Improved Availability of Fluorescence-Guided Surgery of Malignant Brain Tumors: A Headlamp-Loupe System Combined With Generic 5-Aminolevulinic Acid Replaces the Microscope—A Monocentric Feasibility Study

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■ OBJECTIVE: **Until recently, a prerequisite for fluorescence-guided surgery (FGS) was the use of a specialized microscope. With the availability of a system that combines surgical loupes with an FGS-enabled headlamp, the standard approach to FGS of gliomas is challenged. We therefore investigated the potential change in practice of FGS for gliomas, if the surgeon had the choice between both systems.**

■ METHODS: **Patients with a lesion indicating FGS were included. Surgery was performed by 3 specialized neuro-oncological neurosurgeons, who were provided with a headlamp-loupe system (HLLS) (5-aminolevulinic acid headlamp and surgeon-adapted loupes, 3.5X, customized fitted). We recorded surgeons' choice between HLLS and microscope and semi-quantified the statements. Additionally, in one case, specificity and sensitivity of various protoporphyrin IX (PpIX) fluorescence (PpIX-f) were histopathologically evaluated.**

■ RESULTS: **We report 206 procedures in 198 patients. Surgeons opted in 194 (94%) of the cases for HLLS and did not switch from HLLS to microscope in any case. Three biopsies taken from areas with negative, faint, and highly positive PpIX-f, as revealed by the HLLS but not by the microscope, corresponded to normal brain tissue (negative PpIX-f), infiltration zone (faint PpIX-f), and highly cellular tumor tissue with microvascular proliferation (strong PpIX-f).**

■ CONCLUSIONS: **Our center changed the practice of FGS by switching from microscopes to loupes. The reported experience might have an important impact on the general use and availability of FGS, as the HLLS and the in-house preparation of 5-aminolevulinic acid come at a fraction of the costs of the commonly practiced approach.**

INTRODUCTION

Gross total resection of malignant high-grade gliomas significantly improves overall survival and is therefore an integral part of therapy guidelines.[1] To enable a maximal aggressive and safe resection, 5-aminolevulinic acid (5-ALA)-based fluorescence-guided surgery (FGS) has become an important adjunct in neurooncological surgery as this technology optimizes the intraoperative tumor visualization.[2,3] This technology has consistently been proven to improve the extent of resection and has generated a paradigm shift in the neurosurgical management of these tumors.[4-7] Recently, 5-ALA-guided resection has even been demonstrated to be equivalent regarding the extent of resection as compared to intraoperative magnetic resonance imaging.[8] Despite these

Key words
- 5-ALA
- Fluorescence-guided resection
- Glioblastoma
- Head-lamps
- Intrinsic brain tumor resection
- Loupes

Abbreviations and Acronyms
5-ALA: 5-aminolevulinic acid
FGS: Fluorescence-guided surgery
HLLS: Headlamp-loupe system
LGGs: Low-grade gliomas
PpIX: Protoporphyrin IX
PpIX-f: PpIX fluorescence

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convincing data and almost 2 decades since its introduction in Europe, the use of 5-ALA has not become a standard in many countries with low- to middle-income[9] and not even in all specialized centers in Europe (personal experience) or Canada.[10] One of the reasons for this reluctance is the high cost of the drug itself,[11] which might drop by the availability of generic formulations and by the use of pharmacy-compounded solutions.[12] Another reason might be the expensive upgrading or purchase of surgical microscopes, which are adapted to provide the blue light necessary to induce protoporphyrin IX (PpIX) fluorescence (PpIX-f).[9] These specialized microscopes used to be the exclusive source for fluorescence-inducing light and therefore mandatory for the intraoperative use of fluorescence agents. Therefore, surgeons preferring macroscopic techniques or using surgical loupes were excluded from fluorescence-guided resections. As an alternative to the compulsory use of microscopes, alternative sources for the blue light generation were explored. Several groups developed modified headlamps as sources of wavelength-specific light source and were able to demonstrate the feasibility of using these systems for FGS in preclinical and small clinical investigations.[13-16] As the headlamps can be combined with surgical loupes, these systems might offer a feasible alternative to the standard microscopical approach.

