LETTER TO THE EDITOR

To The Editor

Using Fluorescein in the Resection of a Pediatric Posterior Fossa Tumor

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Extent of resection of brain tumors is an important factor affecting progression-free survival.[1–5] Due to the infiltrative nature of tumors[4] and the related intraoperative challenges of identifying tumoral tissue at the resection margin,[6,7] achieving gross total resection may be difficult. Numerous adjuncts are currently employed to facilitate resection; one technique is fluorescent-guidance, in which tumor cells are made to fluoresce during resection.[1–6,8] Fluorescein sodium is an organic fluorescent dye that emits fluorescent radiation at wavelengths of 540–690 nm. Fluorescein accumulates in regions where the blood–brain barrier is disrupted, as in tumoral tissue.[2,6] We describe here our experience with fluorescent-guidance using fluorescein in the resection of a pediatric cerebellar tumor as the index case at our institution, and the first reported case in Canada.

A 5-year-old healthy female presented to the emergency room with her parents due to dizziness, nausea/vomiting, and gait disturbance for approximately one month. Her family confirmed no evidence for seizures, motor weakness, sensory changes, or other focal neurological deficits, apart from gait unsteadiness and frequently holding her head to the right. These findings were confirmed on physical examination. Imaging identified a round contrast-enhancing lesion arising from the inferior/middle cerebellar vermis (Figure 1, A-B). The patient was admitted and consented for resection of the lesion, with use of fluorescein for fluorescent-guidance given concerns for a higher-grade lesion, and coinciding with recent acquisition of a Kinevo 900 robotic microscope (Zeiss Medical) at our institution.

At induction, 5 mg/kg of fluorescein sodium was injected intravenously. Neuronavigation was set-up for intraoperative guidance. A standard suboccipital craniotomy and Y-shaped dural opening were performed. The Kinevo microscope was brought into the field, and the tumor was exposed following opening of the telovelotonsillar fissure. Under the yellow 560-nm filter, the majority of the tumor showed moderate to significant fluorescence (Figure 2, A–D). A cystic component was very easily localized by its fluorescence and expressed a yellow-tinged cerebrospinal fluid-like exudate. Solid portions of the tumor were homogeneous and moderate in fluorescence. We alternated use of the yellow filter and white light to ensure accuracy and safety of resection. Toward the periphery, there was minimal to mild fluorescence which guided additional resection beyond what was revealed by white light; this was readily confirmed as tumor-infiltrated tissue by use of the suction instrument. By providing a visual cue, the incorporation of fluorescence therefore provided reassurance to the tactile feedback of aspirating infiltrated tissue, with very minimal to no apparent extravasation seen beyond the resected tumor borders.

Following the procedure, the patient awoke without complications. Gross total resection was confirmed by magnetic resonance imaging (MRI) within 48 hours (Figure 1, C-D). During her recovery, the patient developed bright yellow-green coloration in her urine, as has been previously described in the literature.[1,6] This resolved within 48 hours following administration of IV fluids. Pathology confirmed the lesion to be consistent with WHO grade IV medulloblastoma, with large cell/anaplastic histology. Molecular subtyping showed MYC amplification. The patient was referred to the Pediatric Neuro-Oncology service for planning of adjuvant chemotherapy and tumor surveillance.

Gross total resection of brain lesions has been linked with improved progression-free survival[1–5]; however, this may pose an intraoperative challenge in cases where the borders of a lesion are poorly delineated. Although often beneficial, typical surgical adjuncts have their limitations. For example, neuronavigation loses accuracy due to the phenomenon of brain "shifting."[4,5,7] Ultrasound is user-dependent and often limited to images of lower quality.[7] Intraoperative MRI is expensive and extends operative time.[7] Fluorescent-guidance is not without limitations but does confer distinct advantages. The ability to delineate the brain–tumor interface and increase tumor visibility in real time, independent of brain shift, can aid resection.[4] In the resection of lower grade tumors, fluorescent-guidance may also reduce sampling error by highlighting anaplastic foci, found in 44–55% of cases.[4]

