

## Endoscope-assisted fluorescence-guided resection allowing supratotal removal in glioblastoma surgery

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**OBJECTIVE** Several studies have proven the benefits of a wide extent of resection (EOR) of contrast-enhancing tumor in terms of progression-free survival (PFS) and overall survival (OS) in patients with glioblastoma (GBM). Thus, gross-total resection (GTR) is the main surgical goal in noneloquently located GBMs. Complete tumor removal can be almost doubled by microscopic fluorescence guidance. Recently, a study has shown that an endoscope with a light source capable of inducing fluorescence allows visualization of remnant fluorescent tumor tissue even after complete microscopic fluorescence-guided (FG) resection, thereby increasing the rate of GTR. Since tumor infiltration spreads beyond the borders of contrast enhancement on MRI, the aim of this study was to determine via volumetric analyses of the EOR whether endoscope-assisted FG resection enables supratotal resection beyond the borders of contrast enhancement.

**METHODS** The authors conducted a retrospective single-center analysis of a consecutive series of patients with primary GBM presumed to be noneloquently located and routinely operated on at their institution between January 2015 and February 2018 using a combined microscopic and endoscopic FG resection. A 20-mg/kg dose of 5-aminolevulinic acid (5-ALA) was administered 4 hours before surgery. After complete microscopic FG resection, the resection cavity was scanned using the endoscope. Detected residual fluorescent tissue was resected and embedded separately for histopathological examination. Nonenhanced and contrast-enhanced 3D T1-weighted MR images acquired before and within 48 hours after tumor resection were analyzed using 3D Slicer. Bias field-corrected data were used to segment brain parenchyma, contrast-enhancing tumor, and the resection cavity for volume definition. The difference between the pre- and postoperative brain parenchyma volume was considered to be equivalent to the resected nonenhancing but fluorescent tumor tissue. The volume of resected tumor tissue was calculated from the sum of resected contrast-enhancing tumor tissue and resected nonenhancing tumor tissue.

**RESULTS** Twelve patients with GBM were operated on using endoscopic after complete microscopic FG resection. In all cases, residual fluorescent tissue not visualized with the microscope was detected. Histopathological examination confirmed residual tumor tissue in all specimens. The mean preoperative volume of brain parenchyma without contrast-enhancing tumor was 1213.2 cm<sup>3</sup>. The mean postoperative volume of brain parenchyma without the resection cavity was 1151.2 cm<sup>3</sup>, accounting for a mean volume of nonenhancing but fluorescent tumor tissue of 62.0 cm<sup>3</sup>. The mean relative rate of the overall resected volume compared to the contrast-enhancing tumor volume was 244.7% ( $p < 0.001$ ).

**CONCLUSIONS** Combined microscopic and endoscopic FG resection of GBM significantly increases the EOR and allows the surgeon to achieve a supratotal resection beyond the borders of contrast enhancement in noneloquently located GBM.

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**KEYWORDS** 5-aminolevulinic acid; endoscope; fluorescence-guided surgery; glioblastoma

**T**HE survival of patients with glioblastoma (GBM) remains poor despite recent advances. A greater extent of resection (EOR) has been associated with better progression-free survival (PFS) and overall survival (OS) in several studies.<sup>1-3</sup> If feasible, gross-total resection (GTR) of contrast-enhancing tumor tissue, as seen on

preoperative MRI, is one of the main surgical goals. The use of 5-aminolevulinic acid (5-ALA) and microscopic fluorescence-guided (FG) resection increases the rate of GTR from 36% to 65%.<sup>4</sup> However, microscopic FG resection is still limited, as fluorescence depends on various factors such as cell density and cellular metabolism.<sup>5</sup> One

**ABBREVIATIONS** 5-ALA = 5-aminolevulinic acid; EOR = extent of resection; FG = fluorescence-guided; GBM = glioblastoma; GTR = gross-total resection; OS = overall survival; PFS = progression-free survival.

