Second Surgery for Tumor Recurrence	Postoperative Survival Time
1	62	Right parietal	Yes	No contrast-enhancing tumor remnant	Yes	Yes	3 y 3 mo 5 d
2	54	Right temporal	Yes	No contrast-enhancing tumor remnant		Yes	1 y 8 mo 2 d
3	67	Left occipital	Yes	Contrast-enhancing cystic tumor remnant 12 × 8 × 5 mm			10 mo 24 d
4	56	Right parietal	Yes	No contrast-enhancing tumor remnant	Yes		8 mo 20 d
5[b]	61	Right parietal	Yes	No contrast-enhancing tumor remnant			8 mo 18 d
6	61	Right parietal	Yes	No contrast-enhancing tumor remnant	Yes		1 y 8 mo 12 d
7	69	Right parieto-occipital	Yes	No contrast-enhancing tumor remnant			1 y 6 mo 25 d
8	37	Right frontal	Yes	No contrast-enhancing tumor remnant			1 y 1 mo 2 d
9	73	Right parieto-occipital	Yes	Small linear contrast-enhancing tumor remnant			5 mo 23 d
10	69	Right temporal	No	No contrast-enhancing tumor remnant			10 mo 14 d
11	65	Right parieto-occipital	Yes	No contrast-enhancing tumor remnant			9 mo 15 d
12	75	Right frontal	Yes	No contrast-enhancing tumor remnant	Yes		9 mo 4 d
13[c]	X	X	X	X	X	X	X
14[d]	38	Right frontal	Yes	Small linear contrast-enhancing tumor remnant			1 y 5 mo 25 d

[a]iMRI, intraoperative magnetic resonance imaging; MRI, magnetic resonance imaging. The patients in rows 5, 13, and 14 were excluded.
[b]Complete absence of intraoperative 5-aminolevulinic acid fluorescence.
[c]Diagnosis of central nervous system lymphoma.
[d]Biopsies and resection of regions that showed contrast enhancement on iMRI not possible due to location in the motor cortex.

A total of 117 samples from the remaining 12 patients were collected before the iMRI was carried out. Of those 117 samples, a total of 93 were taken from fluorescent areas (25 strong, 37 moderate, and 31 weak fluorescence), and histological analysis revealed tumor or a tumor infiltration zone in 95.7%. Twenty-four samples were taken from tissue that did not show fluorescence, and, in these samples, histological analysis revealed tumor or a tumor infiltration zone in 87.5% (Table 2).

Weak fluorescence corresponded to tumor tissue in 87.1% of cases, whereas moderate and strong fluorescence always equated

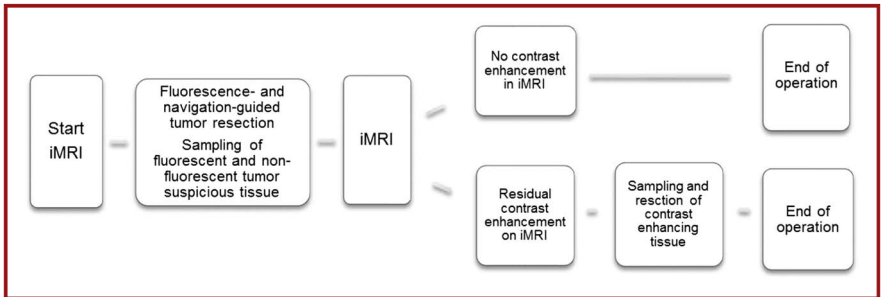

FIGURE 1. *Trial protocol for surgery and tissue sampling. iMRI, intraoperative magnetic resonance imaging.*

