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# The use of the YELLOW 560 nm surgical microscope filter for sodium fluorescein-guided resection of brain tumors: Our preliminary results in a series of 28 patients

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ABSTRACT

*Objective:* Sodium fluorescein (Na-Fl) is a fluorescent dye that accumulates in tumoral tissues via disrupted blood-brain barrier. It has been used in fluorescence-guided surgery for various brain tumors. Herein, we report our initial experience and preliminary results for the first 28 patients who were operated on under Na-Fl guidance with the use of a special filter on the surgical microscope.

*Patient and methods:* Between January and November 2015, 200 mg (2–4 mg/kg) of Na-Fl was administered in 28 patients (30 surgeries) after anesthesia induction. The clinical features, surgical observations, extent of resection on the postoperative magnetic resonance imaging (MRI) and histopathology of the tumors were retrospectively analyzed. The use of YELLOW 560 nm filter was found "helpful" if the discrimination of the pinkish brain tissue and bright yellow stained tumor tissue was clear. Otherwise, it was described as "not helpful.

*Results:* There were 23 high-grade and 7 metastatic tumors in our study group. Na-Fl was found helpful by means of the tumor demarcation in 29 of 30 operations (97%). In 23 of these 29 operations (79%), a total resection was achieved regardless of the tumor pathology. No adverse events were encountered regarding the use of Na-Fl.

*Conclusion:* Na-Fl guidance with the use of a YELLOW 560 filter is safe and effective in high-grade glioma and metastatic tumor surgery. We think it is feasible for increasing the extent of resection in these tumors.



## 1. Introduction

The extent of resection has utmost importance in the prediction of progression-free or overall survival and recurrence in glioma surgery [8,31,33,42]. Similarly, complete resection of a metastatic brain tumor has been accepted as the most significant predictor of overall survival, further treatment efficacy and quality of life [11,15,24,30,34,39]. Numerous technical adjuncts have been employed to increase the extent of resection in brain tumor surgery, including neuronavigation [45], intraoperative ultrasound [44] and intraoperative magnetic resonance imaging [19,28]. These technical modalities have been increasingly and routinely used both to provide extended tumor resection and to prevent surgery-related morbidities.

In the past decade, fluorescence-guided surgery has emerged as a promising new modality to increase the extent of resection in brain tumor surgery, in addition to the above-mentioned technical tools. A natural precursor of hemoglobin, 5-aminolevulinic acid (5-ALA), which is metabolized in tumor tissues, was used as a fluorescent dye in glioma surgery [40,42]. Clinical results of the'ALA-trial' by Stummer et al. draw attention, as they demonstrate a significantly higher extent of resection (65% vs. 36%) and significantly better 6-month disease-free survival (41% vs. 21%) for the 5-ALA group compared to the control group [41]. This prospective, randomized, controlled Phase III trial confirmed the effectiveness of 5-ALA guidance in glioma surgery. However, 5-ALA application for guidance of metastatic brain tumor resection remained widely unsuccessful, because of the relatively low positive 5-ALA staining rates of metastatic brain tumors, which range from 52% to 61% [14,25]. In addition to that, there are drawbacks that limit the clinical application of 5-ALA in brain tumor surgery. In the United States, 5-ALA is still not approved by the Food and Drug Administration (FDA) [5]. The drug should be orally administrated

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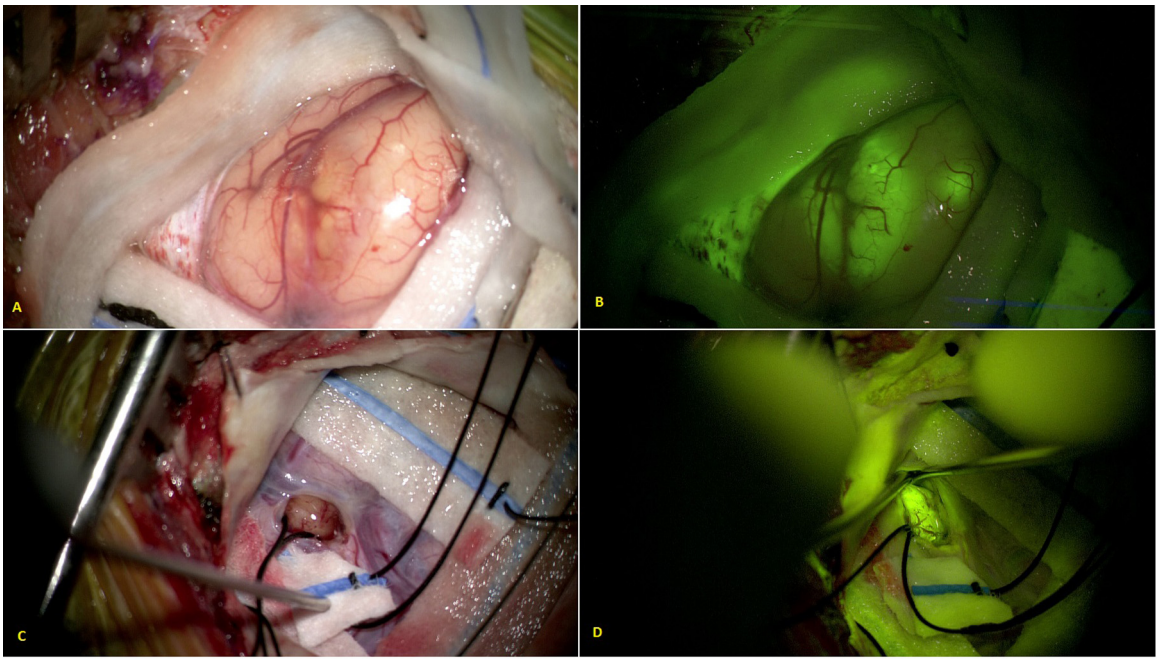