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of the major factors influencing the detectability of tumor by fluorescence is adequate exposure to blue light. A recently published study has shown that the assistance of an endoscope with a white and a blue light source, which is capable of inducing fluorescence, allows one to further increase the percentage of GTR by overcoming the limitations of the microscope.<sup>6</sup> However, the impact of combined microscopic and endoscopic FG resection on EOR has not been quantified. As previous studies have shown that malignant tumor cells spread beyond the areas of contrast enhancement on MRI,<sup>7-9</sup> the aim of our study was to determine if endoscope-assisted FG resection enables supratotal resection beyond the borders of contrast-enhancing GBM by comparing the volume of contrast-enhancing tumor on preoperative MRI with the volume of resected GBM tissue on postoperative MRI after such a resection.

## Methods

We performed a retrospective single-center analysis of a consecutive series of patients with primary GBM presumed to be noneloquently located and routinely operated on in our department between January 2015 and February 2018 using combined microscopic and endoscopic FG resection. Volume measurements were performed by experienced neuroradiologists. The study was reviewed by the local ethics committee. All patients were informed about the intraoperative use of the endoscope. Written consent was obtained from all patients within the standard informed consent process for surgery.

### Inclusion and Exclusion Criteria

Only those patients with data sets containing 3D T1-weighted MR images before and after administration of a contrast agent (0.1 mmol/ml gadobutrol per kg body weight, Gadovist, Bayer Vital GmbH) pre- and post-tumor resection were included. Patients were excluded if the tumor did not reach the brain surface in order to avoid a bias of the volume measurements in case of brain tissue removal within the approach corridor. Recurrent GBM was also an exclusion criterion because it was not possible to distinguish without question contrast-enhancing tumor from postoperative and postradiation alterations, which would have been a potential source of error in the measurement of the preoperative tumor volume.

### Surgical Protocol

A standard 20-mg/kg dose of 5-ALA was given 4 hours prior to surgery. A standard microscopic FG resection (OPMI Pentero 800, Carl Zeiss) was performed. Neuronavigation based on the preoperatively acquired, contrast-enhanced, 3D, T1-weighted MRI data set was used in all patients (VectorVision Sky navigation system and Brainlab software, Brainlab). Since all lesions were presumed to be in a noneloquent location, cortical mapping or intraoperative monitoring was considered unnecessary. After complete microscopic removal of all fluorescent tissue (solid and vague), the resection cavity was scanned using an endoscope (Hopkins II, 4 mm, viewing angle 0°, Karl Storz) with a special light source (D-Light C, Karl Storz) and camera system (Tricam SL II, Karl Storz). The

D-Light allows switching between the white light and the blue light source mode by means of an appropriate band-pass filter in the light transmission path. A long-pass filter at the eyepiece of the endoscope blocks the excitation light, which enables detection of fluorescence signals from the tumor cells. The excitation and detection filter system allows enough blue light to be transmitted so that the red fluorescence from the endogenous fluorochromes and nonspecific protoporphyrin IX (PpIX) fluorescence is suppressed, causing the normal tissue to be visualized as blue.<sup>10</sup> Microscopic fluorescent tissue and endoscopic fluorescent tissue that had not been visualized by the microscope were completely removed and embedded separately for histopathological examination. All patients underwent MRI within 48 hours after surgery.

### Image Analysis Protocol

MRI data acquired in a routine clinical setting were used and retrieved from the hospital's PACS. Data were analyzed using 3D Slicer (version 4.10.1 for Windows, www.slicer.org<sup>11</sup>). For whole-brain volumetry, nonenhanced 3D T1-weighted data sets acquired before and after surgery were used. After bias field correction, brain parenchyma was segmented using the Swiss Skull Stripper extension available via Slicer's extension manager, and label maps were manually corrected as appropriate. Additionally, CSF-containing spaces were removed from the masks using dedicated in-house software. Bias field-corrected, contrast-enhanced, 3D, T1-weighted data sets pre- and postsurgery were used for volumetric analyses of the tumor and the resection cavity, respectively. Tumor and cavity were segmented semiautomatically by applying Slicer's Grow Cut Effect method, and masks were manually corrected if needed. Residual tumor was defined as any visible contrast enhancement  $> 0.175 \text{ cm}^3$  on postoperative MRI. The following parameters were derived using dedicated in-house software: volume of contrast-enhancing tumor on preoperative MRI, volume of resection cavity on postoperative MRI, preoperative volume of brain parenchyma without tumor, and postoperative volume of brain parenchyma without the resection cavity. The difference in the volume of brain parenchyma before and after tumor resection was calculated to yield the volume of resected nonenhancing tissue. The volume of the overall resected tissue was then calculated as the sum of the contrast-enhancing tumor volume plus the volume of the nonenhancing tissue. The EOR, expressed as a percentage, was calculated as follows:  $[(\text{contrast-enhancing tumor volume} + \text{nonenhancing tissue}) / \text{preoperative tumor volume}] \times 100$ .