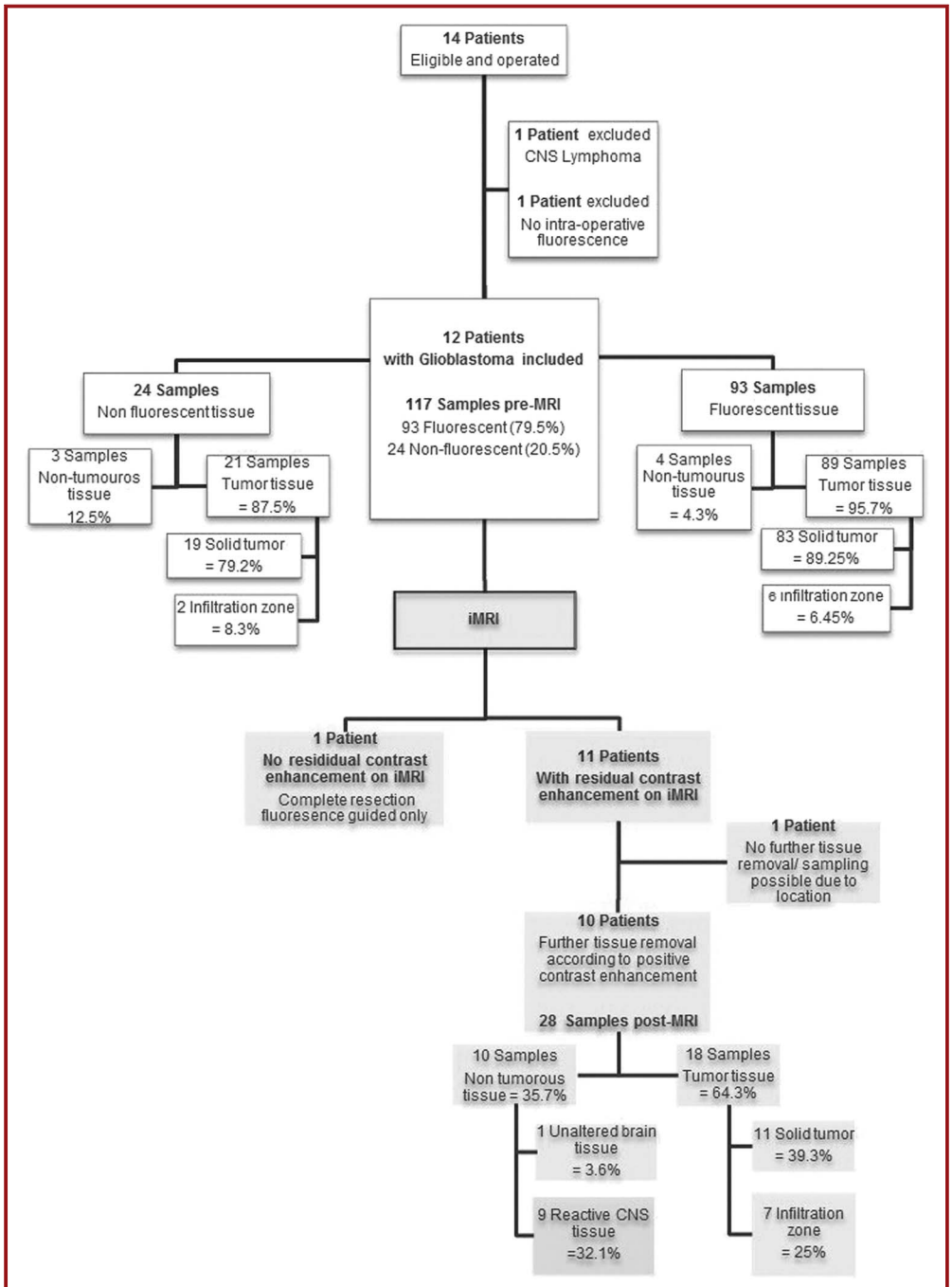

FIGURE 2. *Overview of patient distributions and histological results of tissue sampling. CNS, central nervous system; iMRI, intraoperative magnetic resonance imaging; MRI, magnetic resonance imaging.*

with tumor. The mean proliferation index (Ki-67) was 17.6% in nonfluorescent tumor tissue and 16.7%, 17.1%, and 21.4% in weakly, moderately, and strongly fluorescent tissue, respectively (Table 2).

