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CASE REPORT

# The utilization of sodium fluorescein in pediatric brain stem gliomas: a case report and review of the literature

Cameron M. Erdman[1] · Catherine Christie[2] · M. Omar Iqbal[3] · Catherine A. Mazzola[2] · Luke Tomycz[2]

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## Abstract

**Introduction** A major challenge in the surgical resection of brainstem tumors is distinguishing tumor from normal tissue. One approach for addressing this problem is the use of fluorescent tracers such as sodium fluorescein (NaFl). NaFl disseminates through a disruption in the blood-brain barrier (BBB) and accumulates in the extracellular space of brain tumors. Intraoperative fluorescence microscopy can be performed to identify tumor tissue and avoid damage to adjacent, normal tissue. Here, we present the case of a 16-year-old male who underwent a left retrosigmoid craniotomy with splitting of the tentorium to remove a large exophytic brainstem tumor involving the cerebellar peduncle and with superior extension into the midbrain and thalamus.

**Objectives** The primary objective of this study was to investigate the effectiveness of sodium fluorescein as an intraoperative technique and evaluate its potential benefit for resection of tumors in eloquent regions in the pediatric population. To do so, we focused on a case study approach; however, we also performed a literature review and evaluated different intraoperative fluorescent techniques and their benefits for tumor resection.

**Methods** We performed a literature search using PubMed and Google Scholar by the key words "sodium fluorescein," "brain stem tumor," and "central nervous system neoplasms." Twenty-nine articles including both pediatric and adult populations were selected for analysis and qualitative review.

**Results** In this case study, sodium fluorescein helped the surgeons to identify and obtain a gross total resection of a large brainstem tumor. The marker was especially helpful for discerning the inferior pole of the tumor buried inconspicuously in cerebellar tissue. We evaluate different fluorescent tracers, 5-ALA and ICG, and discuss their application and benefits in tumor resection surgery. We present different cases that found sodium fluorescein to be helpful in achieving a gross total resection.

**Conclusion** The application of sodium fluorescein proved to be a safe and effective technique for the resection of brain stem tumors as shown in this case study. It helped to expose concealed areas and illuminate the tumor capsule. Further studies should test the clinical use of sodium fluorescein on brain stem tumor resection.

**Keywords** Fluorescence-guided resection · Sodium fluorescein · Brain tumor · Intraoperative microscope · YELLOW 560 · Gross total resection

## Introduction

Resection of juvenile pilocytic astrocytomas (JPA) located in the brain stem may involve the risk of major neurological damage if proper techniques are not employed because of the high functionality of this region. Different strategies have been utilized by several groups to obtain a gross total resection (GTR) of brain stem gliomas while limiting the rate of morbidity. These techniques include stereotactic volumetric technique [5], direct stimulation [18], computerized neuronavigation [4], diffusion tensor imaging (DTI) [4], and intraoperative neurophysiological monitoring (IONM) [4]. Various anatomic descriptions have been described for safe zones of entry when operating on brainstem lesions [2, 18]. Intraoperative use of sodium fluorescein (NaFl) could have a special role in the approach to brainstem tumors in accurately delineating tumor from nearby eloquent tissue [7, 10, 22]. It is often quite difficult to distinguish low-grade tumor from

✉ Luke Tomycz
tomyczluke@gmail.com

1 Vassar College, 124 Raymond Avenue, Poughkeepsie, NY 12603, USA

2 New Jersey Pediatric Neuroscience Institute, 131 Madison Avenue, Morristown, NJ 07960, USA

3 Rutgers University, 90 Bergen Street, Newark, NJ 07101, USA

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healthy brain tissue with the naked eye and a natural light source; therefore, the utilization of sodium fluorescein in neurosurgical operations has become a useful tool in the resection of high-grade and select low-grade vascular brain tumors along with other useful adjuncts including IONM [12].