### Statistical Analysis

Statistical analysis was performed using SPSS (version 23, IBM Corp.). Descriptive statistics were used for the assessment of patient characteristics. Mean values and standard deviations were calculated for the volume measurements. The volume of the overall resected tissue was also related to the preoperatively assessed tumor volume in terms of percentage. The tumor volume was compared to the overall resected tissue and the resection cavity using

an unpaired t-test. A Pearson correlation was performed for tumor volume and the volume of overall resected tumor tissue. A p value < 0.05 was considered statistically significant.

## Results

Twenty-three patients with primary GBM had been operated on using microscopic as well as endoscopic FG resection. Twelve patients (8 male, 4 female) with primary GBM were included in our analysis; 4 patients with recurrent GBM and 7 patients with deep-seated GBM were excluded. The mean age was 65 (range 47–77) years. Tumor location was frontal in 6 patients, temporal in 5 patients, and parietal in 1 patient (Table 1). In 7 patients, O6-methylguanine-DNA methyltransferase (MGMT) promoter was methylated. In all patients, residual fluorescent tissue at the margin of the resection cavity was detected by the endoscope after completed microscopic FG resection (Fig. 1). That fluorescent tissue was completely resected. All patients had complete tumor resection without residual contrast-enhancing tumor on early postoperative MRI.

## Volume Measurements

The mean (± SD) preoperative volume of brain parenchyma without contrast-enhancing tumor tissue and CSF was 1213.2 cm<sup>3</sup> (± 98.5 cm<sup>3</sup>). The mean postoperative volume of the brain parenchyma without the resection cavity and CSF was 1151.2 cm<sup>3</sup> (± 106.3 cm<sup>3</sup>). The mean contrast-enhancing tumor volume was 52.2 cm<sup>3</sup> (± 31.8 cm<sup>3</sup>). The mean volume of the resection cavity was 32.9 cm<sup>3</sup> (± 21.1 cm<sup>3</sup>). The mean volume of the nonenhancing tumor tissue was 62.0 cm<sup>3</sup> (± 46.1 cm<sup>3</sup>), and the volume of the overall resected fluorescent tissue was 114.2 cm<sup>3</sup> (± 70.0 cm<sup>3</sup>; Table 1).

## Extent of Resection

In 9 of 12 patients (75%), the resection cavity was smaller than the contrast-enhancing tumor (Table 1). The mean volume of the resection cavity was significantly smaller than the contrast-enhancing tumor volume (95% CI 4.89–35.99, p = 0.015). There was no correlation between the tumor volume and the volume of the resection cavity (Pearson correlation coefficient r = 0.21, 95% CI –0.527 to 0.800, p = 0.513; Fig. 2). The volume measurements showed a significantly larger EOR on postoperative MRI compared to the mean preoperative contrast-enhancing tumor volume (95% CI 32.49–91.24, p < 0.001). In all patients (100%), the EOR was greater than the contrast-enhancing tumor volume (Fig. 3). The correlation between the contrast-enhancing tumor volume and the overall resected volume was excellent (Pearson correlation coefficient r = 0.851, 95% CI 0.332–0.962, p < 0.001). The mean relative size of the overall resected volume compared to the tumor volume was 244.7% (± 102.2%).

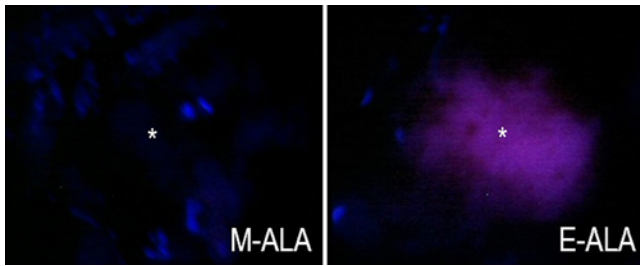
## Histopathological Findings

Twenty-four microscopic fluorescent specimens and 32 endoscopic fluorescent specimens were collected. Twelve of the microscopic fluorescent specimens from the central