Finally, a commercially available headlamp system became available with optimized excitation and fluorescent filters (Designs for Vision, Bohemia, New York, USA, REVEAL FGS 5-ALA fluorescent Tri-Beam headlight). First clinical data in small case series and comparative sample analysis underlined the feasibility and efficacy of this method.[9,17-20]

With the availability of this system, the standard approach to FGS of high-grade glioma is challenged. As most neurooncological surgeons are trained and practice with the microscope, the first challenge regarding the use of this system is implementing a switch from the established, standard use of the microscope to surgical loupes.

Secondly, the perception of PpIX-f, as a marker of the neoplastic target tissue, as revealed by the microscopical standard is potentially different from as revealed by the loupe system.

Both systems have specific advantages and disadvantages, highly depending on the individual surgeon's preferences. It is therefore of interest to record the potential change in practice if a neurosurgeon has the free choice between both methods and to analyze the underlying decision-making process.

Here, we present a consecutive case series study, which analyzed the choice and the reason for the decision to use either microscope or loupes in a specialized neurooncological center and address the issues of specificity and sensitivity as well as the impact on the availability of FGS.

PATIENTS AND METHODS

Study Design and Ethical Approval

This consecutive case series study was approved by the ethics committee of the medical faculty at Heinrich-Heine University Duesseldorf (Ethic ID: 2024−2861). All participants gave written informed consent.

Patients

Patients were included in a period from August 2023 to December 2024. All patients were electively admitted to the neurooncological center of the neurosurgical department of the University Hospital Duesseldorf. Inclusion criteria comprised 1) all patients with lesions suspicious of glioma and the indication for the application of 5-ALA. 2) Surgery had to be performed by 3 specialized neurooncological neurosurgeons (>800 glioma surgeries as a lead neurosurgeon) who were provided with customized fitted loupes. 3) Unrestricted availability of the loupe system and the surgical microscope at the time of the planning and execution of the procedure was necessary. All patients were >18 years old 4), and written informed consent was obtained 5).

Fluorescent Agents and Surgical Procedure

5-ALA was supplied as an in-house preparation by the Hospital Pharmacy (Chiracon GmbH, distributor Caesar & Lorenz GmbH, 4.600 € net/100 g). API identity was analyzed by infrared spectroscopy (2.2.24 Ph.Eur.) and chloride detection (2.3.1 Ph.Eur.). 5-ALA was administered orally 2−4 hours before surgery in a dose of 20 mg per kilogram body weight.[6] The study did not influence or change the established surgical procedures of the center.

Headlamp-Loupe System and Microscope

We used the "Designs for Vision" headlight with 3 HDiTM LEDs (Bohemia, New York, USA, REVEAL 5-ALA TriBeam High-Definition Imaging; HDiTM) and surgeon-adapted loupes (3.5 magnification, Figure 1). Photo documentation of the headlamp-induced PpIX-f was done with an iPhone 15 Pro Max using the Smart Device Emission Filter (Designs for Vision, Bohemia, New York, USA). The team trained the use of the system on a model which was previously described.[21]

For the use of a microscope, the Zeiss Kinevo Blue 400 microscope (Carl Zeiss AG, Oberkochen, Germany) was available in our center.

Surgeons' Evaluation

Firstly, surgeons 1−3 evaluated the feasibility of using loupes. If loupes were not indicated for surgical reasons, the reason was noted and the case was classified as "Foreseen technical difficulties." If the surgeons' initial choice was for loupes, but loupes were not available (until October 2023 customized fitted loupes were only available for surgeon 1), this was also noted. As a camera set for the loupes was not available, procedures in which the visualization of the surgical field was mandatory (i.e., teaching), the microscope was used and the case was classified as a "teaching" procedure. A potential switch from microscope to loupes and vice versa was noted as well. If loupes were chosen, surgeons were immediately postoperatively asked to rate the statements "superior visualization of loupes versus microscope regarding white light and PpIX-f," "superior handling of loupes versus microscope" and "no disadvantage of loupes versus microscope." To semi-quantify this assessment, we used a 10-Likert scale from 1 (I do not agree) to 10 (I completely agree). For analysis, we summarized this scaling as follows: "1−3" = "I (strongly) disagree," "4−6" = "I neither agree nor disagree," and "7−10" = "I (completely) agree." In a free text, the surgeons were

Figure 1. Picture of (**A**) Headlight system with three HDiTM LEDs by Designs for Vision (Bohemia, New York, USA), type REVEAL 5-aminolevulinic acid, TriBeam High-Definition Imaging (HDiTM, A) and (**B**) surgeon-adapted loupes (3.5 magnification).

asked to state the main advantages and disadvantages of the loupe system as compared to the microscope.