Of the 12 patients showing fluorescence intraoperatively, only 1 showed no contrast enhancement suspicious for tumor on iMRI on completion of fluorescence-guided resection. In this patient, no further tissue sampling was conducted, and the

TABLE 2. Histological Results of Tissue Samples Taken Before iMRI Was Performed[a]

Pre-MRI Samples (13 Cases)	Total Samples	No Fluorescence (Total)	Positive Fluorescence (Total)	Fluorescence 1 (Weak)	Fluorescence 2 (Moderate)	Fluorescence 3 (Strong)
No. (%)	117 (100)	24 (100)	93 (100)	31 (100)	37 (100)	25 (100)
Histology, no. (%)						
Tumor	110 (94)	21 (87.5)	89 (95.7)	27 (87.1)	37 (100)	25 (100)
Solid tumor	102	19	83	25	34	24
Infiltration zone	8	2	6	2	3	1
Reactive CNS tissue	7 (6)	3 (12.5)	4 (4.3)	4 (12.9)	0	0
Unaltered CNS	0	0	0	0	0	0
P/MIB-1 (Ki-67), %						
PI, mean	18.16	17.60	18.15	16.70	17.13	21.44
PI, range	<1-60	<1-50	<1-60	<1-60	<1-35	8-40

[a]MRI, magnetic resonance imaging; CNS, central nervous system.

operation was concluded. In 1 patient, contrast enhancement on iMRI was located in the motor cortex, and no samples were taken.

From the remaining 10 patients in whom iMRI showed contrast-enhancing regions after the 5-ALA fluorescence–guided surgery was completed, 28 samples were taken (Table 3). All samples were taken under precise navigational guidance from the area in which iMRI showed contrast enhancement. Despite careful inspection, none of these areas showed any visible fluorescence on second look. Of those 28 samples, solid tumor was found in 39.3% (11/28) and an infiltration zone in 25% (7/28) of samples, totaling 64.3% (18/28) of biopsy samples containing tumor tissue. In 32.1% (9/28), reactively altered brain tissue was found, and 1 sample (3.6%) showed no pathological changes. In the 10 patients from whom these 28 samples obtained, tumor tissue was found in 8.

TABLE 3. Histological Results of Tissue Samples Taken From Regions That Showed Contrast Enhancement on iMRI[a]

	Postoperative iMRI Samples of Contrast-Enhancing Regions
No. (%)	28 (100)
Histology, no. (%)	
Tumor	18 (64.3)
Solid tumor	11 (39.3)
Infiltration zone	7 (25)
Reactive CNS tissue	9 (32.1)
Unaltered CNS	1 (3.6)
P/MIB-1 (Ki-67), %	
PI, mean	10
PI, range	1-50

[a]iMRI, intraoperative magnetic resonance imaging; CNS, central nervous system.

Sensitivity, Specificity, and Positive and Negative Predictive Values of 5-ALA Fluorescence

For a summary of the results based on the 117 samples taken before iMRI, see Table 4. The sensitivity of 5-ALA for detecting tumor tissue was 81%, and the specificity was 43%. The 5-ALA positive predictive value for tumor detection was 96% and the negative predictive value was 12.5%.

Positive Predictive Value of iMRI Contrast Enhancement

Based on the histological results of the 28 samples taken after iMRI, the positive predictive value of iMRI contrast enhancement was 64.3%.

48-Hour Postoperative MRI

Of the 10 patients in whom iMRI had shown contrast enhancement and from whom a biopsy sample was taken before the resection of the contrast-enhancing regions, complete resection of enhancing tumor (CRET) was achieved in 8; including the patient in whom no residual contrast enhancement was seen on iMRI, the CRET rate was 82%.

