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ORIGINAL ARTICLE

Sodium fluorescein–guided brain tumor surgery under the YELLOW-560-nm surgical microscope filter in pediatric age group: feasibility and preliminary results

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Abstract

Objective To evaluate the feasibility and safety of sodium fluorescein (Na-Fl)–guided surgery with the use of the PENTERO 900 surgical microscope (Carl Zeiss, Meditec, Oberkochen, Germany) equipped with the YELLOW-560-nm filter and low-dose Na-Fl (2 mg/kg) in pediatric brain tumor surgery.

Methods The study included 23 pediatric patients with various intracranial pathologies, who underwent Na-Fl-guided surgery between April 2015 and February 2018. Clinical features, surgical observations, extent of resection, and tumor histopathology 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 11 female and 12 male patients with a mean age of 9.4 years. There were 7 brain stem/tectal plate gliomas, 6 supratentorial tumors, 4 intraventricular tumors, 2 pineal tumors, 2 infratentorial tumors, 1 clivus tumor, and 1 tumor with supra- and infratentorial extensions in the current series. Na-Fl was found helpful by means of the tumor demarcation in 20 instances (87%). In 11 of these 20 operations (55%), a total resection was achieved regardless of the tumor pathology. A subtotal resection was achieved in the remaining 9 patients (45%). No adverse events or side effects were encountered with regard to Na-Fl use.

Conclusion Na-Fl guidance with the use of the YELLOW-560 filter is safe and effective during brain tumor surgery in pediatric age group.

Keywords Sodium fluorescein · Surgical microscope · YELLOW 560 · Pediatric · Brain tumor · Fluorescence-guided surgery

Introduction

In glioma surgery, the strongest predictor of progression-free or overall survival, as well as recurrence, has been accepted as the extent of resection (EOR) [7, 22, 24, 31]. Also, in metastatic brain tumor surgery, EOR is the most significant predictor of overall survival, further treatment efficacy, and quality of life [10, 12, 16, 21, 25, 30]. Similarly, for meningiomas, EOR, indicated by the Simpson grade, has been considered as the most important prognostic factor alongside histopathological features [4, 6, 28]. Such as these tumors, also in other tumors of the central nervous system (CNS), maximal safe resection is the goal in most cases. Numerous technical adjuncts have been employed to increase EOR in brain tumor surgery, including neuronavigation, intraoperative ultrasound, and intraoperative magnetic resonance imaging [13, 19, 32, 33]. Alongside these technical adjuncts, fluorescein-guided neurosurgery has been emerged in recent years as a new technology to increase EOR. With the employment of the 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, very promising results have been

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Table 1 The patient demographics, symptoms and signs, tumor histopathologies, intraoperative fluorescein enhancement, and extent of resection are summarized. (*ST* subtotal resection, *T* total resection)

No.	Age/sex	Symptoms/signs	Localization	Pathology	Na-Fl	Resection
1	15/m	Diplopia	Clivus	Chondrosarcoma	Helpful	ST
2	6/f	Cerebellar ataxia	Brain stem (recurrent tumor)	Medulloblastoma	Helpful	T
3	15/m	Vertigo	Left cerebellar	Pilocytic astrocytoma WHO grade I	Helpful	T
4	4/f	Headache, dizziness	Suprasellar (recurrent tumor)	Craniopharyngioma (adamantinomatous)	Helpful	ST
5	16/m	Seizure	Right mesial temporal	Dysembryoplastic neuroepithelial tumor (DNET) WHO grade I	Not helpful	T
6	3/f	Ptosis	Brain stem	Pilomyxoid astrocytoma WHO grade II	Helpful	ST
7	14/f	Seizure	Left temporal	Dysembryoplastic neuroepithelial tumor (DNET) WHO grade I	Not helpful	T
8	7/f	Ptosis, headache	Right cavernous sinus, petrous apex, cerebellopontine angle	Atypic meningioma WHO grade II	Helpful	ST
9	3/m	Headache, dizziness	Intraventricular	Choroid plexus papilloma WHO Grade I	Helpful	T
10	16/m	Dysphasia	Left temporoparietal (recurrent tumor)	WHO grade IV sarcoma	Helpful	T
11	6/m	Ataxia, dysphagia	Brain stem (recurrent tumor)	Anaplastic ependymoma	Helpful	ST
12	2/f	Ataxia	Left cerebellar (recurrent tumor)	Diffuse astrocytoma WHO grade II	Helpful	T
13	5/m	Diplopia, ataxia, dysphagia	Brain stem	Diffuse intrinsic pontine glioma WHO grade III	Helpful	ST
14	17/m	Headache	Pineal region	Germinoma	Helpful	T
15	3/m	Incidental (following trauma)	Right frontal	Diffuse astrocytoma WHO grade II	Not helpful	T
16	17/m	Proptosis	Left orbital	Ewing sarcoma	Helpful	T
17	16/f	Headache	Intraventricular	Choroid plexus papilloma WHO grade I	Helpful	T
18	4/f	Seizure	Intraventricular	Ependymoma	Helpful	T
19	16/m	Headache	Tectal plate	Germinoma	Helpful	T
20	2/f	Apathy, somnolence	Intraventricular	Pilocytic astrocytoma WHO grade I	Helpful	ST
21	18/f	Headache	Pineal region	Pineocytoma	Helpful	T
22	7/f	Diplopia, ataxia, dysphagia	Brain stem	Diffuse intrinsic pontine glioma WHO grade IV	Helpful	ST
23	4/m	Headache, ataxia	Brain stem	Anaplastic astrocytoma WHO grade III	Helpful	ST