In one patient with an assumed first diagnosis of glioblastoma, we intentionally compared the intensity of PpIX-f as revealed intraoperatively by the headlamp-loupe system (HLLS) system with the intensity of the PpIX-f as revealed by the microscope. We defined 3 areas with negative 1), faint 2), and strong 3) PpIX-f as revealed by the loupes, marked these and evaluated these areas regarding their intensity with the microscope, which was positioned at the normal working distance to the surgical field (Figure 2A–C). Samples were taken from these areas and neuropathologically evaluated (Figure 3A–C).

RESULTS

We report 206 procedures in 198 patients. The vast majority of the cases were first diagnosis of glioblastoma, IDH-wildtype (n = 86; 43%), followed by recurrent glioblastoma, IDH-wildtype (n = 51; 25%), and recurrent glioma, IDH-mutant, CNS WHO grade 3 (n = 28; 14%). In total, 18 (8%) cases were diagnosed as grade 2 gliomas. For simplification, subgroups (oligodendroglioma, IDH-mutant and 1p/19q-codeleted and astrocytoma, IDH-mutant) were summarized by grading (Table 1).

All patients were operated on by 3 specialized neuro-oncological neurosurgeons (surgeon 1 n = 84, surgeon 2 n = 71, surgeon 3 n = 51).

The central finding of our study was that the surgeons opted in 194 (94%) of the cases for the HLLS system and did not switch from loupe to microscope in any case.

In 12 (6,1%) patients, the surgeons opted for the microscope for the following reasons:

1. Since the loupes are customized, the system was initially not available to all surgeons. This accounted for 7 (59%) cases in the category “loupes not available.”

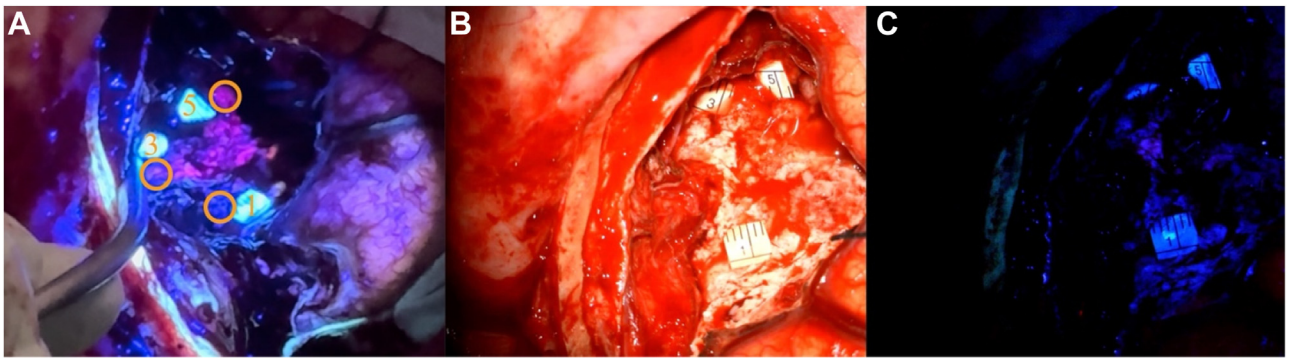

Figure 2. (**A**) Intraoperative view using HLLS with blue light illumination in a patient with first diagnosis of glioblastoma, IDH-wildtype. Numbers correspond to 1 = PpIX negative, 3 = faint PpIX fluorescence, and 5 = strong PpIX fluorescence. (**B**) Same surgical site by white light illumination (Zeiss/Kinevo). (**C**) Same surgical site as B switched to blue light with a microscope (Zeiss/Kinevo). Note that no PpIX fluorescence is detected by the microscope. HLLS, headlamp-loupe system; PpIX, protoporphyrin IX.