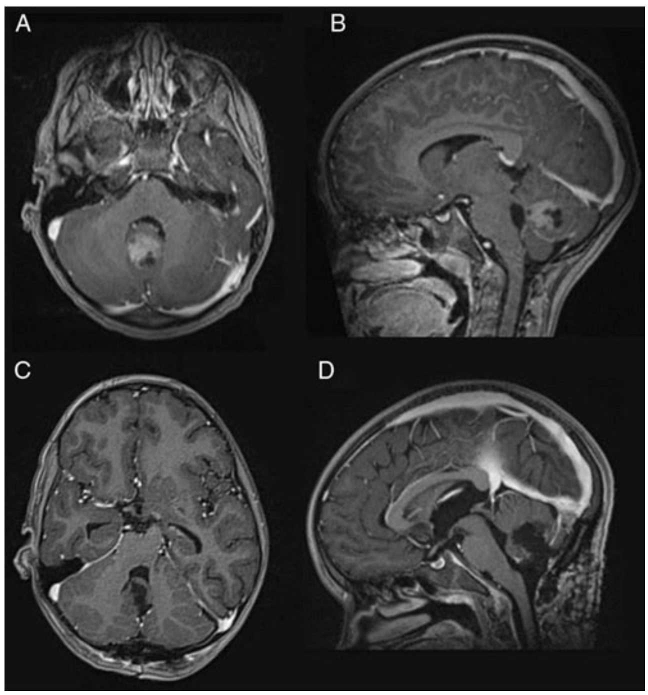

__Figure 1:__ Pre- and postoperative MR images of a solitary cerebellar vermian lesion resected via posterior fossa craniotomy. A) Axial and B) sagittal contrast-enhanced T1-weighted MR images demonstrating a lesion arising within the inferior/middle cerebellar vermis with moderate mass effect on the fourth ventricle. C) Axial and D) sagittal contrast-enhanced T1-weighted MR images revealing complete resection of the lesion.

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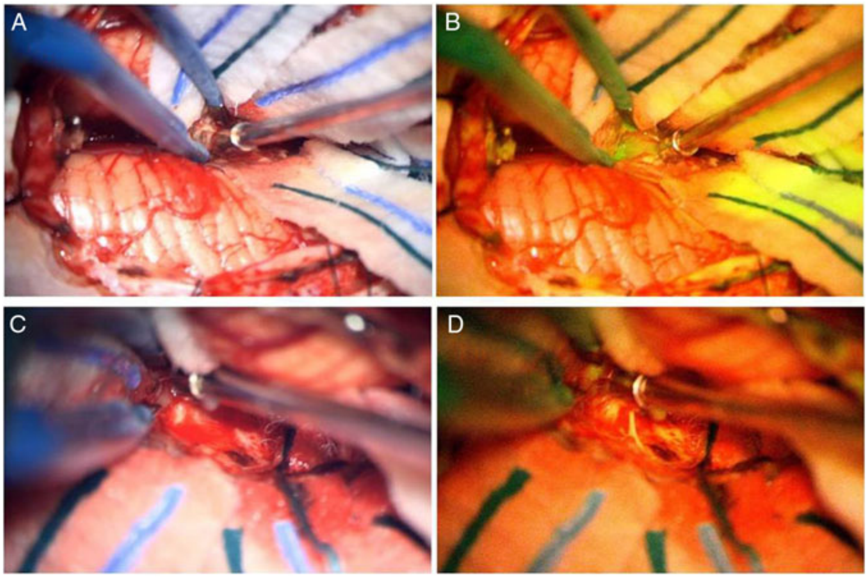

Figure 2: *Intraoperative photographs taken under a Zeiss Kinevo 900 microscope following the administration of IV fluorescein, taken under white light illumination (A, C) and compared against yellow 560-nm light filtration (B, D). Note the increased fluorescence of the tumor under the yellow 560-nm light as compared to the surrounding nonstained tissue, providing increased contrast and visualization of the remaining tumor to be resected.*

5-Aminolevulinic acid (5-ALA) is another fluorophore that has been studied in high-grade glioma surgery.[7] However, 5-ALA is associated with skin sensitization to sunlight and porphyria[1] and requires administration hours prior to the induction of anesthesia.[6] In contrast, fluorescein is largely nontoxic, can be administered at the time of induction, is less costly, and is widely available, making it a suitable alternative for fluorescent-guided surgery.

Although this case shows promise for the use of fluorescein as a surgical adjunct in the resection of pediatric posterior fossa tumors, further studies must be conducted. The optimal dose for resection should be determined, as higher doses may cause stronger fluorescence, which may be helpful in weakly enhancing tumors. Higher dosages, however, may cause increased side effects, including the transient staining of skin, mucosa, and urine. Rarely, anaphylaxis has been described, when very high doses (~20 mg/kg) were used.[1,6] Lower doses appear to be safe, but when in doubt, preoperative allergy skin testing may be used.[1] The optimal timing of administration also needs to be clarified to avoid nonspecific extravasation of fluorescein into regions of perifocal edema.[4] Lastly, the accuracy of identifying tumoral tissue in lesions that are weakly enhancing should be evaluated. Although some evidence exists on quantifying fluorescence and its specificity for glioblastoma detection,[5] more work is required for other pathologies. Ultimately, evaluating the impact of fluorescent-guidance on extent of resection and progression-free survival remains an important initiative, prior to adopting fluorescent-guidance into routine operative practice.

Overall, the use of fluorescent-guidance is a promising surgical adjunct for intracranial tumor resections with distinct advantages. To the best of our knowledge, this is the first reported case in Canada wherein IV fluorescein was used for fluorescent-guided resection of a pediatric brain tumor under a yellow 560-nm light filter.

Disclosures

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

Statement of Authorship

AA was responsible for acquisition and interpretation of data, drafting and revising the manuscript. CMH, AG, MH, and CM were responsible for data acquisition and revising the manuscript. CK and DS were responsible for the conception and design of the study, acquisition and analysis of data, and revising the manuscript. All authors approved the final manuscript for publication.

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