In this report, we present the case of a 16-year-old male patient with tumor progression despite chemotherapy. He underwent a left retrosigmoid craniotomy with splitting of the tentorium for tumor resection with the utilization of sodium fluorescein. This technique was employed to enhance the visibility of the tumor with the goal of achieving a GTR. We discuss the effectiveness of intraoperative fluorescence and offer a comparison of the frequency of GTR in the presence and absence of NaFl in tumor resection surgery in both the adult and pediatric population.

## Methods

We performed a literature search using PubMed and Google Scholar for relevant published articles regarding the use of sodium fluorescein in brain tumor resections. We searched using the keywords "sodium fluorescein," "brain stem tumor," and "central nervous system neoplasms." These articles were then filtered under the criteria of being published in English and utilizing human subjects. The initial search presented 76 articles. Articles describing the influence of intraoperative sodium fluorescein on extent of resection and outcomes were reviewed. Twenty-nine articles were selected for final analysis and qualitative review. Of the articles selected, we focused on articles published in English, with descriptions of technical processes and outcomes. The available articles included both pediatric and adult patients. More specifically, our focus was on articles that included gross total resections. We made an emphasis to include articles that mentioned NaFl, or 5-ALA, in combination with different modalities such as neuronavigation and neuromonitoring.

## Case report

### History and presentation

Our patient first presented to an outside neurosurgeon at 9 years of age with an episode of unresponsiveness and urinary incontinence in the setting of a 2-month history of headaches and lethargy. Initial examination revealed mild (4+/5) right-sided upper and lower extremity weakness and a right-sided facial droop. CT scan and subsequent MRI performed with and without intravenous contrast revealed obstructive hydrocephalus secondary to a 4.5 cm × 2.6 cm brainstem tumor, spanning from the infratentorial to the supratentorial compartment. The patient underwent a temporary ventricular drain placement and a left occipital craniotomy for tumor debulking by another pediatric neurosurgeon. Following exposure and biopsy, surgery was terminated in the setting of an intraoperative decrease in both motor and somatosensory evoked potentials, as well as significant intraoperative difficulty in defining tumor within the brainstem. A ventriculoperitoneal (VP) shunt was placed for hydrocephalus after the external drain could not be successfully weaned.

For the next 6 years, the patient was conservatively followed with serial MRIs. Most of his initial symptoms were relieved by shunt placement, and his parents refused further surgery. Instead, after radiographic progression was documented, he was treated with chemotherapy, but the mass continued to enlarge leading to progression of his hemiparesis. In the setting of a multidisciplinary tumor conference, it was determined that repeat surgical intervention should be pursued with an intention to attempt a more radical resection. At the time of repeat resection, the tumor had grown to 6 × 4 cm (Fig. 1).

### Operative techniques

The patient was administered an intravenous (IV) injection of 10% sodium fluorescein at a dose of 2 mg/kg approximately 1 h prior to skin incision. He was positioned supine with his head turned to the right and held in place with a Mayfield head holder. Stealth neuronavigation was employed in order to carefully map and mark the appropriate approach as well as function as an additional intraoperative aid during resection. Given the size of the tumor and the location within both the infratentorial and supratentorial compartments, a large retrosigmoid incision was made. A subperiosteal dissection was performed exposing the asterion, and self-retaining retractors were placed. A burr hole was drilled at the asterion, and a standard retrosigmoid craniotomy was performed exposing the transverse-sigmoid sinus junction. The dura was opened in a curvilinear fashion with a small cuff along the transverse-sigmoid sinuses. The surgical team then utilized the Zeiss YELLOW 560 microscope, with normal white light function for approach and exposure.

