Fluorescein Sodium in the Surgical Treatment of Recurrent Glioblastoma Multiforme

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BACKGROUND: **Glioblastoma multiforme (GBM) is the most common primary brain tumor and has a high recurrence rate. Maximizing the extent of resection (EOR) in recurrent GBM has proved to be the cornerstone of neurosurgical retreatment. The development of surgical microscopes fitted with fluorescein-specific filters has facilitated fluorescein-guided microsurgery and the identification of tumor tissue. Use of fluorescein sodium (FL) in primary high-grade glioma resection has shown promising results. Here, we present our experience with FL and the dedicated surgical microscope filter YELLOW 560 nm in 106 patients with recurrent GBM.**

METHODS: **A total of 106 patients with recurrent GBM were included (53 women, 53 men; mean age, 53 years). A total of 5 mg/kg bodyweight of FL was intravenously injected approximately 45 minutes before craniotomy. A YELLOW 560 nm filter (PENTERO 900 [Carl Zeiss Meditec, Oberkochen Germany]) was used for microsurgical tumor resection and resection control. Surgical reports were reviewed regarding the degree of fluorescent staining. Postoperative magnetic resonance images were examined within 48 hours after surgery regarding the EOR and postoperative course regarding neurologic outcome, complications, and any adverse events.**

RESULTS: **Bright fluorescent staining was present in all patients, which markedly enhanced tumor visibility and was deemed helpful for tumor resection. Seventeen patients (16%) showed residual tumor tissue on postoperative magnetic resonance imaging (MRI). Therefore, gross total resection was achieved in 89 patients (84%). No adverse events were registered postoperatively.**

CONCLUSIONS: **FL and YELLOW 560 nm are readily available methods for fluorescence-guided tumor resection, similar to contrast enhancement in T1-weighted MRI. FL may improve resection in recurrent GBM with minimal risk, and tumor margins are clearly visualized. FL and the YELLOW 560 nm filter are safe and feasible tools for safe maximal resection of recurrent glioblastoma.**

INTRODUCTION

Patients with glioblastoma multiforme (GBM) will inevitably experience recurrence of the disease, even after successful first treatment. This makes GBM one of the most aggressive forms of cancer. Surgical tumor resection and adjuvant treatment are widely regarded as first-line therapy,[1] but no standard treatments are yet available in the case of recurrent disease. Resurgery is common practice at many neurosurgical centers after tumor board reviews. The ultimate aim of surgery is safe gross total resection (GTR) of the tumor while preserving function because any deficit because of surgical intervention will

Key words
- Fluorescein sodium
- Fluorescence-guided surgery
- High-grade glioma
- Neurosurgery
- PENTERO 900
- Recurrent glioblastoma
- Surgical microscope
- YELLOW 560 nm filter

Abbreviations and Acronyms
BBB: Blood–brain barrier
EOR: Extent of resection
FL: Fluorescein sodium
GBM: Glioblastoma multiforme
GTR: Gross total resection
HGG: High-grade glioma
iMRI: Intraoperative magnetic resonance imaging
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
STR: Subtotal resection

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Table 1. Demographic Data

Location	Patients	Women:Men	GTR	STR
Regensburg, Germany	46	25:21	35	11
Milan, Italy	40	18:22	37	3
Odense, Denmark	16	8:8	14	2
Istanbul, Turkey	4	2:2	3	1
Combined	106	53:53	89 (84%)	17 (16%)

Values are number of patients or as otherwise indicated.
GTR, gross total resection; STR, subtotal resection.

lead to an undesirable risk/benefit ratio. Surgery has a fundamental role in the management of recurrent GBM because of the established incremental benefit of the extent of resection (EOR) on progression-free survival (PFS) and overall survival (OS).