Follow-up

Progression-free survival at 6 months in all 11 patients in whom completion of surgery was achieved was 36.4%. Of the 9 patients showing CRET on 48-hour postoperative MRI, 44% were progression free at 6 months. The 2 patients without CRET showed progression at 6 months.

All patients received combined postoperative radiation and temozolamide therapy. Two patients underwent a second resection due to tumor progression. The mean overall survival of these 11 patients was 15.3 months (range, 173-1193 days). The CRET group showed a mean survival of 18.9 months, whereas the 2

TABLE 4. Sensitivity, Specificity, Positive Predictive Value (ie, the Probability of Tumor Detection When Fluorescence Is Positive) and Negative Predictive Value (ie, the Probability That Nonfluorescent Tissue Is Truly Negative for the Presence of Tumor) of 5-ALA Fluorescence[a]

Preoperative iMRI Total (N = 117)	Condition Positive (Tumor/Infiltrated Tissue) (n = 110)	Condition Negative (Reactive/Normal Tissue) (n = 7)	
Test positive, N = 93 (positive fluorescent)	A, true positive, no = 89	B, false positive, n = 4	PPV, (A/A + B) 0.96 = 96%
Test negative, N = 24 (negative fluorescent)	C, false negative, n = 21	D, true negative, n = 3	NPV, (D/C + D), 0.125 = 12.5%
	Sensitivity, (A/A + C), 0.81 = 81%	Specificity, (D/D + B), 0.43 = 43%	

[a]5-ALA, 5-aminolevulinic acid; iMRI, intraoperative magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value.

patients with incomplete resection survived for 10.8 and 5.8 months, respectively.

DISCUSSION

Because evidence that the degree of resection has a positive effect on survival time is increasing, all available technical means with the potential to improve resection accuracy should be assessed and applied. For 5-ALA fluorescence and for low-field iMRI, Class I evidence derived from randomized, controlled trials has demonstrated an increase in the extent of resection (EOR).[13,19] We have used 5-ALA fluorescence and iMRI routinely for glioblastoma surgery for several years, and, with this study, we aimed to assess the efficacy of tumor resection when both techniques are combined.

During the initial phase of surgery, defined as that in which tumor was resected until no suspicious areas remained under white or blue light, we collected 93 fluorescent and 24 nonfluorescent tissue samples. Histological examination revealed that the fluorescent tissue contained tumor in 95.7% and in the nonfluorescent tissue in 87.5% of samples. However, strongly and moderately fluorescent samples were always tumor tissue (Table 1). The high probability of finding tumor in areas that appear to the surgeons to be tumor under white light despite the absence of fluorescence is in line with the findings of Roberts et al,[28] who found fluorescent samples to contain tumor in 95% of cases, whereas nonfluorescent samples still contained tumor in 74%.

The previously described correlation of strong fluorescence indicating solidly proliferating tumor and weak fluorescence indicating infiltrating tumor[13] was also seen our series, especially with respect to the strongly fluorescent samples, which showed solid tumor tissue in 23 of 24 samples.

Concurring with Stummer et al,[13] Valdes et al,[29] and Roberts et al,[28] we found that strong fluorescence was associated with a higher degree of malignancy (MIB-1 index) than weak or moderate fluorescence (Table 1). However, it must be noted that the mean MIB-1 index of our samples *without* fluorescence (17.6%) was similar to that in samples with weak or moderate fluorescence (16.7% and 17.1%, respectively). The variability of our individual MIB-1 values (even within the same tumor of a single patient) was very large in all categories of fluorescence, rendering statistical analysis nonsignificant between all groups.