Using dynamic suction retraction of the superior cerebellum, abnormal tissue of the brain tumor capsule was immediately identifiable at the incisura. The capsule was exposed, and the tumor was internally debulked using bipolar forceps and suction. When the YELLOW 560 filter was employed, the tumor appeared bright green due to the fluorescein and was readily distinguishable from healthy brain tissue. Further exposure of the capsule was facilitated by tumor fluorescence. The tentorium was then carefully devascularized and sharply cut to expose the supratentorial compartment of the tumor, taking care to preserve and protect the fourth cranial nerve as well as in passage branches of the superior cerebellar artery. The anterior border of the tumor was well visualized and was clearly demarcated from normal brain, while

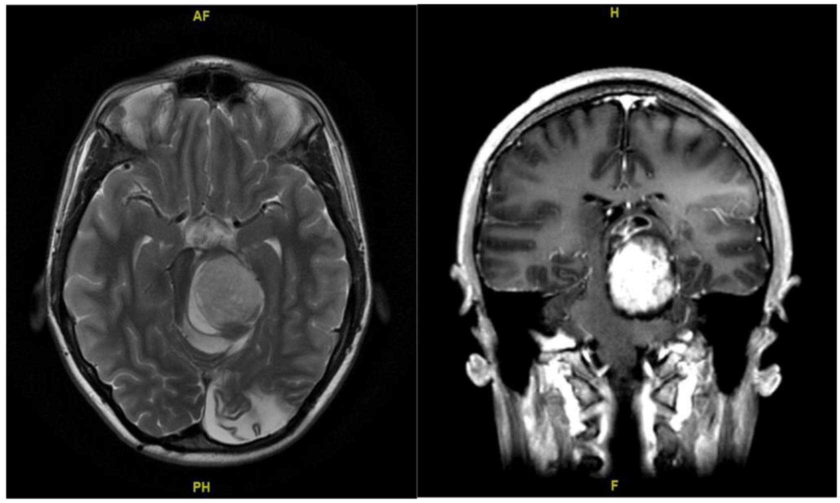


**Fig. 1** Preoperative MRI demonstrating a 6 cm × 4 cm mass located on the brain stem. *Left* is an axial T2 MRI and *Right* is a coronal T1 MRI with contrast

posteriorly and inferiorly, the distinction of a tumor border was less clear. Further resection in this expanded exposure was completed until all visible tumor was removed. At this point, hemostasis was obtained, and the wound was closed in standard fashion. Intraoperatively, there was a loss of motor potentials in the right leg (but not the arm) that eventually returned to half-baseline and was felt to be due to technical issues.

### Postoperative course

The patient enjoyed an unremarkable postoperative course. He received levetiracetam for seizure prophylaxis for 7 days post-surgery. The patient was able to ambulate with assistance and underwent physical and occupational therapy (PT/OT) each day post-surgery with steady progression until equal bilateral strength was achieved. Postoperative MRI of the brain showed a gross total resection of the tumor (Fig. 2). The patient was discharged from the hospital 6 days postoperation to an inpatient acute rehabilitation center. A 1-month follow-up appointment revealed increased strength in the upper extremities and improvement in ambulation. Since a GTR was attained, adjunctive therapy is not needed, and the patient will undergo annual surveillance MRI scans.

### Pathological examination

Histopathological examination revealed a juvenile pilocytic astrocytoma (WHO Grade I) with duplication of the BRAF gene.

## Discussion

This case study supports the safe and effective application of NaFl for the resection of brainstem and thalamic astrocytomas in the pediatric population when enhanced visualization is necessary. IV sodium fluorescein with a YELLOW 560 filter in the microscope was clearly beneficial in identifying residual tumor tissue. NaFl adequately stained the tumor while leaving the surrounding parenchyma untainted, consequently creating a distinguishable border between tumor and healthy brain