TABLE 1. Baseline characteristics and volume measurements in 12 patients with GBM

Case No.	Age (yrs)	Sex	Localization	CE Tumor Vol (cm <sup>3</sup> )	Vol of Resection Cavity (cm <sup>3</sup> )	Preop Brain Vol w/o CE Tumor (cm <sup>3</sup> )	Postop Brain Vol w/o Resection Cavity (cm <sup>3</sup> )	Vol of Resected Unenhanced Tissue (cm <sup>3</sup> )	Vol of Overall Resected Tissue (cm <sup>3</sup> )	Vol of Overall Resected Tissue in % Tumor Vol (EOR)
1	73	M	Frontal	65.95	19.41	1285.11	1272.22	12.89	78.84	119.54%
2	53	M	Frontal	85.91	27.95	1382.72	1279.55	103.17	189.08	220.09%
3	58	F	Temporal	46.94	29.55	1315.33	1246.93	68.40	115.34	245.74%
4	47	M	Temporal	31.08	13.25	1185.84	1184.16	0.68	31.76	102.19%
5	68	F	Temporal	15.38	20.79	1153.24	1112.03	41.21	56.59	367.99%
6	61	F	Parietal	28.05	33.4	1305.95	1216.40	89.55	117.60	419.21%
7	64	M	Frontal	74.38	38.02	1158.34	1112.35	45.98	120.37	161.82%
8	67	M	Temporal	66.32	33.21	1137.07	1100.46	36.61	102.93	155.21%
9	58	M	Frontal	35.69	29.55	1286.68	1202.41	84.27	119.96	336.10%
10	75	F	Temporal	37.94	17.72	1184.53	1136.38	48.15	86.09	226.90%
11	72	M	Frontal	122.40	94.92	1083.02	910.48	172.53	294.93	240.96%
12	77	M	Frontal	16.61	36.45	1080.63	1040.70	39.93	56.54	340.43%
Mean (SD)	65			52.2 (± 31.8)	32.9 (± 21.1)	1213.2 (± 98.5)	1151.2 (± 106.3)	62.0 (± 46.1)	114.2 (± 70.0)	244.7% (± 102.2%)

CE = contrast-enhancing.



**FIG. 1.** Views of the resection site through the microscope (M-ALA, left) and the endoscope (E-ALA, right). The same tissue visualized by the microscope or the endoscope is marked by *asterisks*. No residual fluorescent tissue is visible after completed microscopic FG resection (M-ALA). After using the endoscope with a blue light source, the tissue at the margin of the resection cavity becomes fluorescent (E-ALA). Histopathological examination of the biopsies taken from the residual fluorescent area confirmed tumor tissue.

tumor area showed solid tumor tissue, whereas 12 of the microscopic specimens from the tumor margin and all of the endoscopic specimens showed brain tissue diffusely infiltrated by tumor (Fig. 4).

**Postoperative Course**

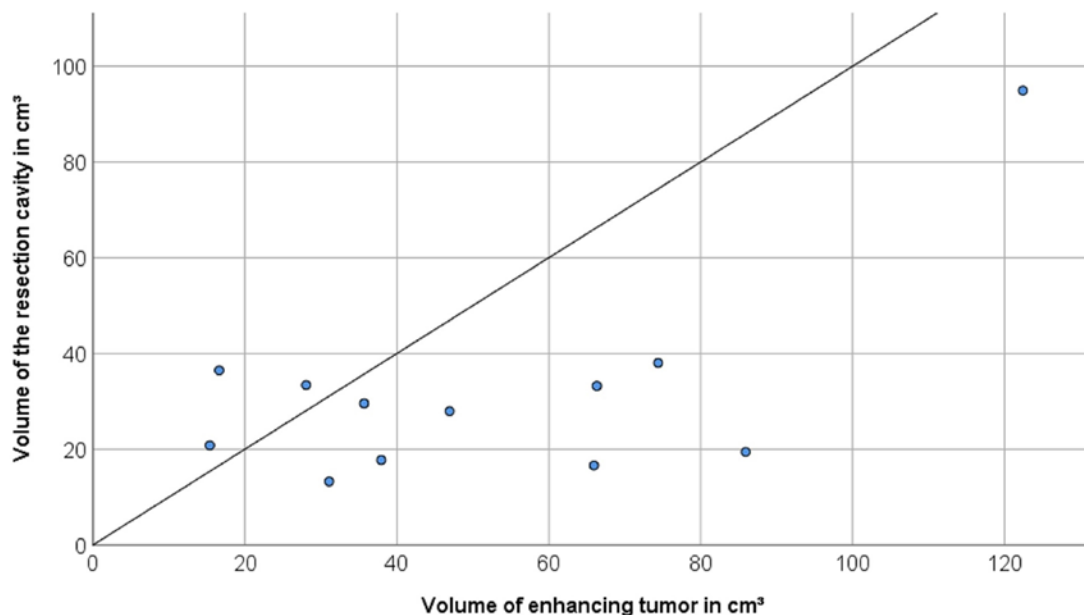
Preoperatively, 3 patients had presented with slight arm paresis caused by edema. Four patients had experienced preoperative seizures. No new or worsened neurological deficits were recorded after surgery. All preexisting neurological deficits improved under oral steroids during hospitalization. No postoperative seizures occurred. The mean Karnofsky Performance Status (KPS) at discharge was 90.8% (± 12.4%). The mean length of stay was 9.7 (± 1.1) days.