The reasons for the high probability of nonfluorescent tissue, which appears suspicious for tumor under white light, ultimately being confirmed to be tumor or a tumor infiltration zone, are probably several. It has been discussed that shading of the surgical field or overlying nonfluorescent layers of tissue, blood, or necrotic debris prevent the visualization of fluorescing tumor beneath.[5,15,28,30,31] Although we cannot rule out these scenarios, they are unlikely to be the main cause of the low negative predictive value of 5-ALA fluorescence (Figure 3). In our series, each case was operated on and examined for fluorescence by 2 experienced neurosurgeons, and great care was taken not to miss any fluorescent tissue. All areas that showed contrast enhancement on iMRI were carefully reinspected under navigation guidance, and no fluorescence was found. One of our histologically proven glioblastoma patients was completely fluorescence negative, despite double-checking by 2 pathologists and verification by the nursing staff that the 5-ALA was ingested preoperatively. This tumor did not contain large necrotic zones, and we did not encounter any intraoperative technical difficulties. Similar cases of a total absence of fluorescence have been previously reported,[30,32,33] and the reason remains unknown. Presumably, some tumor tissue emits levels of fluorescence that cannot be perceived by the surgeons with the current technical setup. This was recently confirmed by Stummer et al,[31] who detected spectrometric fluorescence in marginal tumor tissue that did not show intraoperative, macroscopic fluorescence.

On completion of tumor resection without leaving any traces of fluorescent tissue, iMRI unexpectedly revealed contrast enhancement suspicious of remnant tumor in 11 of 12 patients (91.7%). The contrast-enhancing areas were mostly thin and linear, whereas small nodular enhancements (as seen in Figure 4) were the exception. Our rate of contrast-enhancing areas on iMRI on completion of the 5-ALA–guided resection was remarkably high and was probably related to the fact that we considered even small contrast-enhancing linings as suspicious for tumor remnant. A proportion of these thin rims along the surface of the resection

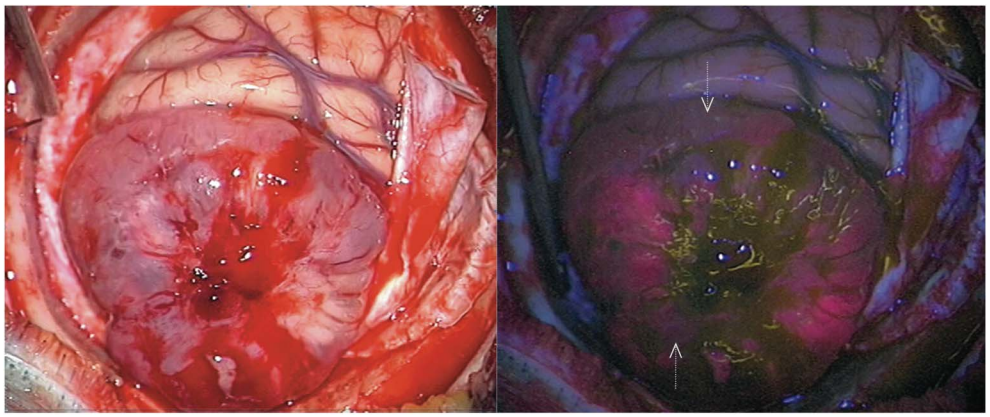

FIGURE 3. *Tumor appearance under white light (**left**) and blue light, showing 5-ALA induced fluorescence (**right**). Note that fluorescence is reduced in areas covered with blood and also in some areas that are not blood covered (**white arrows**). 5-ALA, 5-aminolevulinic acid.*

cavity may have been related to surgery-induced breakdown of the blood-brain barrier and subsequent contrast enhancement on iMRI. Under careful examination, none of these areas showed signs of fluorescence during the process of taking biopsy samples and subsequent tumor removal with ultrasonic aspiration. Because approximately two-thirds these samples, obtained from 8 of 10 patients, contained either tumor (39.3%) or a tumor infiltration zone (25%), these figures have great implication. The data prove that, despite an optimal technical setup, some tumor tissue might remain undetected because either it does not exhibit fluorescence or because the strength of fluorescence cannot be perceived with currently available means. Bearing in mind the one-third probability of iMRI enhancement not corresponding with tumor tissue, we conclude that resection of these areas should only be carried out when functional deficits are highly unlikely.