Consequently, technical means to improve the EOR have emerged. Proven technical adjuncts aiding safe and complete resection of high-grade gliomas (HGGs) are neuronavigation,[2,3] intraoperative magnetic resonance imaging (iMRI),[4] ultrasound,[5] and fluorophores such as 5-aminolevulinic acid.[6]

Another fluorophore, fluorescein sodium (FL), has been evaluated under white light and, more recently, under filtered light. It has been over 40 years since fluorescent molecules were evaluated and approved for diagnostic use in ophthalmology.[7] Since the emergence of a fluorescein-specific microscope filter,[8] FL has been evaluated in different pathologies of the central nervous system.[9-15] The presumed mechanism of action is passive staining of the extracellular space in areas with a disrupted blood–brain barrier (BBB), corresponding to the gadolinium uptake on magnetic resonance imaging.[16] Neira et al.[17] showed that FL could mark tumor tissue beyond the limits of gadolinium enhancement. This effect can also be exploited in glioma surgery, in which even single perivascular glioma cells disrupt the BBB.[18,19] FL-guided resection has been safely shown in cases of HGG.[20-22] To our knowledge, this is the first retrospective study to evaluate the use of low-dose FL, aided by a microscope-integrated filter, for the removal of recurrent GBM, regarding the EOR, feasibility, and safety.

METHODS

Patients

Patient records and neuropathologic databases at the University of Regensburg, Germany; Istituto Carlo Besta in Milan, Italy; Odense University Hospital, Denmark; and Liv Hospital in Istanbul, Turkey, were retrospectively reviewed to identify a consecutive series of all patients with recurrent GBM who had undergone FL-guided tumor resection at any center between May 2012 and December 2016. Only patients with tumor recurrence eligible for GTR prior to reoperation were included. Patients were excluded from the study when complete removal of the contrast-enhancing lesion was deemed impossible. Eloquent areas were defined as lesions involving the language or motor system. Inclusion criteria were age 18 years and over, informed consent about the off-label use of FL, recurrent GBM in a noneloquent area, and no known allergy to FL. The retrospective study was approved by the respective institutional review boards and in Denmark by the Danish Health Authority and the Danish Data Protection Agency.

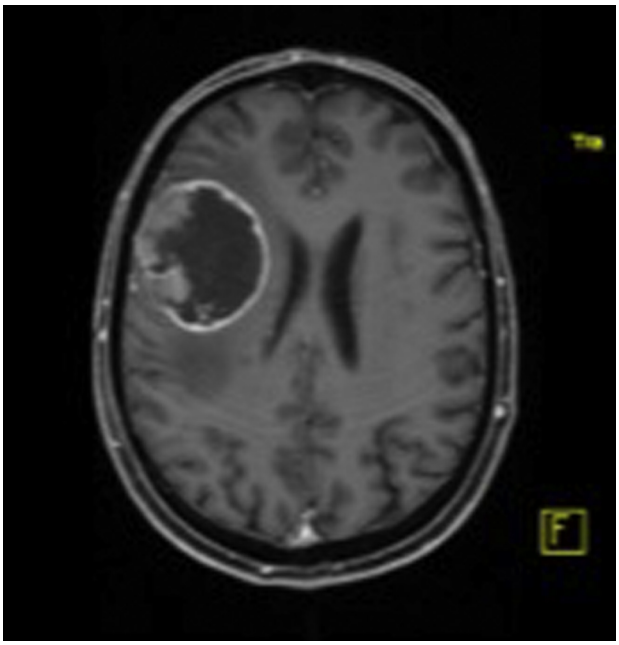

Figure 1. Preoperative gadolinium-enhanced T1 magnetic resonance imaging showing circular contrast enhancement.

A total of 106 patients, 53 women and 53 men (mean age, 53 years; range, 23–80 years) with recurrent GBM who had undergone fluorescence-guided tumor resection with FL, fulfilling inclusion/exclusion criteria, were identified and included for further analysis (Table 1).

Surgical Protocol

During the feasibility phase, patients of the 4 centers had intravenously received 200 mg or 5–10 mg/kg bodyweight[12] of FL (Alcon Pharma, Freiburg im Breisgau, Germany; Monico SpA, Venice, Italy; Alcon Laboratuvarları, Istanbul, Turkey; and Novartis Healthcare, Copenhagen, Denmark) after induction of anesthesia.[8] After careful evaluation, and in accordance with reports published in 2014, this dose was changed to a weight-adjusted dose (5 mg/kg bodyweight) administered approximately 30–45 minutes prior to craniotomy. Tumorous tissue was removed under FL-induced fluorescence with a YELLOW560 filter integrated into the microscope (PENTERO 900 [Carl Zeiss Meditec, Oberkochen, Germany]). When applicable, the Cavitron Ultrasonic Surgical Aspirator was used. Resection was stopped when the yellow-green staining of the enhancing tissue fainted and pinkish nonenhancing tissue appeared at the circumference of the tumor. Naturally FL-enhancing areas, such as the ventricular wall, were carefully identified. Unless continuation of surgery was deemed unsafe, for instance because of venturing into eloquent