published regarding the extent of tumor resection [1–4, 8, 11, 23, 26, 27].

However, the feasibility and safety of low-dose Na-Fl usage under YELLOW 560 nm in pediatric age group has not been addressed well to date. To our knowledge, there have been no studies regarding this issue in the published literature. The purpose of this study was to evaluate the feasibility and safety of fluorescence-guided neurosurgery involving the use of the YELLOW-560-nm filter and low-dose Na-Fl (2–4 mg/kg) in pediatric patients with various intracranial pathologies.

Patients and methods

Twenty-three consecutive pediatric patients (11 female and 12 male, mean age 9.4 years (range 1.5 to 18 years)) with various brain tumors regardless of the pathology underwent Na-Fl-guided surgery between April 2015 and February 2018. All patients with various CNS tumors and aged under 18 years at the time of operation were included. 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. Patients with tumors in eloquent areas were operated with neuromonitorization control. The PENTERO 900 surgical microscope equipped with a YELLOW-560-nm filter was used in all instances. The study was approved by the Local Ethics Committee. Na-Fl was used off-label in each patient. Each

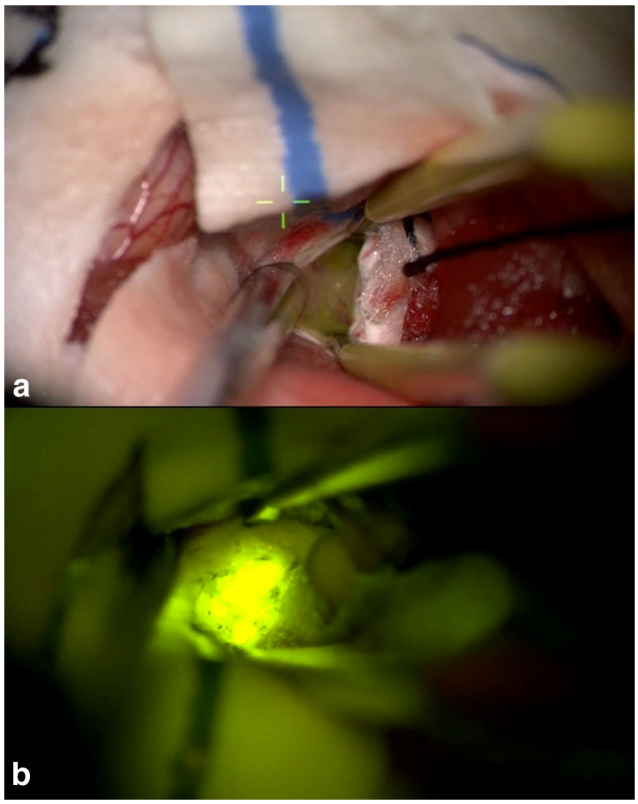

Fig. 1 **a** Intraoperative view of an intraventricular tumor (choroid plexus papilloma) under white microscope light illumination. Note that the tumor is already showing some Na-Fl enhancement visible under white light (the yellow-greenish color on the tumor surface) despite the low dose used. **b** The same tumor shows significant Na-Fl enhancement under YELLOW 560 filter

patient provided informed consent signed by their parents for participation in the study.