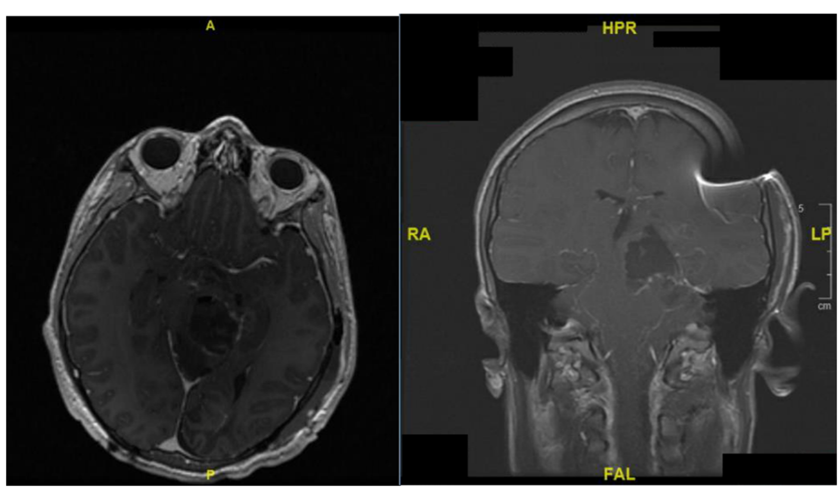


**Fig. 2** Postoperative MRI depicting a gross total resection of the brain stem lesion. *Left* is an axial T2 MRI and *Right* is a coronal T1 MRI with contrast

tissue visualized under the microscope. The operating microscope with the specialized filter helped to assist in a gross total resection, verified by postoperative MRI. There were no complications associated with NaFl in its administration or any adverse side effects noted.

Over the last two decades, sodium fluorescein has been used in various neurosurgical operations [25]. NaFl exhibits peak excitation between 465 and 490 nm and fluoresces between 540 and 590 nm [12]. The intraoperative fluorescence microscope is equipped with a special filter (YELLOW 560 nm) that is tailored to detect low doses of NaFl at the excitation and fluorescein wavelength ranges mentioned above. The operating microscope with specialized filter allows surgeons to alternate between a white light, blue light, and yellow filter combination. When the blue light with the yellow filter is activated, fluorescently stained structures are highlighted, and nonfluorescent tissue is shown in their natural color, which significantly enhances the detection and removal of tumors (Fig. 3). NaFl is typically injected either preoperatively or during the opening of the dura. Approximately 20–40 min after administration, sodium fluorescein accumulates in the tumor tissue, which exhibits enhanced yellow fluorescence [37]. NaFl acts as a vascular fluorophore and can illuminate gliomas and other brain tumors because they contain regions with a broken blood-brain barrier (BBB) leading to the coalescence of dye [6, 17]. After the administration of 500 mg of NaFl, it is estimated to take 48–72 h for the fluorescent to achieve total systemic clearance [12]. Sodium fluorescein has very few side effects overall but does include severe anaphylactic reactions which are seen in approximately 1 in 15,000 cases and a mortality rate which is estimated to be roughly 1 in 222,000 patients [16].

5-Aminolevulinic acid (5-ALA) is another fluorescent commonly used in tumor resection surgeries. It is metabolized to fluorescent protoporphyrin IX (PpIX) in tissues as a result of the heme biosynthesis pathway [35]. Malignant gliomas show an increased accretion of PpIX after administration of 5-ALA and fluoresce under blue light with peak excitation at wavelength 400–410 nm [11, 21, 29, 30]. Intraoperative use of PpIX has been shown in multiple series to provide enhanced visualization of the tumor and increase the likelihood of GTR [23, 29, 32–34]. Although 5-ALA is reported to be beneficial in increasing rates of GTR, it does have limitations, including subjective fluorescence interpretation particularly at tumor borders [14]. Valdes et al. discussed the use of an intraoperative probe, a highly sensitive spectrally resolved fluorescence imaging system that corrected the distorting effects of tissue optical properties, which showed a statistically significant improvement ($p < 0.0001$) of tumor detection of 87% accuracy, compared with 66% without the probe [35]. Unlike NaFl, 5-ALA is ideally administered 2–3 h prior to tumor resection because fluorescent marking of tumor cells is dependent upon an enzyme-kinetic conversion, which may limit its use in emergency cases [9]. Post-surgery, patients should be limited to low light conditions for 24–48 h due to the possible development of erythema from the drug's phototoxicity [21, 28, 31]. In addition, a study published by Lee et al. describes a novel method utilizing near-infrared (NIR) imaging with second window indocyanine green (ICG) as a contrast agent during glioma resections. ICG is Food and Drug Administration (FDA) approved as a NIR contrast agent and demonstrated a sensitivity of 98% and a specificity of 45% to localize gadolinium-enhancing tumors. ICG relies on passive diffusion as its method of drug delivery and therefore must be delivered well before surgery (~ 22.7 h) to take full effect. This technique is proven to reveal gadolinium-enhancing tumors with measurable NIR contrast, with a signal-to-background ratio of $9.5 \pm 0.8$ [13].