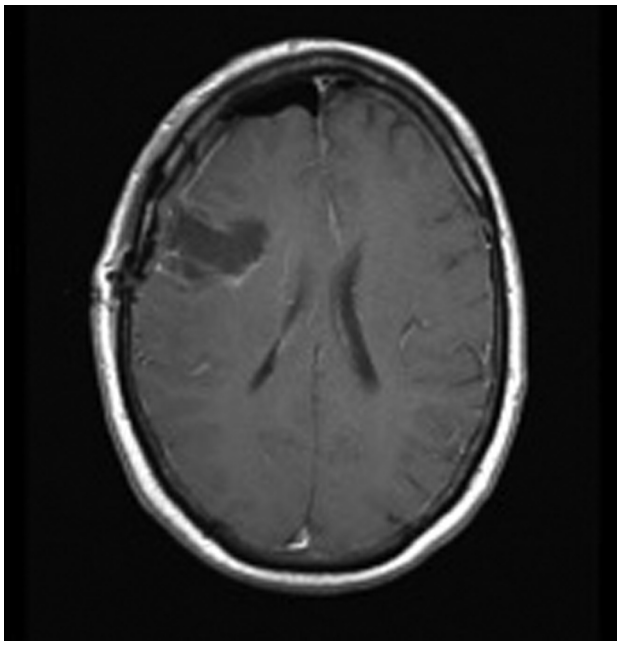

Figure 2. T1 axial postoperative magnetic resonance imaging with no residual contrast enhancement.

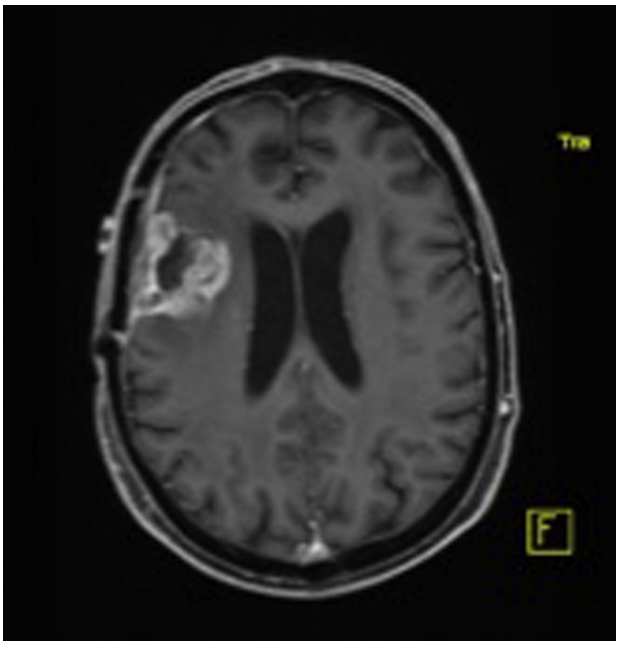

Figure 3. Recurrent tumor was detected at routine follow-up imaging 13 months after surgery.

areas, surgical intervention was finished after removal of all fluorescing tissue as confirmed by filter view. Intraoperative monitoring, intraoperative ultrasound, and neuronavigation were used in selected cases.

Pre- and Postoperative Radiologic Assessment

Each patient had received a preoperative gadolinium-enhanced magnetic resonance imaging (MRI) scan and a postoperative MRI within 48 hours after surgery to rule out hemorrhage and to confirm the EOR.

A treatment-blinded neuroradiologist distinguished between no residual enhancement (>0.175 cm^3 = GTR) and residual tumor tissue (subtotal resection [STR]).

Intraoperative Fluorescence Characteristics

Surgical reports were screened for subjective evaluation of the grade of fluorescent staining of the targeted lesion. Screening was conducted for any reference to the degree of fluorescent staining (bright/helpful vs. effectively no fluorescence/not helpful).

Furthermore, medical reports were evaluated for any possible adverse effect or allergic reaction to FL.