Following anesthesia induction, 2 mg/kg of Na-Fl 10% was injected intravenously through a central venous catheter. Dura is always found to be stained with Na-Fl under the YELLOW-560-nm 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 sulcal dissection to deep structure was made under alternating white light and the YELLOW-560-nm filter. The tumor was then removed with standard microneurosurgical technique by the alternating use of white light and YELLOW-560-nm filter illumination. 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."

The patients were followed up in the intensive care unit (ICU) postoperatively. A postoperative cranial MRI was obtained within 24 h with and without contrast in all instances. The extent of resection was defined according to the presence or absence of contrast enhancement or residual tumor as follows: total resection (TR), no residual tumor tissue; near-total resection (NTR), less than 5% of residual tumor tissue, compared to the tumor volume on the preoperative MRI; and subtotal resection (STR), residual tumor tissue more than 5%.

The patients were followed up carefully to monitor possible side and adverse events related to Na-Fl use intra- and postoperatively. They were then discharged from the hospital and followed up in the outpatient clinic at the first week and the first, third, and sixth months.

Results

The patient demographics, tumor histopathologies, intraoperative fluorescein enhancement, and EOR are summarized in Table 1. Enhancement of tumor tissue was visible under YELLOW-560-nm filter 20 to 30 min after the Na-Fl administration and lasted until the procedure ended.

A total of 23 surgeries were performed. Na-Fl was found helpful by means of the tumor demarcation in 20 instances (87%). In 11 of these 20 operations (55%), a total resection was achieved regardless of the tumor pathology. A subtotal resection was achieved in the remaining 9 patients (45%). The three patients in whom the Na-Fl was not found to be helpful were sharing the same radiological features. The tumors in those patients (two dysembryoplastic neuroepithelial tumors (DNET) WHO grade I and a diffuse astrocytoma WHO grade II) were not contrast enhancing or only weakly contrast enhancing. In addition to that, we must underline the fact that in patients with brainstem/tectal plate gliomas, surgical aim was only partial resection in order to establish a histopathological diagnosis and to reduce the tumor volume. Also, the patient who had an extra-axial tumor with supra- and infratentorial extensions received only a subtotal resection as planned preoperatively.

The observations during surgery revealed that Na-Fl enhancement pattern of tumors is similar to the contrast enhancement pattern on the preoperative MRI (Figs. 1 and 2). Central necrotic parts of the high-grade tumors showed no fluorescein enhancement; however, gadolinium-enhanced tumor parts on the MRI clearly showed fluorescein enhancement during surgery (Figs. 3, 4, and 5).

No side effects or adverse reactions were encountered due to the intravenous use of Na-Fl in this series. There were no permanent new neurological deficits postoperatively. There was a need of shunt insertion in a patient with an intraventricular tumor (choroid plexus papilloma) 1 month following the initial surgery. Two patients (one patient with grade IV sarcoma and one patient with brain stem glioma) died during follow-up period due to tumor progression 14 and 11 months after their initial surgery, respectively. Two patients (one extra-axial tumor with supra- and infratentorial extensions and one