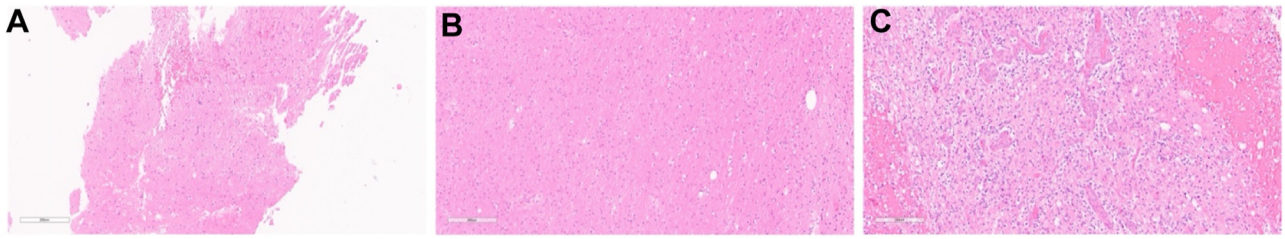

Figure 3. Histopathological evaluation from probes number 1/3/5 in Figure 2. Samples (**A**–**C**) show the morphological characteristics corresponding to **A** = normal brain tissue (negative PpIX fluorescence), (**B**) infiltration zone (faint PpIX fluorescence), and (**C**) highly cellular tumor tissue with microvascular proliferation (strong PpIX fluorescence) of glioblastoma, IDH-wildtype (CNS WHO grade 4). PpIX, protoporphyrin IX.

2. As no camera for the loupes was available, teaching purposes necessitated the use of the microscope (with observer tube or screen) in one (8.0%) case (category "teaching").
3. In 3 cases (25%), the surgeons preferred to use the microscope. The explanation for this choice was given in the free text section of the evaluation. Two reasons were given:
   a) Fear of insufficient illumination in 2 deep-seated cases. These were cases in the initial phase of the study (4th and 12th consecutive case).
   b) In one case, the surgeon opted for the microscope, as the surgeon felt that an assistant neurosurgeon with the same visual information was necessary.

Summarized results of surgeons' choice can be found in Table 2.

Subjective Assessment of the HLLS

All surgeons opted for the category "7–10" = "I (completely) agree" regarding the statements "superior visualization of HLLS versus microscope," "superior handling of HLLS versus microscope," and "no disadvantage using HLLS versus microscope" (Figure 4).

In the free text section of the evaluation, all surgeons claimed that the main advantage of the Reveal system was a better visualization of the PpIX-f as compared to the PpIX-f by microscopes. Surgeon 2 underlined that, in contrast to the microscope (with the same view for all), the 2 different visual aspects of the surgical field were a substantial advantage as the experienced assistant was able to analyze the various aspects of the situs and integrate these into the surgical procedure (Figure 5). The same surgeon, however, felt that in one case, an assistant neurosurgeon with the same visual information was necessary. All surgeons commented on the disadvantage of poor visualization for the