Several reports and case studies have documented the benefits of using fluorescent markers (e.g., NaFl, 5-ALA) for "difficult-to-resect" brain tumors, defined as having low visibility between brain parenchyma and glioma due to their invasive nature [3, 30]. Details of mechanisms of action and pediatric dosing of fluorescent markers can be found in Table 1. Chen et al. determined that the employment of sodium fluorescein impacted the rate of GTR for high-grade gliomas. Of the 22 patients undergoing surgery, the ten treated with sodium fluorescein obtained a GTR rate of 80% as compared with 33% GTR in the 12 who did not receive the

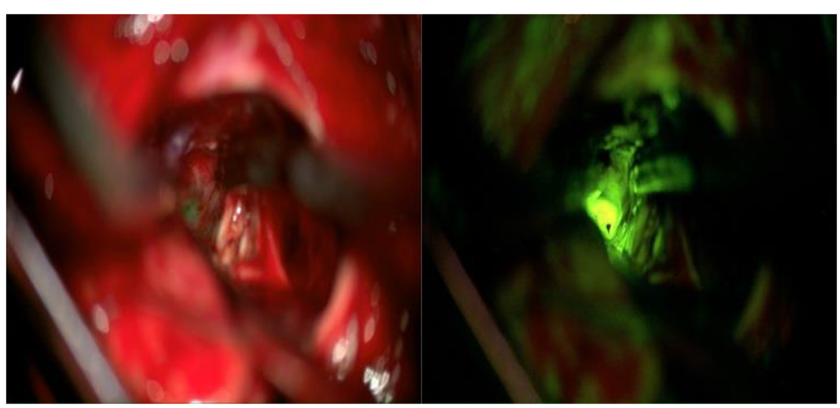

**Fig. 3** Intraoperative images obtained by using Zeiss intraoperative fluorescence microscope with a YELLOW 560 filter. Photograph of the lesion under natural white light *Left* and with the YELLOW 560 filter engaged *Right*. It is clear that only the tumor enhanced, while the surround parenchyma retained its natural color

**Table 1** Details of mechanisms of action and pediatric dosing of fluorescent markers

| Type of fluorescent markers | Quality | Dosage for pediatrics | Method of injection | Article | Reference |
|---|---|---|---|---|---|
| Sodium fluorescein (NaFl) | Accumulates in areas with disrupted blood-brain barrier | 2 mg/kg | Intravenous | Göker et al. (2019) | [6] |
| | | | | Zhang et al. (2017) | [14] |
| | | | | Hamamcıoğlu (2016) | [16] |
| 5-Aminolevulinic acid (5-ALA) | Dependent on tumor cell protoporphyrin IX metabolism | 20 mg/kg in 50 mL of water | Orally | Yano et al. (2017) | [18] |
| | | | | Hefti et al. (2008) | [23] |
| Indocyanine green (ICG) | Relies on passive diffusion and must be administered well in advanced | 2.5 mg/kg | Intravenous | Lee et al. (2016) | [35] |

fluorescent ($p = 0.047$) [3]. Additionally, a randomized and controlled phase 3 trial conducted by Stummer et al. compared the conventional white light microsurgery to surgery with the utilization of 5-ALA fluorescence guidance in regard to resection of malignant gliomas. Although progression-free survival at 6 months was higher in patients who were administered 5-ALA compared with solely the white light (GTR 65), overall survival did not significantly differ between the two groups.