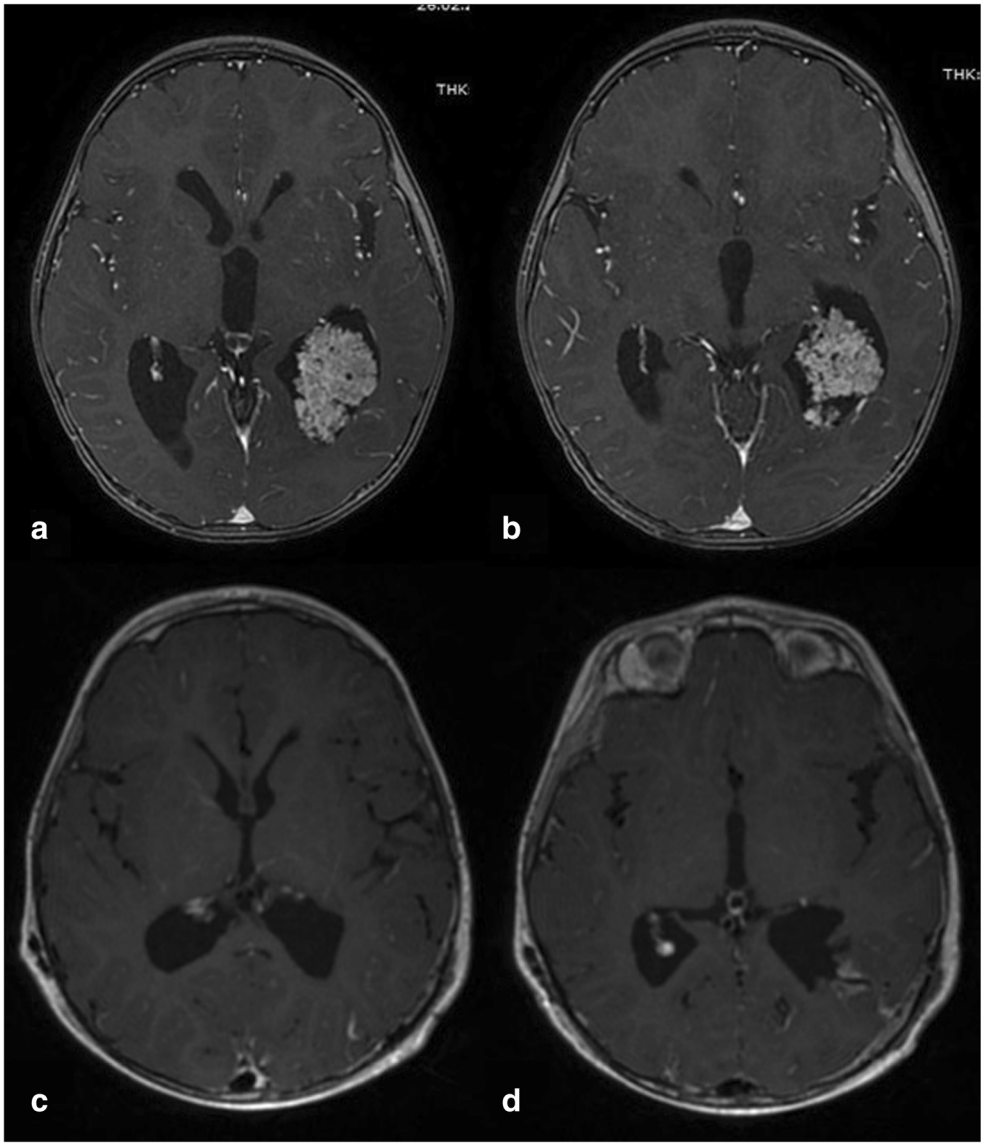

Fig. 2 **a** and **b** The intraventricular tumor (choroid plexus papilloma) at the occipital horn of the lateral ventricle shows gadolinium enhancement on preoperative MRI. **c** and **d** Postoperative MRI of the same patient shows total removal of the lesion

with the suprasellar tumor) were lost to follow-up. There was no evidence of tumor progression, recurrence, or any complications during the relatively short follow-up period in other patients.

Discussion

Na-Fl is a sodium salt and an organic fluorescent dye with peak excitation at 490 nm and emission between 500 and 550 nm [29]. It has been safely used in humans for many years, especially in ophthalmology for retinal angiography [14, 15, 20]. It has been even used in premature infants without any side effects both for intravenous and oral administrations [5, 9]. The cost of the drug is relatively low, approximately 5 Euros per vial [2]. The use of Na-Fl for the demarcation of intracranial tumors has been first described in 1947 [17, 18]. Na-Fl accumulates in the tumor tissue through the dysfunctional blood-brain barrier (BBB).

With the development of the new surgical microscope (PENTERO 900, Carl Zeiss, Meditec, Germany) and the new filter (YELLOW 560 nm), Na-Fl can be used with very low doses (2–4 mg/kg) in brain tumor surgery. Recent studies demonstrated promising results with the use of this new microscope equipped with the special filter by means of EOR [1–4, 9, 11, 23, 26, 27]. The practical use of the YELLOW 560 filter was also described in previous publications [1–4, 9, 11, 23, 26, 27].