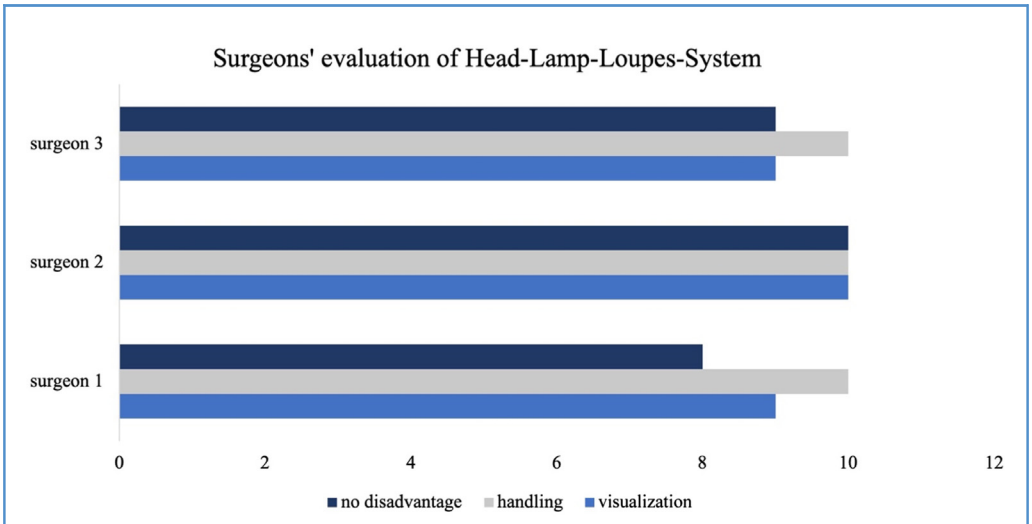

Figure 4. Surgeons' postoperative evaluation of the headlamp-loupes-system (HLLS). Visualization corresponds to: "superior visualization of loupes versus microscope regarding white light and PpIX-f." Handling corresponds to "superior handling of loupes versus microscope" and no disadvantage corresponds to "no disadvantage of loupes versus mic." Scale from 1 (I do not agree) to 10 (I completely agree). PpIX-f, PpIX fluorescence.

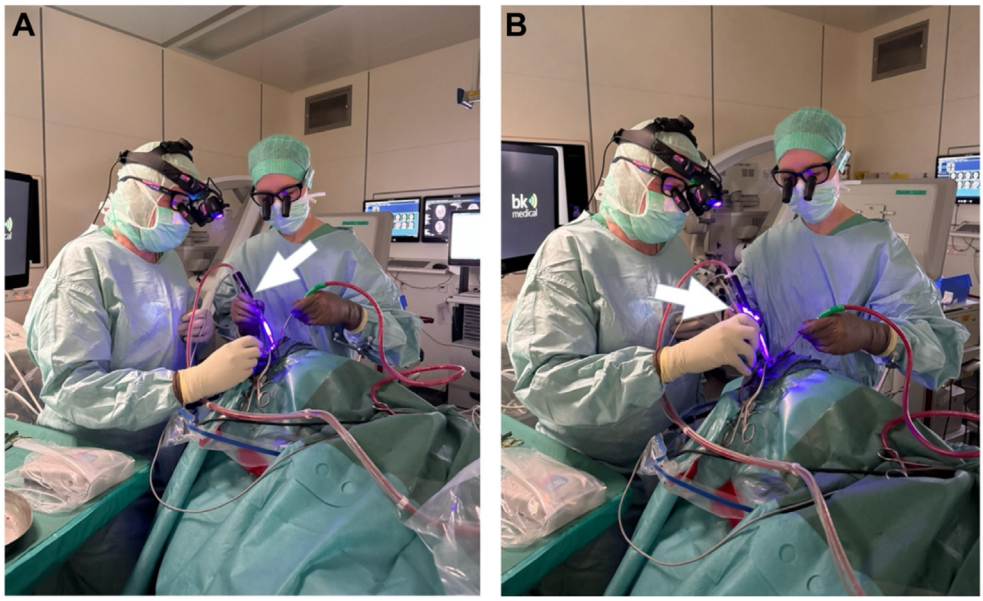

Figure 5. In contrast to the microscope, surgeons can obtain different aspects and views of intraoperative situs by using the HLLS and can integrate these into the surgical procedure. See the switch of the tissue ablation tool (ultrasound aspirator, *white arrow* **A** and **B**) between the surgeons' hands as different target areas by different visualization angles are identified at the same time. HLLS, headlamp-loupe system.

scrub nurse and observers due to the lack of screen transmission when using the HLLS. For better clarity, we have summarized the identified advantages and disadvantages in a table (Table 3).