**Discussion**

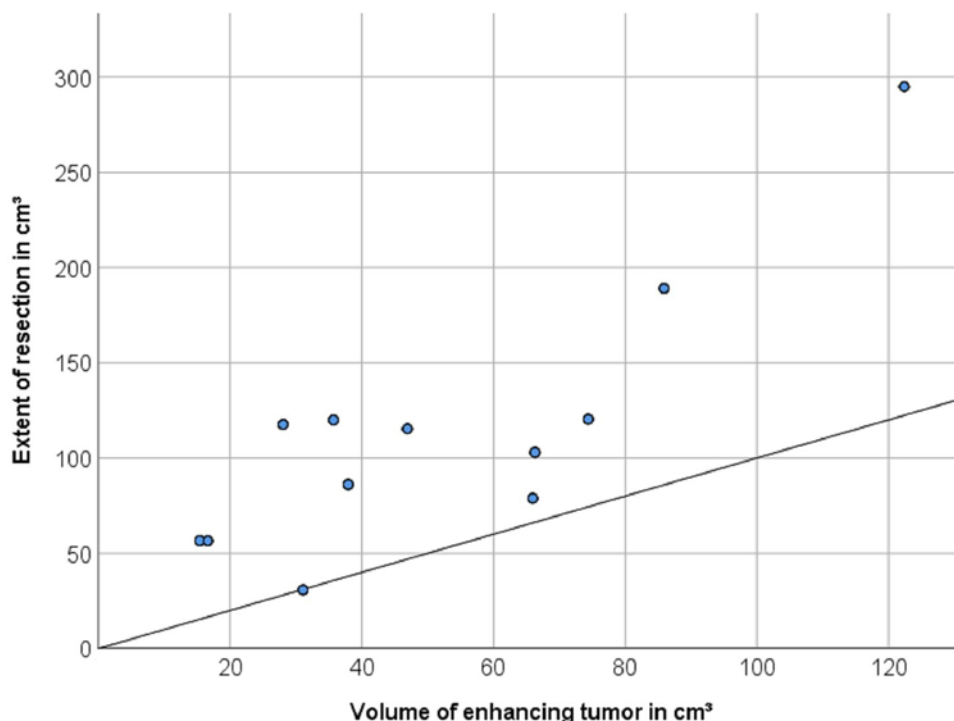
Combined microscopic and endoscopic FG resection enables the surgeon to achieve supratotal resection beyond the borders of contrast enhancement in GBM surgery. The overall resected tumor volume was significantly larger than the contrast-enhancing tumor volume on MRI. In all cases, residual fluorescent tissue was detected by the endoscope that had not been visualized by the microscope. Histopathological examination confirmed variable infiltration of tumor cells in the separately preserved endoscopic biopsies.