**Fig. 1.** (a) Intraoperative view of a left frontal tumoral lesion under white microscope light illumination. (b) Tumor shows significant Na-Fl enhancement under YELLOW 560 filter, which is visible on the cortex. (c) Intraoperative view of a right temporal high-grade glioma under white microscope light, below the cortical surface and the arachnoid plan. (d) Same lesion shows marked enhancement under YELLOW 560 filter.

three hours prior to the induction of general anesthesia, in order to provide adequate 5-ALA uptake by the tumor cells [2,35,40]. Direct exposure of the patients to sunlight or strong room light must be avoided within the first 24 h after drug administration, due to the risk of skin sensitization and eye irritation [2]. The drug is expensive, with an approximate 900 Euro price per application [2,35]. Finally, it is difficult to procure the drug in many countries, especially outside the European Union.

Due to these limitations, sodium-fluorescein (Na-Fl) recently has become an attractive alternative to 5-ALA. Na-Fl is a sodium salt and an organic fluorescent dye with peak excitation at 490 nm and emission between 500 and 550 nm [38]. It has been safely used in humans for many years, especially in ophthalmology for retinal angiography [22,23,29]. The cost of the drug is relatively low compared to 5-ALA, approximately 5 Euros per vial [2]. The use of Na-Fl for the demarcation of intracranial tumors has been known since 1947 [26,27]. Na-Fl accumulates in the tumor tissue through the dysfunctional blood-brain barrier (BBB). Various studies showed the promising effects of high-dose Na-Fl on the extent of resection under normal microscope light in skull base tumors [7], metastatic brain tumors [30] and high-grade gliomas [13,17,20,37]. With the employment of a newly developed microscope (PENTERO 900, Carl Zeiss, Meditec, Oberkochen, Germany) equipped with a special filter (YELLOW 560 nm) designed for the detection of low-dose Na-Fl for the demarcation of the tumor tissue, more promising reports have been published regarding the extent of tumor resection [1,2,9,32,35,36]. We present our initial experience and preliminary results of Na-Fl guidance with the use of YELLOW 560 nm filter in brain tumor surgery, in order to discuss the efficacy and usefulness of Na-Fl.

## 2. Patients and methods

Twenty-eight consecutive patients (15 female and 13 male, mean age 53.9 years, range 6 to 78 years) with suspected and newly diagnosed high-grade and metastatic tumors (based on the MRI and clinical findings) underwent Na-Fl-guided surgery between January and November 2015. All patients with suspicious high-grade gliomas and singular or multiple solitary cerebral metastatic lesions were included. A total of 30 surgeries were performed. Patients with renal or hepatic insufficiency or with a known allergy to Na-Fl were excluded from the study. Patients were evaluated with preoperative cranial magnetic resonance imaging (MRI) (Discovery 750 MRI 3T, GE, USA) with and without contrast. MRI-Neuronavigation (StealthStation® S7® System, Medtronic, Louisville, USA) was used in all instances intraoperatively for craniotomy planning and tumor localization, and in a manner to prevent postoperative morbidity. All patients underwent surgery under general anesthesia, except one patient who underwent awake craniotomy with neuromonitorization control, due to the localization of the tumor. The PENTERO 900 surgical microscope equipped with a YELLOW 560 nm filter was used in all instances (PENTERO 900, Carl Zeiss, Meditec, Oberkochen, Germany). The filters can be easily and rapidly switched with the use of one button.

After the anesthesia induction, 2 ml (200 mg/2–4 mg/kg) of Na-Fl 10% was injected intravenously through a central venous catheter. It was observed that dura is always stained with Na-Fl under theYELLOW560 filter, following the craniotomy. After dural opening under white light, the filter was switched. Superficial tumors could be localized directly if there was Na-Fl staining. For deep located tumors, a surgical plan created in neuronavigation console was used and dissection to deep structure was made under alternating white light and the YELLOW560 nm filter. The tumor was then removed with standard microneurosurgical technique by using both white light and YELLOW560 nm filter illumination in an alternating fashion. YELLOW560 nm filter was dominantly preferred during the resection stage. Particular interest was given at the final stage, in order to evaluate tumor margins and “hidden corners” of surgical cavity. The use of YELLOW560 nm filter was found “helpful” if the discrimination of the pinkish brain tissue and bright yellow stained tumor tissue was clear. Otherwise, it was described as “not helpful”.