In one case, 3 biopsies were taken from areas with negative, faint, and strong PpIX-f as revealed by the HLLS but not by the microscope (no PpIX-f for all intensities; Figure 2). The biopsies corresponded to normal brain tissue (negative PpIX-f), infiltration zone (faint PpIX-f), and highly cellular tumor tissue with

Table 1. Summarized Neuropathological Diagnosis According to the "The World Health Organization Classification of Tumors of the Central Nervous System, Fifth Edition, 2021[1]

Neuropathological Diagnosis (198 Patients, 206 Procedures)	n = 206 (100%)
FD grade 2 glioma, IDH-mutant	9 (4.0%)
FD grade 3 glioma, IDH-mutant	14 (7.0%)
FD grade 4 astrocytoma, IDH-mutant	3 (1.5%)
FD grade 4 glioblastoma, IDH-wildtype	86 (42%)
Rec grade 2 glioma IDH-mutant	9 (4.0%)
Rec grade 3 glioma IDH-mutant	28 (14%)
Rec grade 4 astrocytoma, IDH mutant	6 (2.5%)
Rec grade 4 glioblastoma IDH wildtype	51 (25%)

Rec, recurrent diagnosis; FD, first diagnosis. For simplification, a differentiation was only made between IDH-mutant astrocytoma CNS WHO grade 4 and IDH-wildtype glioblastoma. CNS WHO grade 4. Grade 2 and 3 gliomas include both, oligodendroglioma, IDH-mutant, and 1p/19q-codeleted and astrocytoma, IDH-mutant.

Table 2. Summary of Surgeons' Choice

	n = (%)
Surgeons' Choice	
Loupes first choice	194 (94.1%)
Microscope first choice	12 (6.1%)
Reason for microscope first choice	
Loupes not available	7 (59.0%)
Teaching surgery	1 (8.0%)
Unknown	1 (8.0%)
Foreseen technical difficulties	3 (25%)
Switch between modalities	
Switch from loupes to microscope	0 (0%)
Switch from microscope to loupes	0 (0%)

All numbers refer to the number of procedures.

Table 3. Tabular Summary of the Pros and Cons of Loupes and Microscope Techniques

Pro Loupes	Con Loupes
■ Full range of movement ■ Advantage of resection by visualization of the situs from different angles by two experienced surgeons ■ Better PpIX fluorescence compared to microscope ■ Financial advantage due to lower acquisition costs leads to… ■ Better availability in low-income and developing countries → expanded access to fluorescence-guided resections	■ Learning curve for deep-seated lesions, especially in the posterior fossa ■ Without additional camera for transmitting the surgical site, no teaching is possible, and nursing staff have no insights into the situs
Pro Mic	**Con Mic**
■ Teaching aspect much easier	■ Hands sometimes need to be removed from the situs, disrupting the surgical flow ■ Very expensive to acquire ■ Range of motion may be limited depending on the instrument and microscope settings ■ Less ALA signal

PpIX, protoporphyrin IX.

microvascular proliferation (strong PpIX-f) of glioblastoma, IDH-wildtype (CNS WHO grade 4) (Figure 3).

DISCUSSION

We report the impact of the availability of an HLLS on the clinical practice of FGS. In our specialized neurooncological center. Neurosurgeons had the free choice between the use of surgical loupes combined with a blue light-providing headlamp system and the use of a state-of-the-art surgical microscope.

The authors included 16 (8%) patients with preoperatively radiologically defined low-grade gliomas (LGGs), which were indicated for FGS. The use of 5-ALA in radiologically defined LGGs is controversial as there is a frequent absence of visible fluorescence within pure LGG. Given the negligible side effects of 5 -ALA and the low-cost situation in our setting, the authors support the use of FGS in LGGs to visualize potential intralesional regions with malignant transformation (anaplastic foci) to avoid the risk of histopathological under grading, which is an accepted approach.[22]

The main result of our study is an impressive, near-complete change toward the use of the HLLS. In 94% of cases, surgeons preferred the loupe system and, importantly, did not feel the need to switch back to the microscope. All surgeons agreed that they felt the superiority of the loupe system regarding handling and visualization of the tissue, both for the white light illumination and the PpIX-f. No surgeon felt a disadvantage of the loupe system as compared to the microscope. In fact, in only 3 (1,45%) early cases in the study surgeons preferred the microscope. This indicates a steep learning curve and a rapid adaptation to the system. We believe that the availability of an adapted training system on a cow-brain model supported this process.[23]

One substantial difference between working with loupes versus microscope is the different visualization of the surgical field. Using the microscope, both surgeon and assistant surgeon see the same. Using the loupe system, however, exposure to the field is different as it depends on the individual position of the surgeon. This necessitated, in one case, the use of the microscope as assistance based on the same visualization was required. On the other hand, this technical aspect was also felt as a substantial advantage as an experienced assistant can analyze the different aspects of the surgical situs and integrate these into the surgical procedure (Figure 5).