RESULTS

Fluorescence

In all patients (N = 106), intense yellow-green fluorescent staining of tumor tissue was noted. The fluorophore accumulated in the tumor tissue providing distinct contrast between tumor and surrounding tissue and was deemed helpful for improved resection. Intraoperative fluorescent characteristics did not differ between primary GBM and recurrent tumor. Unspecific uptake of FL could be noted in scar tissue. No technical difficulties regarding the use of the microscope filter were encountered during the surgical interventions.

EOR

Seventeen patients (16%) showed residual tumor tissue on postoperative MRI. Therefore, GTR (residual enhancement <0.175 cm^3) was achieved in 89 patients (84%).

Adverse Events

We did not encounter any morbidity or mortality attributable to the use of FL. Furthermore, no major side effects related to fluorescein were found throughout the observation period apart from yellow-colored urine and, in some patients, slight yellow discoloration of the skin.

Representative Case

A 50-year-old man underwent surgery because of a right frontotemporal GBM (Figures 1 and 2). The preoperative gadolinium-enhanced T1 MRI showed circular contrast enhancement, and the postoperative imaging did not show any residual enhancement.

Recurrent tumor was detected at routine follow-up 13 months after surgery, resulting in subsequent reoperation (Figures 3 and 4). Postoperative imaging showed complete removal of the contrast-enhancing tumor.

Intraoperative images (Figures 5–7) showed scar tissue under white light and under the YELLOW 560 filter (Figure 6, *) with

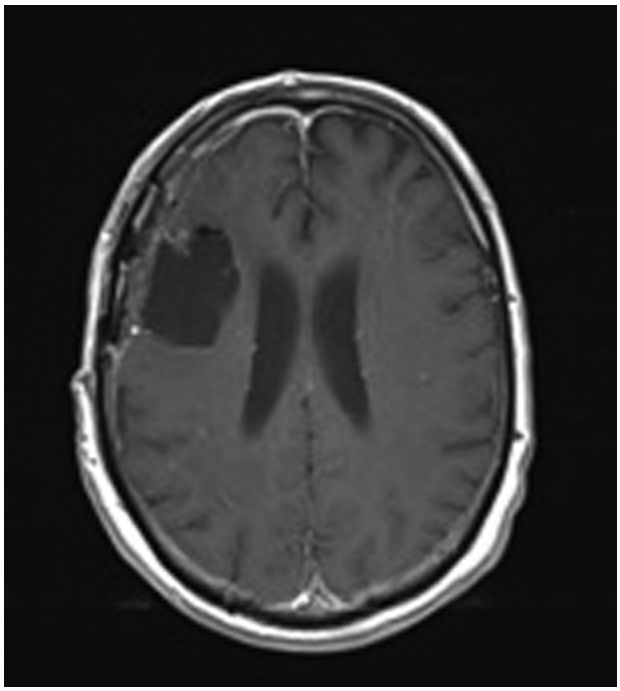

Figure 4. T1 axial postoperative magnetic resonance imaging with contrast confirmed total removal of the lesion.

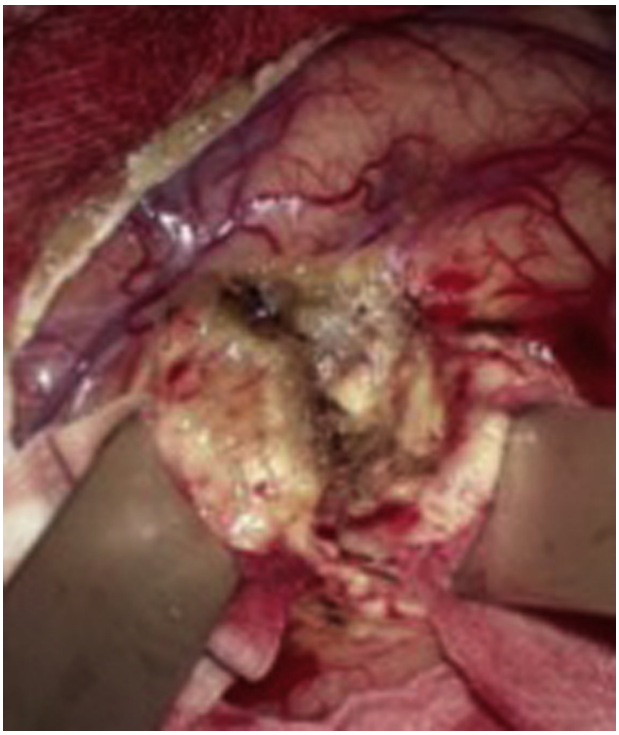

Figure 5. Microscopic visualization under white light, after dural opening, with no clear demarcation of recurrent tumor.

unspecific enhancement. After dissection, bright yellow staining of recurrent tumor tissue (Figure 7, +) can be seen.