To our knowledge, this is the first study based on histological sampling to assess the predictive value of iMRI after completion of

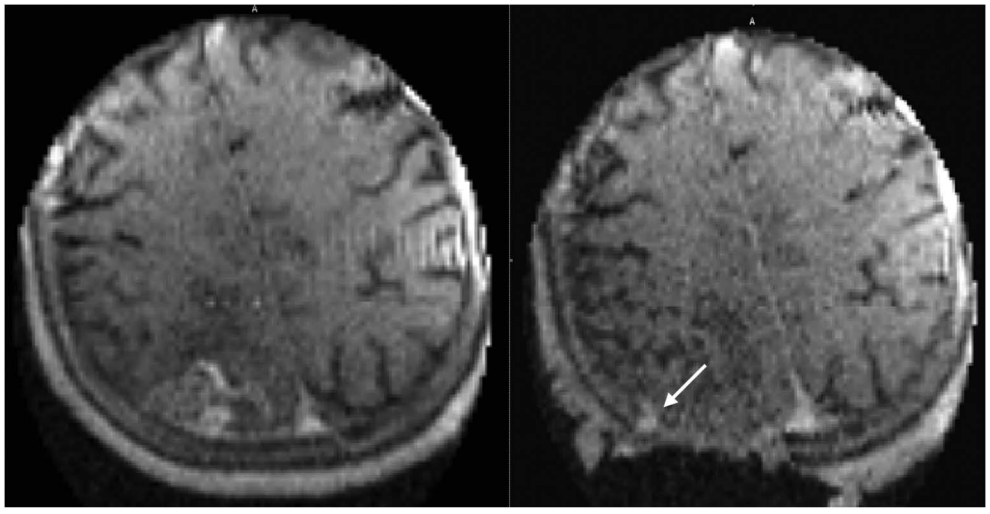

FIGURE 4. *Intraoperative MRI of the case illustrated in Figure 3. Identical axial slice before (**left**) and after (**right**) resection guided by 5-ALA fluorescence. Note the contrast-enhancing area (**arrow**) suspicious for remnant tumor. Two tissue samples were taken from this area, which also on second inspection did not show any 5-ALA fluorescence. Both tissue samples revealed a tumor infiltration zone with PI (MIB-1/Ki-67) indices of 2% and 10%, respectively. Postoperative 1.5-T MRI did not show any contrast-enhancing tumor remnant. 5-ALA, 5-aminolevulinic acid; MRI, magnetic resonance imaging.*

5-ALA fluorescence–guided glioblastoma resection. In 2011, Tsugu et al[33] reported a synergistic effect of the combination of 5-ALA and iMRI for glioma surgery. However, their EOR on postoperative 1.5-T MRI was only marginally different between the groups of fluorescence only (91.8%) vs fluorescence plus subsequent iMRI (92.6%), and, in cases of absence of intraoperative fluorescence, they found iMRI to be most useful in increasing EOR. Because the study lacked histological data, the predictive values for tumor tissue of both methods remains unknown. Eyupoglu et al[34] reported an improved EOR by combining 5-ALA–aided resection and subsequent iMRI in patients with malignant glioma localized close to eloquent areas, with residual tumor seen on iMRI in 32.4% of patients on completion of 5-ALA– guided resection. They thought that missing fluorescent areas were mainly attributable to layers of overlying, nonfluorescent tissue. Coburger et al[35] performed white-light GTR (not using 5-ALA fluorescence) in high-grade glioma surgery and then took samples from areas showing 5-ALA florescence and from structures showing contrast enhancement on 1.5-T iMRI. For the detection of pathological tissue, particularly at the border of the resection cavity, they reported a significant advantage of 5-ALA fluorescence over iMRI, with higher rates of sensitivity (91% for 5-ALA vs 66% for iMRI) and specificity (80% for 5-ALA vs 60% for iMRI).