Interestingly, all surgeons reported a higher intensity of the PpIX-f of the loupe system as compared to the previous standard. All surgeons had performed a substantial number of FGS with the microscope before (surgeon 1 and 2 > 2000 FGS, surgeon 3 > 800). Therefore, this observation, though subjective, merits further evaluation. In the case presented in this paper, the faint and even the strong PpIX-f intensity as revealed by the loupe system was completely undetected by the microscope. As the illumination intensity is highly dependent on the distance to the sample tissue,[24] we excluded this factor by positioning the microscope at the normal working distance. A more likely explanation for this observation is that the fluorescence induced by the headlight is not running through the microscope's optical system, including the beam splitter, which inevitably reduces the efficiency of the fluorescence. This explanation is in line with previous observations.[24,25]

Importantly, the specificity of the fluorescence was striking as demonstrated in Figure 2. This observation is supported by a previous report.[18] Despite these first encouraging results on the specificity of the headlamp-induced PpIX, the potential higher sensitivity of the loupe system could induce a more aggressive resection, as the principle of FGS is the removal of the PpIX-positive tissue. The safety data on FGS with 5-ALA are derived from a study that used blue light filters in first-generation microscopes.[6] If the loupe system would indeed reveal additional fluorescence, resection should only proceed under rigorous intraoperative mapping and monitoring techniques, as strictly applied in our practice.[26]

Overall, our center changed the practice of FGS by switching from microscopes to HLLS. This experience could also have an important impact on the general use of FGS.

The availability of FGS for all patients, worldwide, should be the common goal of all neurooncologists. Apart from the potential technical advantages of the HLLS, the low cost of a complete system (around 12.000 €) as compared to a state-of-

the-art microscope can dramatically increase the availability of the technical requirements for FGS. Nevertheless, the high cost of 5-ALA still excludes a majority of patients worldwide from profiting from this option.[10] As described in the method section, our hospital used an in-house preparation of 5-ALA, which reduces the costs to approximately 14-fold (1 gr/in-house 46 € vs. 1gr/653€ Gliolan, MEDAC).

Study Limitations and Strength

Here we present the impact of an HLLS for FGS in a highly specialized neurooncological center, clearly demonstrating an impressive change in our current practice. In combination with the in-house preparation of 5-ALA, our study could lead to an increased availability of FGS for glioma patients. It was therefore our intention to communicate our experience to stimulate more research and discussion on this topic, even though several important issues are not addressed by our study. As yet there is no insight on the impact on the extent of resection nor clinical effects on the patients. This is of utmost importance, as we and others suspect a higher sensitivity of the HLLS[24,25] as compared to the microscope. More data on the specificity of the HLLS-induced fluorescence are needed as well,[18] especially as recent findings have questioned the correlation between PpIX-f and tumor cellularity.[27]

CONCLUSION

By switching from microscope to loupes, our highly specified neurooncological center changed the practice of FGS. Our experience might have an important impact on the general use and availability of FGS, as the HLLS and the in-house preparation of 5-ALA come at a fraction of the costs of the commonly practiced approach.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Michael Sabel: Conceptualization, Methodology, Supervision, Writing — original draft. **Franziska Staub-Bartelt:** Conceptualization, Project administration, Writing — original draft, Writing — review & editing. **Jonas Tödter:** Data curation, Writing — review & editing. **Julia Steinmann:** Data curation, Writing — review & editing. **Sebastian Jeising:** Conceptualization, Data curation, Writing — review & editing. **David Pauck:** Data curation, Writing — review & editing. **Marion Rapp:** Conceptualization, Methodology, Supervision, Writing — review & editing.

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