DISCUSSION

Ultimately, GBM is one of the most aggressive forms of cancer with devastating consequences for the patient. Only approximately 20%–30% of patients with recurrent GBM are amenable to second surgery, which is recommended by the European Association of Neuro-Oncology guideline[1] in large but circumscribed tumors causing neurologic deterioration. The timing of repeat surgery in the case of tumor recurrence has failed to prove as a prognostic factor.[23] Earlier reports advocated to aim for the maximum EOR,[24,25] which seems to increase the rate of functional neurologic deterioration in resections >80%.[26] Lately, the impact of EOR on survival has shown to be pivotal when conducting GTR.[27] EOR ≥90 to <100 and ≥50 to <90 showed comparable survival rates (median, 9.3 vs. 8.4 months, respectively). The effect of the EOR on survival in GBM surgery (6-month PFS ranging from 21.1% to 41.0%, OS did not reach significance) was shown by Stummer et al.[6]

Sanai et al.[28] stated that OS incrementally improves with the percentage of tumor volume resected. A post hoc analysis of the Dose-Intensified Rechallenge with Temozolomide, One Week on One Week Off versus Three Weeks on One Week Off in Patients with Progressive or Recurrent Glioblastoma trial cohort[29] by Suchorska et al.[30] showed that, in comparison with incomplete resection, GTR significantly improved survival and led to a smaller volume of recurrent tumor tissue. Marko et al.[31] developed a mathematical model suggesting the superiority of a maximum safe resection strategy over rigid EOR thresholds. There is increasing evidence that GTR is superior to nonsurgical treatment in recurrent GBM, but incomplete resection is noninferior to the best medical treatment. Seystahl et al.[32] provided a flowchart facilitating the early diagnosis of recurrent tumor that can identify small-sized tumors in patients with good Karnofsky Performance Status Scale scores. Surgical morbidity may be minimized through conducting regular follow-ups with MRI at 3-month intervals. A recent meta-analysis showed that GTR significantly improves PFS and OS compared with STR or biopsy alone. Therefore, GTR should be preferred when clinically feasible.[33]

In many cases, surgeons still have to rely on visual cues and tactile differentiation when resecting tumorous tissue. From a surgical point of view, treatment options become more and more limited over the course of the disease and can be reduced to safely maximize the EOR.

To maximize the EOR, the armamentarium available to neurosurgeons has been substantially extended over the past decades (e.g., through the operating microscope, gadolinium-enhanced MRI, ultrasound, neuronavigation). The latest addition has been fluorescent agents to help surgeons to better distinguish between healthy and tumor tissue. The fluorescent agent 5-aminolevulinic acid and iMRI have both been reported as reliable means to maximize the EOR. When exploring the role of 5-aminolevulinic

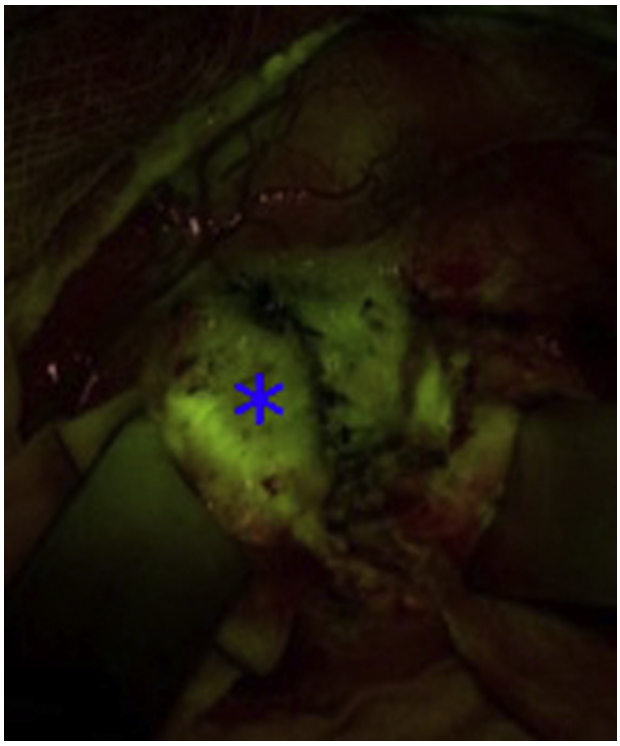

Figure 6. The same area as in **Figure 5** under YELLOW 560 nm filter showing scar tissue (*asterisk*) with unspecific enhancement.