Acerbi et al. and Hamamcıoğlu et al., in a study of 20 and 28 patients, respectively, found the use of intraoperative guidance in combination with NaFl to achieve GTR rates of nearly 80% [1, 8]. Several studies have highlighted the promising use of intraoperative fluorescents for achieving a gross total resection in cases of lymphoma (B cell non-Hodgkin) [24], glioblastomas [8, 20, 27, 36], metastatic brain tumors [8, 19], oligodendroglioma (WHO Grade III) [8], gliosarcoma (WHO Grade IV) [8], anaplastic astrocytoma (WHO Grade III) [8], anaplastic oligodendroglioma (WHO Grade III) [8], astrocytoma (WHO Grade III) [8], primary CNS lymphoma [15], and medulloblastoma (WHO Grade IV) [8].

Although fluorescent tracers are beneficial in helping to achieve a gross total resection, there are specific limitations that could potentially be problematic. First, 5-aminolevulinic acid (5-ALA) is very expensive and costs approximately $1115 USD per patient, while sodium fluorescein only costs about $5 USD, making it much more affordable and readily available to the public [16]. It is recommended that when one is using fluorescent tracers, specific microscopes are utilized during the operation to enhance the fluorescence. The Zeiss OPMI Pentero 800 microscope with the 560-nm filter to visualize NaFl and the Zeiss OPMI Pentero 800 microscope with the blue 400-nm filter to enhance 5-ALA are both expensive and not easily accessible, especially in low-resource situations or third-world countries. Lovato et al. designed a device with light filters, using 3-D printing, that could fit on any microscope and enables surgeons to alternate between the white light and fluorescent mode. The total cost of the device is approximately $380USD, and if it is used in multiple surgeries, the cost would go down exponentially making it more affordable in resource-limited conditions; 100 patients decrease the price to approximately $9.50 per patient including the dose of sodium fluorescein [16]. Moreover, a study done by Shinoda et al. determined that 10x the dose (20 mg/kg) of NaFl was sufficient to detect the fluorescence signal under natural light and without a filter [26].

## Conclusion

Sodium fluorescein tumor enhancement with the use of the Zeiss YELLOW 560 microscope is a safe, affordable, and effective technique for the resection of brainstem juvenile pilocytic astrocytomas as shown in this case study. It is particularly helpful in exposing concealed areas of tumor as well as delineating the tumor capsule from the brain stem. Along with subcortical motor mapping, computerized neuronavigation, and other methods, sodium fluorescence should be considered a tool in the armamentarium of surgeons operating on deep-seated tumors in eloquent territories.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Acerbi F, Broggi M, Eoli M, Anghileri E, Cavallo C, Boffano C, Cordella R, Cuppini L, Pollo B, Schiariti M, Visintini S, Orsi C, la Corte E, Broggi G, Ferroli P (2014) Is fluorescein-guided technique able to help resection of high-grade gliomas? Neurosurg Focus 36(5):E5
2. Burkhard C, Di Patre PL, Schuler D, Schuler G, Yasargil MG, Yonekawa Y et al (2003) A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma. J Neurosurg 98:1170–1174
3. Chen B, Wang H, Ge P, Zhao J, Li W, Gu H, Wang G, Luo Y, Chen D (2012) Gross Total resection of glioma with the intraoperative fluorescence-guidance of fluorescein sodium. Int J Med Sci 9(8): 708–714
4. Coelho J, Nunes S, Salgado D (2015) Spontaneous malignant transformation of a pilocytic astrocytoma of cerebellum. Child Neurol Open 2(1):2329048X1456681