**Impact on EOR**

After publication of a technical note in 2014, a first clinical series showed that residual fluorescent tumor tissue not visualized with the microscope could be detected with endoscopic assistance.<sup>6,10</sup> This finding is not surprising because inducing fluorescence is mainly related to adequate exposure to blue light. According to the inverse-square law (“illumination of a surface receiving its flux from a point source is inversely proportional to the square of the distance between the surface and the source”), the endoscope, as compared to the microscope, is capable of significantly reducing the distance between the light source and the tissue.<sup>6</sup> Besides the barriers of the depth of the surgical field, the presence of overhanging tissue or collapse of the resection cavity can lead to insufficient visualization of the tumor margins.<sup>12</sup> Furthermore, blind spots for microscopic FG resection can exist in the area of the craniotomy<sup>10</sup> as well as at the margin of the tumor due to collapse of the resection cavity.<sup>6</sup> These blind spots can be visualized with the endoscope. Thus, endoscopic assistance appears to be a useful adjunct to increase the radicality of resection in GBM surgery.<sup>6</sup>



**FIG. 2.** The resection cavity was smaller than the contrast-enhancing tumor volume in 9 of 12 cases. There was no correlation between the volume of contrast-enhancing tumor and the resection cavity (Pearson correlation coefficient  $r = 0.21$ , 95% CI  $-0.527$  to  $0.800$ ,  $p = 0.513$ ).



**FIG. 3.** The EOR was at least 101% compared to the contrast-enhancing tumor volume, and in 8 of 12 cases it was greater than 200%. The correlation between the contrast-enhancing tumor volume on preoperative MRI and the overall resected volume on postoperative MRI was excellent (Pearson's correlation coefficient  $r = 0.851$ ,  $p = 0.00045$ ).

Whether combined microscopic and endoscopic FG resection is truly superior to microscopic FG resection must be defined in a prospective comparative study. Schucht et al. showed similar results for the mean EOR (242%) using microscopic FG resection in a small retrospective cohort.<sup>13</sup> However, segmentations were not performed by neuroradiologists in that study. Furthermore, the SD of the mean EOR was 4 times higher than that in our cohort, suggesting very high heterogeneity of the EOR in their cohort. In fact, the EOR remained lower than 200% in half of the patients in that cohort, whereas only 33% of the patients in the present study had such an EOR. Taking this into account, it can be suggested that the combined use of a microscope and an endoscope may be superior to the use of the microscope alone in terms of visualizing residual fluorescent tissue, thereby increasing the EOR substantially.

### Volumetric Measurements

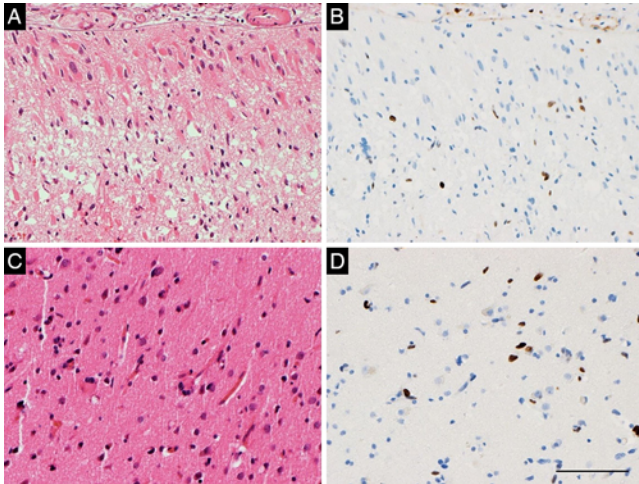
As our volumetric analysis showed, the EOR was significantly larger (245%) than the tumor volume by using endoscope-assisted FG resection. As previous studies have confirmed, EOR can be increased by FG resection<sup>4</sup> or intraoperative MRI (iMRI)<sup>14,15</sup> compared to that obtained with standard neuronavigated microscopic resection. However, whether supratotal resection was achieved in these studies remains unclear, as only residual tumor volume, not the volume of the EOR, was quantified. Despite the unquestionable advantages of iMRI regarding an increased rate of GTR,<sup>14–17</sup> its high costs in terms of money

and time are reasons for its reduced availability in neurosurgical centers.<sup>18–20</sup> Therefore, FG resection is mostly performed in Europe. As mentioned before, fluorescent tissue is mainly dependent on adequate exposure to blue light, which can be limited using microscopic fluorescence guidance. The endoscopic assistance appears very useful to increase the EOR in GBM surgery.<sup>6</sup>

Recently published studies have suggested that the enhancing tumor volume underestimates the full extent of the tumor burden since tumor infiltration spreads beyond the borders of contrast enhancement, which are characteristically hyperintense on FLAIR sequences.<sup>21–23</sup> We did not perform volumetric analyses of the resected hyperintensity parts on the FLAIR sequences because of missing 3D data sets. Future studies should investigate whether the EOR of FLAIR hyperintense lesions can be increased by endoscopic assistance.