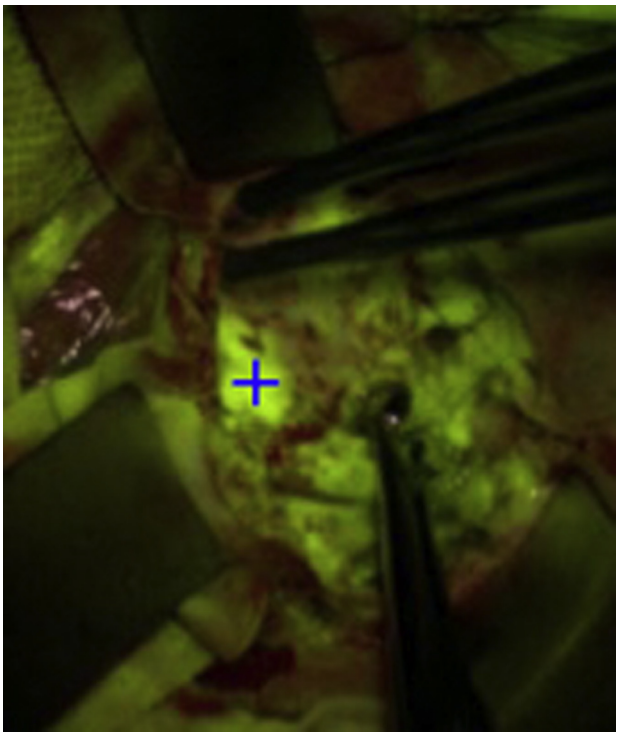

Figure 7. After dissection, bright yellow staining of recurrent tumor tissue (*plus sign*) can be seen.

acid in combination with iMRI during GBM surgery, Gessler et al.[34] found a slightly higher sensitivity of iMRI than of 5-aminolevulinic acid to detect residual tumor (75% vs. 70%, respectively). In a further study using both means in recurrent GBM, they found decreased fluorescence of 5-aminolevulinic acid compared with gadolinium-enhanced iMRI.[35]

The benefit of FL-guided surgery in HGG and nonglioma surgery has been extensively evaluated over the past years.[11,13] Almost every author investigating this subject reported improved visualization and suggested a positive effect on the EOR.[12,20,21,36,37] The recent results of the FLUOGLIO study, a multicentric prospective phase II trial, confirmed that FL-guided surgery is safe and enables a high percentage of contrast-enhancing tumor (82.6%) in patients with primary HGG.[22]

GTR facilitated by the use of FL in our study (84%) was much higher than the reported historic EOR in newly diagnosed GBM. Stummer et al.[6] reported a GTR percentage of 36% under white light in the 5-aminolevulinic acid trial. McGirt et al.[24] stated a GTR rate of 39% in primary GBM. Both groups only included patients with tumors amenable to complete resection. A similar GTR percentage of 54.5% was found for recurrent GBM by Ringel et al.[27] in a large multicenter retrospective trial in which 237 of 435 patients underwent re-resection at first recurrence. In a retrospective monocentric study of 107 patients by Bloch et al.,[38] GTR was initially achieved in 52 patients, but only in 31 patients (60%) at recurrent disease.

The rate of approximately 17% of STR in our cohort was possibly because of surgical challenges, such as complete resection prevented by blind spots related to the approach or by proximity to eloquent areas detected by intraoperative monitoring. As with every other fluorophore, the added benefit relies on adequate exposure to visualize fluorescence.

We did not encounter any technical difficulties related to the use of FL or the filter, particularly regarding the workflow or surgical ergonomics. Furthermore, no side effects attributable to the use of FL occurred intraoperatively or during the hospital stay, which is consistent with earlier experiences using FL for other intracranial pathologies.