Based on the 48-hour postoperative MRI, we achieved CRET in 82% of cases. This is slightly better than the rates reported by Stummer et al[13] using 5-ALA florescence (65%) and slightly below the CRET rates reported by Senft et al[19] (96%). The latter refers to a randomized trial to assess the efficacy of low-field iMRI (PoleStar) in high-grade glioma surgery *without* the use of 5-ALA fluorescence.

Despite the combined use of 5-ALA fluorescence and iMRI leading to good CRET rates on postoperative MRI, the 6-month progression-free survival rate of our study was not improved (36.4% vs 41% in the 5-ALA group reported by Stummer et al[13]). Neither was overall survival prolonged in our cohort (17.1 months in the <55 age group and 14.9 months in those older than 55 vs 18 and 14.1 months, respectively as reported by Stummer et al[13]). However, it should be noted that we had a significantly lower rate of surgical reintervention for tumor recurrence (18.1% vs 55%-82%[13]), and this is highly likely to have influenced overall survival time. Our low reoperation rate is probably due to a variety of factors, including a tendency to refrain from repeat surgery at the cost of surgery-induced neurological deficits.

Limitations

Our study was limited by small patient numbers and the surgeon-dependant assessment of fluorescence. Even when applying meticulous effort to search for fluorescence, the currently commercially available adaptations of the microscope will fail to detect very low fluorescence levels, and the assessment is nonquantitative. The question of whether the accuracy of iMRI assessment of remnant tumor may be improved by using higher field iMRI is the subject of ongoing research. Data directly comparing imaging information on low- vs high-field iMRI are scarce. Hirschl et al[36] retrospectively compared findings on low-field iMRI (0.12 T Polestar) and postoperative 1.5-T MRI for glial tumors. They found low-field MR to have a sensitivity of 82% and a specificity of 95% in detecting residual tumor. Bergsneider et al[37] retrospectively compared the extent of volumetric resection of a mixed group of high- and low-grade gliomas that were either operated on with intraoperative guidance from a 0.2-T or a 1.5-T scanner. They found no difference between the groups.

Resecting fluorescently stained tumor tissue and the application of iMRI for residual tumor detection are 2 methods that have been proved to improve the prognosis of glioblastoma multiforme. By combining both methods, we were not able to show a further extension of survival time, but we did shine light on the limitations and advantages of both methods. 5-ALA fluorescence lacks sensitivity in defining infiltrating tumor and also demonstrates a low negative prediction accuracy in cases of tissue macroscopically appearing to be tumor. On the other hand, iMRI is able to detect tumor tissue located beyond the current technical range of 5-ALA visualization, albeit with a 35.7% risk of overresection. Refined methods for the detection of tumor fluorescence, as well as high resolution and functional intraoperative imaging, will continue to improve tumor visualization and thus maximize tumor resection while minimizing risk. Curing glioblastoma is not achievable with surgical means alone, but precise resection is likely to improve the efficacy of adjuvant therapeutic regimes.

CONCLUSION

Not all glioblastoma tissue exhibits intraoperative 5-ALA fluorescence and not all areas of iMRI contrast enhancement represent tumor. iMRI performed after complete resection of 5-ALA fluorescent tissue shows contrast-enhancing regions suspicious for tumor in a high percentage of cases (91.6%), whereas these regions in fact contain tumor in only 64.3%. This reveals the sensitivity limitations of 5-ALA fluorescence and the rather low predictive value of iMRI for remnant tumor. iMRI is a suitable supplementary method for fluorescence-guided glioblastoma surgery, but the extended resection of iMRI contrast-enhancing areas must be considered with caution in eloquent sites.

Disclosure

The authors have no personal or institutional financial interest in drugs, materials, or devices described in this submission.

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