### Impact on OS

Several studies have shown a benefit of GTR compared with subtotal resection in GBM surgery.<sup>1,2,14,21</sup> A study by Esquenazi et al. showed a significant benefit from supratotal resection with a mean OS of 34.2 months.<sup>8</sup> A benefit in OS has also been demonstrated when fluorescent tissue is completely removed, even if residual tumor is not displayed as contrast enhancement on MRI.<sup>1</sup> As these data suggest and as most of the recurrences appear at or near the resection cavity,<sup>24</sup> supratotal resection beyond the borders of contrast enhancement may be beneficial in GBM surgery. Since our cohort is small and selective, the impact



**FIG. 4.** Histopathological examination of E-ALA-positive tumor samples (undetected by M-ALA) showed infiltration of tumor-adjacent gray matter by neoplastic GBM cells. H & E staining of an M-ALA-positive tumor sample (A) shows complete replacement of the cortical neuronal layers by GBM cells, best detected by immunostaining with the proliferation marker Ki-67 (B). Gray matter with a discrete increase in cell density in an E-ALA-positive sample (C), undetected by M-ALA, with moderate infiltration by GBM cells (D) immunolabeled with Ki-67. Bar = 100  $\mu$ m.

on OS was not quantified because it would be inconclusive. A benefit of endoscope-assisted FG resection in OS has to be confirmed in a prospective study with a larger cohort.

### Study Strengths and Limitations

Our study has several limitations. Our cohort is small and selective. All tumors were easy to access since they reached the brain surface and were located in noneloquent areas. Although the advantage of endoscopic assistance may especially apply for deeper-seated lesions, given increasingly insufficient illumination of the resection cavity by the microscope, these lesions were excluded since the eventually necessary removal of healthy brain tissue within the approach corridor would have biased the volume measurements. Furthermore, the value of endoscopic assistance is limited in tumors that are located in eloquent areas because supramaximal resection will result in neurological deficits and is therefore avoided. Still, the feasibility, safety, and possible benefit of a combined endoscope-guided tumor resection and intraoperative monitoring in an eloquently located lesion could be the subject of further studies.

Our volumetric measurements were indirect, and the volume of the resected tissue, which was additionally resected with the assistance of the endoscope, could not be quantified. Furthermore, changes in cerebral blood volume as well as edema volume after tumor resection could not be quantified. Hence, the results of this study must be interpreted with care. Since all patients received perioperative steroids, a reduction in peritumoral edema might lead to incorrect volumetric measurements of the EOR. However, we believe that the impact of this possible bias is low, as all preoperative MRI studies were performed within 3 days prior to surgery, and all postoperative MRI studies within

48 hours after surgery. As residual fluorescent tumor tissue was detected in all cases after completed microscopic FG resection, we believe that endoscopic assistance is a useful adjunct in GBM surgery.

### Conclusions

Endoscope-assisted FG resection of GBM significantly increases the EOR and allows the surgeon to achieve a supratotal resection beyond the borders of contrast enhancement in noneloquently located GBM. Residual fluorescent tumor tissue at the margins of the resection cavity, not previously visualized by a microscope, can be detected by an endoscope, indicating that the assistance of the endoscope allows supramaximal resection by visualizing the zone of tumor infiltration. A possible benefit in PFS and OS still has to be determined in a larger cohort.

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## Disclosures

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

## Author Contributions

Conception and design: Bettag, Rohde, Mielke. Acquisition of data: Bettag, Schregel, Langer, Thomas, Behme, Stadelmann, Mielke. Analysis and interpretation of data: Bettag. Drafting the article: Bettag. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bettag. Statistical analysis: Bettag. Administrative/technical/material support: Schregel, Langer, Thomas, Behme, Stadelmann, Mielke. Study supervision: Rohde, Mielke.

## Supplemental Information

### Previous Presentations

Portions of this work were presented at the annual meeting of the German Society of Neurosurgery held in Lübeck, Germany, on June 21–24, 2020.

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