What does FL achieve in the surgery of HGGs? Experimental and clinical research have shown that glioma cells precipitate the breakdown of the BBB, enabling FL to extravasate into the extracellular space via these disruptions. Such extravasation facilitates fluorescence, presumably making it a marker of the tumor path into the healthy brain.[9,16,18] Vascular leakage and breakdown of the BBB are caused by increased blood vessel formation because of GBM.[39,40] According to present knowledge, all intracerebral lesions enhanced by gadolinium on preoperative MRI will also intraoperatively display fluorescence because gadolinium and FL are both distributed via increased vascular permeability. A recent study by Neira et al.[17] suggests that objective intraoperative staining of FL is equivalent to the intensity of gadolinium uptake on preoperative MRI. Furthermore, the authors found that FL enhancement extends

beyond gadolinium contrast-enhancing regions, which might be because of the smaller molecular weight of FL than gadolinium. In primary GBM, the calculated sensitivity/specificity of FL ranges from 79%/100% (Rey-Dios et al.[41]) to 94%/89.5% (Acerbi et al.[42]) to 82.2%/90.9% (Diaz et al.).[9] No data are available for recurrent GBM in this respect. The refinement of FL-guided surgery with a specific filter has made this technique inexpensive and safe, which is confirmed by a high percentage of GTR in primary GBM. Nevertheless, FL is still undergoing feasibility tests, particularly in combination with the YELLOW 560 nm microscope filter. Approval of the drug by the respective competent authorities is pending. The recent evaluations of FL did not include any reports on relevant side effects, apart from yellowish discoloration of skin, scleras, and urine, which is usually fully reversible within 48 hours. FL has been extensively evaluated in ophthalmology, and very few adverse events have been registered during intracranial surgery.[43,44]

In this multicentric retrospective feasibility study of 106 patients with recurrent GBM, we discovered bright and clear visualization of recurrent GBM lesions under FL guidance, resulting in a high number of GTR cases. As stated in the surgical report, FL was useful for identifying recurrent GBM tissue, guiding safe resection, and improving differentiation from noncontrast enhancing tissue. Many authors have evaluated the effect of the EOR on survival in GBM, also elucidating the benefit of resurgery. In a retrospective analysis, Lacroix et al.[45] found an EOR of more than 98% to impact survival (median survival, 13 vs. 8.8 months, respectively). Later, Sanai et al.[28] found this effect with a threshold of 78% of EOR in a cohort of 500 consecutive patients with primary GBM. More recently, Chaichana et al.[46] detected a minimum EOR threshold of 70% for survival and recurrence in a retrospective analysis of 259 patients. At the same time, the residual tumor volume was less than 5%, resulting in prolonged survival. Grabowski et al.[47] defined a residual contrast-enhancing tumor volume of less than 2 cm^3 or an EOR larger than 98% to significantly impact survival. In primary GBM, FL-guided resection resulted in an EOR between 75% and 100%.[17,20,21,36,37,42,48] Furthermore, all authors noted improved visualization compared with white-light resection. Apart from better surgical adjuncts, other independent prognostic factors for identifying patients who will benefit from repeat surgery have come into focus. Age and the Karnofsky Performance Status Scale seem to play a major role.[49] In a retrospective analysis of 204 patients with GBM, Tully et al.[50] found that only 49 patients (24%) received reoperation at recurrence. These patients were mainly younger and initially presented with smaller tumors, which resulted in an EOR of 50% or more. Similarly, in a retrospective study by Ening et al.,[51] a Karnofsky Performance Status Scale score of greater than 70 throughout the course of disease was the threshold for patients to undergo a second operation.

This study has several limitations apart from its retrospective nature. Whether increasing GTR rates by means of FL improves survival is still subject to evaluation. Also, discerning pseudoprogression from recurrent GBM (i.e., evaluating the specificity and sensitivity for recurrent tumor tissue and scar tissue) needs to be investigated in future studies. Because of the multidisciplinary treatment of our cohort in multiple centers, no consistent data on adjuvant treatment were available.

To our knowledge, this is the first report evaluating FL in recurrent GBM.

CONCLUSIONS

We conclude that FL and the YELLOW 560 nm filter are safe and feasible tools for increasing the EOR in patients with recurrent GBM.

However, this effect needs to be confirmed in a randomized controlled trial with adequate power to precisely assess the outcomes within a predefined observation period.

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