As mentioned above, the lack of the data on the pediatric age group patients in the current literature has been driven us to conduct this study and to share our experience with pediatric patients. We mainly focused on the possible adverse and

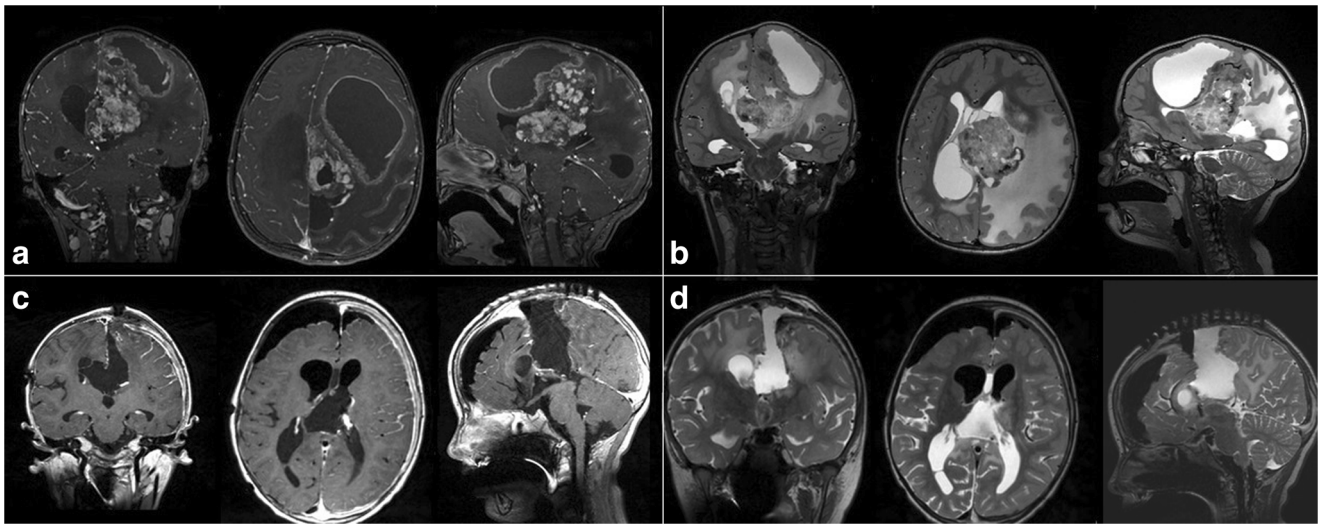

Fig. 3 **a** Preoperative MRI of the 4-year-old female patient with a cystic-solid intraventricular ependymoma shows an irregular, contrast enhancement in T1-weighted images with gadolinium. **b** T2-weighted images showed the diffuse peritumoral edema around the lesion which extends from the third ventricle to vertex. **c** and **d** Postoperative T1-weighted images with contrast and T2-weighted images confirm total removal of the lesion

side effects of Na-Fl use in the current study, rather than the impact of the Na-Fl on the EOR. One of the reasons for this approach is the variety of tumor locations and histopathologies. For instance, there were 7 patients in this study with diffuse brain stem/tectal plate gliomas. Total resection was not aimed in any of these seven cases. There were also two patients with pineal tumors. After confirming the histopathological diagnosis with frozen section (germinoma) in one these cases, a total resection was not forced either. Due to these reasons, the percentage of patients with total tumor resection was found considerably low compared to our previous studies [4, 11]. On the other hand, the usefulness of Na-Fl for the tumor demarcation was found 87% in this study and we think that this might be related to the contrast enhancement pattern of the lesions in this series.

There are supra- and infratentorial extra-axial tumors and intraventricular tumors in the current series. These tumors already have a distinct clivage from the normal brain tissue and the use of Na-Fl might be criticized in these particular tumors. However, one of the most important contributions of Na-Fl guidance is the clear demonstration of adjacent vascular and neural structures, which eases tumor-brain interface dissection. Although the employment of fluorescein-guided surgery is not a "must" for many instances, it clearly demonstrates the tumor margins and adjacent anatomical structures which might have a positive impact on the surgical dissection. Also, in brainstem/tectal plate gliomas, contrast-enhanced parts of the tumors were clearly visible under YELLOW 560 filter, which makes the partial resection in these highly eloquent areas safe.