5. Collins VP, Jones DTW, Giannini C (2015) Pilocytic astrocytoma: pathology, molecular mechanisms and markers. Acta Neuropathol 129(6):775–788
6. Diaz RJ, Dios RR, Hattab EM, Burrell K, Rakopoulos P, Sabha N, Hawkins C, Zadeh G, Rutka JT, Cohen-Gadol AA (2015) Study of the biodistribution of fluorescein in glioma-infiltrated mouse brain and histopathological correlation of intraoperative findings in high-grade gliomas resected under fluorescein fluorescence guidance. J Neurosurg 122:1360–1369
7. Göker B, Kırış T (2019) Sodium fluorescein–guided brain tumor surgery under the YELLOW-560-nm surgical microscope filter in pediatric age group: feasibility and preliminary results. Childs Nerv Syst 35(3):429–443
8. Hamamcıoğlu MK, Akçakaya MO, Göker B, Kasımcan MÖ, Kırış T (2016) The use of the YELLOW 560nm surgical microscope filter for sodium fluorescein-guided resection of brain tumors: our preliminary results in a series of 28 patients. Clin Neurol Neurosurg 143:39–45
9. Hefti M, von Campe G, Moschopulos M, Siegner A, Looser H, Landolt H (2008) 5-aminolevulinic acid induced protoporphyrin IX fluorescence in high-grade glioma surgery: a one-year experience at a single institution. Swiss Med Wkly 138:180–185
10. Höhne J, Brawanski A, Schebesch K-M (2017) Fluorescence-guided surgery of brain abscesses. Clin Neurol Neurosurg 155:36–39
11. Krammer B, Plaetzer K (2008) ALA and its clinical impact, from bench to bedside. Photochem Photobiol Sci 7:283–289
12. Lane BC, Cohen-Gadol AA (2013) Fluorescein fluorescence use in the management of intracranial neoplastic and vascular lesions: a review and report of a new technique. Curr Drug Discov Technol 10(2):160–169
13. Lee JY, Thawani JP, Pierce J, Zeh R, Martinez-Lage M, Chanin M, Singhal S (2016) Intraoperative near-infrared optical imaging can localize gadolinium-enhancing gliomas during surgery. J Neurosurg 79(6):856–871
14. Li Y, Rey-Dios R, Roberts DW, Valdes PA, Cohen-Gadol AA, Intraoperative Fluorescence-Guided Resection of High-Grade Gliomas (2014) A comparison of the present techniques and evolution of future strategies. World Neurosurg 82(1/2):175–185
15. Lin F-H, Zhang X-h, Zhang J, He Z-q, Duan H, Ke C, Sai K, Jiang X-b, al-Nahari F, Xi S-y, Mou Y-g (2018) Fluorescein sodium-guided biopsy or resection in primary central nervous system lymphomas with contrast-enhancing lesion in MRI. J Neuro-Oncol 139(3):757–765
16. Lovato RM, Vitorino Araujo JL, Esteves Veiga JC (2017) Low-cost device for fluorescein-guided surgery in malignant brain tumor. World Neurosurg 104:61–67
17. Neira JA, Ung TH, Sims JS, Malone HR, Chow DS, Samanamud J et al (2017) Aggressive resection at the infiltrative margins of glioblastoma facilitated by intraoperative fluorescein guidance. J Neurosurg 127:111–122
18. Ohgaki H, Kleihues P (2005) Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 64:479–489
19. Okuda T, Kataoka K, Yabuuchi T, Yugami H, Kato A (2010) Fluorescence-guided surgery of metastatic brain tumors using fluorescein sodium. J Clin Neurosci 17(1):118–121
20. Okuda T, Yoshioka H, Kato A (2012) Fluorescence-guided surgery for glioblastoma multiforme using high-dose fluorescein sodium with excitation and barrier filters. J Clin Neurosci 19(12):1719–1722
21. Panciani PP, Fontanella M, Schatlo B, Garbossa D, Agnoletti A, Ducati A, Lanotte M (2012) Fluorescence and image guided resection in high grade glioma. Clin Neurol Neurosurg 114:37–41