No adverse or side effects were encountered in this series related to the use of Na-Fl. The reason for that might be that we used the lower threshold (2 mg/kg) of the Na-Fl dose in pediatric age group. Considering 2–4 mg/kg [4, 9] or 3–5 mg/kg [1, 2] was defined as low dose in adults, and no adverse events were encountered in the published literature which consist of hundreds of patients so far; it is very normal not to encounter any adverse events with such a low dose of Na-Fl.

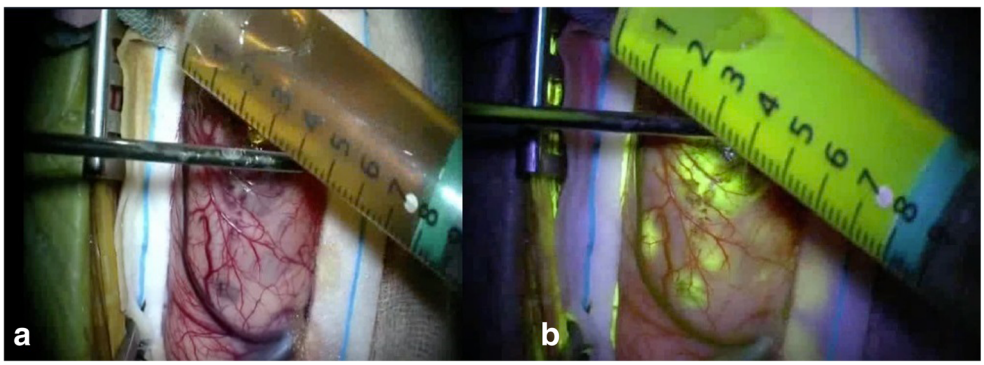

Fig. 4 **a** Intraoperative view of the cystic-solid intraventricular tumor (ependymoma) under white microscope light illumination right after cyst puncture. **b** The cyst content shows marked Na-Fl enhancement under YELLOW 560 filter

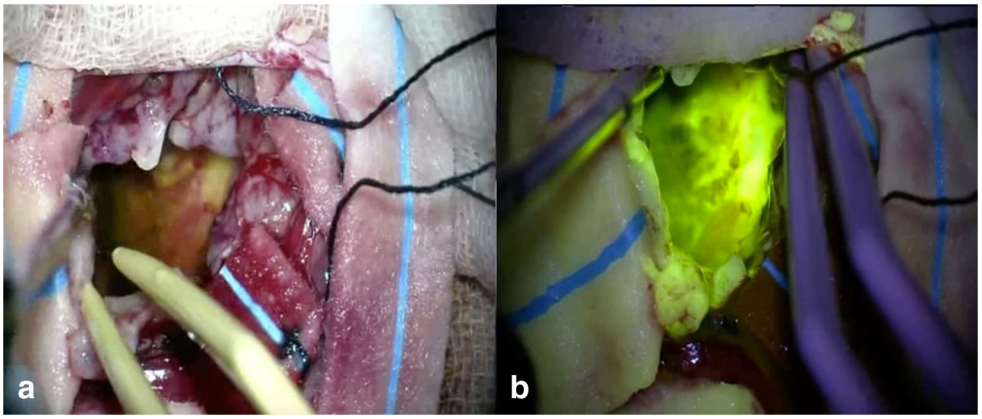

Fig. 5 **a** Cavity control after gross total tumor resection under white microscope light illumination. **b** There was a significant Na-Fl enhancement under YELLOW 560 filter on the cavity wall indicating that there was still a tumoral tissue on the surgical field

Conclusion

Na-Fl guidance with the use of YELLOW-560-nm filter is safe and effective in pediatric brain tumor surgery. Our data demonstrated that it is also feasible for increasing the extent of resection in this age group too. To confirm the efficacy and to prove the impact on patient survival, prospective randomized studies with larger and homogeneous patient samples and with long-term follow-up need to be done.

Compliance with ethical standards

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

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