22. Rey-Dios R, Cohen-Gadol AA (2013) Intraoperative fluorescence for resection of hemangioblastomas. Acta Neurochir 155(7):1287–1292
23. Roberts DW, Valdés PA, Harris BT, Fontaine KM, Hartov A, Fan X, Ji S, Lollis SS, Pogue BW, Leblond F, Tosteson TD, Wilson BC, Paulsen KD (2011) Coregistered fluorescence-enhanced tumor resection of malignant glioma: relationships between d-aminolevulinic acid-induced protoporphyrin IX fluorescence, magnetic resonance imaging enhancement, and neuropathological parameters. J Neurosurg 114:595–603
24. Schebesch K-M, Hoehne J, Hohenberger C, Acerbi F, Broggi M, Proescholdt M, Wendl C, Riemenschneider MJ, Brawanski A (2015) Fluorescein sodium-guided surgery in cerebral lymphoma. Clin Neurol Neurosurg 139:125–128
25. Schebesch K-M, Brawanski A, Hohenberger C, Höhne J (2016) Fluorescein sodium-guided surgery of malignant brain tumors: history, current concepts, and future project. Turk Neurosurg 26:185–194
26. Shinoda J, Yano H, Yoshima S, Okumura A, Kaku Y, Iwama T, Sakai N (2003) Fluorescence-guided resection of glioblastoma multiform by using high-dose fluorescein sodium. J Neurosurg 99:597–603
27. Shinoda J, Yano H, Yoshimura S-I, Okumura A, Kaku Y, Iwama T, Sakai N (2003) Fluorescence-guided resection of glioblastoma multiforme by using high-dose fluorescein sodium. J Neurosurg 99(3):597–603
28. Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ (2000) Fluorescence-guided resection of glio- blastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg 93:1003–1013
29. Stummer W, Reulen HJ, Novotny A, Stepp H, Tonn JC (2003) Fluorescence-guided resections of malignant gliomas-an overview. Acta Neurochir 88:9–12
30. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7:392–401
31. Tonn JC, Stummer W (2008) Fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid: practical use, risks, and pitfalls. Clin Neurosurg 55:20–26
32. Tsugu A, Ishizaka H, Mizokami Y, Osada T, Baba T, Yoshiyama M, Nishiyama J, Matsumae M (2011) Impact of the combination of 5-aminolevulinic acid-induced fluorescence with intraoperative magnetic resonance imaging-guided surgery for glioma. World Neurosurg 76:120–127
33. Valdes PA, Fan X, Ji S, Harris BT, Paulsen KD, Roberts DW (2010) Estimation of brain deformation for volumetric image updating in protoporphyrin IX fluorescence-guided resection. Stereotact Funct Neurosurg 88:1–10
34. Valdes PA, Kim A, Brantsch M, Niu C, Moses ZB, Tosteson TD, Wilson BC, Paulsen KD, Roberts DW, Harris BT (2011) Delta-aminolevulinic acid-induced protoporphyrin IX concentration correlates with histopathologic markers of malignancy in human gliomas: the need for quantitative fluorescence-guided resection to identify regions of increasing malignancy. J Neuro-Oncol 13:846–856
35. Valdes PA, Leblond F, Kim A, Harris BT, Wilson BC, Fan X, Tosteson TD, Hartov A, Ji S, Erkmen K, Simmons NE, Paulsen KD, Roberts DW (2011) Quantitative fluorescence in intra- cranial tumor: implications for ALA-induced PpIX as an intraoperative biomarker. J Neurosurg 115:11–17
36. Yano H, Nakayama N, Ohe N, Miwa K, Shinoda J, Iwama T (2017) Pathological analysis of the surgical margins of resected glioblastomas excised using photodynamic visualization with both 5-aminolevulinic acid and fluorescein sodium. J Neuro-Oncol 133(2):389–397
37. Zhang N, Tian H, Huang D et al (2017) Sodium fluorescein-guided resection under the YELLOW 560 nm surgical microscope filter in malignant gliomas: our first 38 cases experience. Biomed Res Int 2017:1–10