Glioblastoma is an aggressive primary malignant brain tumor with a mean survival time in adults of 12–16 months after resection. Recurrent tumor can be found at the prior resection cavity, at a distant site, or anywhere else throughout the brain, including along the ependymal lining of the ventricles. It is known that a greater extent of tumor resection at initial presentation is associated with better survival outcome for patients with glioma. Likewise, the goal at repeat resection is the same—to achieve as extensive a resection as possible to decrease tumor burden, thereby improving overall patient survival time as well as quality of life. Although MRI is the standard method of preoperative tumor detection, MRI alone may not be able to completely visualize the full extent of diffuse infiltrative glial tumors. In cases where there is a concern for diffuse tumor spread, supplemental techniques for tumor detection such as intraoperative 5-aminolevulinic acid (5-ALA) may be helpful in linking the recurrence to the primary site. Here we describe a case of recurrent GBM, in which the lesion identified 7 years after initial resection was found to be tracking along the subependymal and ependymal layers of the lateral ventricle connecting the recurrence to the previous tumor site.

Magnetic resonance imaging may not completely detect the presence of diffuse tumor infiltrating the ependymal or subependymal spaces. Therefore, adjunct intraoperative use of fluorescence-assisted visualization with 5-ALA may be helpful in highlighting and detecting infiltrative tumor to accurately detect tumor burden and distinguish it from a separate multicentric recurrence.

(http://thejns.org/doi/abs/10.3171/2013.1.JNS121537)

**Key Words**
- glioma
- 5-aminolevulinic acid
- brain tumor
- ependyma
- oncology

Abbreviations used in this paper: EGFR = epidermal growth factor receptor; GBM = glioblastoma; 5-ALA = 5-aminolevulinic acid.
Subependymal spread of glioblastoma

Case Report

Clinical Presentation. This 56-year-old right-handed man presented with distant tumor recurrence seen on MR images. Seven years earlier (in 2005), the patient presented with a gradually worsening central scotoma. After retinal and optic nerve evaluation, MRI of the brain revealed a 2.8 × 1.8–cm bilobed rim-enhancing lesion with peripheral nodularity in the right occipital lobe (Fig. 1). He underwent gross-total resection of the lesion, and a diagnosis of WHO Grade IV GBM was confirmed by pathological examination. Subsequently, he was treated with temozolomide and radiation therapy followed by Rindopepimut (CDX-110) (Cellindex Therapeutics), an EGFR V3 peptide vaccine drug.

Four years later (in 2009), a lesion was noted on MRI in the right cerebellum. This was accompanied by worsening visual field symptoms thought to represent focal visual seizures. A biopsy of the new lesion was performed. The results were consistent with astrogliosis, and the patient was subsequently treated with Avastin and CDX-110. Despite therapy, his symptoms progressed, and MRI showed hemorrhagic areas at the prior biopsy site. Therefore, Avastin was discontinued.

Seven years after the initial resection (2012), he again reported more frequent transient visual disturbances. An MRI study revealed 3 new foci of contrast enhancement in the right temporal lobe (Fig. 2A and B). The first was 2.4 × 1.3 cm and the second was 2.1 × 1.5 cm, with central necrosis located in the right anterior temporal pole and the right anterior superior temporal gyrus, respectively. The third nodular lesion measured 4 mm in diameter and was located just lateral to the lateral wall of the temporal horn of the right lateral ventricle. MR spectroscopy of these lesions revealed elevation of the lactate and choline peaks, consistent with recurrent tumor. In addition, a subtle area of FLAIR signal abnormality surrounding the 4-mm nodule and running in the anatomical subependymal region at the anterior portion of the right temporal horn of the lateral ventricle was detected (Fig. 2C and D). Because of evidence of tumor recurrence on MRI and worsening visual disturbances, the patient was offered resection of these new lesions. It should be noted that the primary site in the occipital lobe did not demonstrate tumor recurrence.

Surgery. To aid with intraoperative tumor localization, the patient took an oral dose of 5-ALA approximately 4 hours prior to surgery. A craniotomy was performed to expose the right temporal region, and with the aid of Brainlab guidance, the tumor identified on MRI was resected (Fig. 3A). Next, 400-nm blue light was employed to visualize 5-ALA activity in the tumor at the base of the resection cavity. Fluorescent signal in the tumor and along the wall of the right lateral ventricle was visualized (Fig. 3B and C). Using the fluorescence as a guide,
the subependymal extension of tumor was detected and much of it was surgically resected leaving the faint ALA fluorescent enhancement along the ependymal wall of the ventricle (Fig. 3C). Postoperative MRI revealed gross-total resection of the three enhancing lesions seen in the right temporal lobe.

Pathology Results. Histopathological analysis of the tumor was performed by neuropathologists at our institution, and the diagnosis was consistent with WHO Grade IV GBM (Fig. 4). Hematoxylin and eosin staining revealed extensive areas of necrosis within the tumor, surrounded by peripheral palisading cells. Fluorescence in situ hybridization analysis was positive for PTEN deletion at chromosome 10. In addition, the DNA methylation assay was positive for CpG methylation of the MGMT promoter, EGFR amplification was negative, and approximately 15% of tumor cells analyzed were positive for p53. Though histopathological testing for 5-ALA is not performed on surgical tumor specimens, the tumor analyzed included tissue confirmed intraoperatively to be positive for fluorescent signal as seen in Fig. 3C.

Discussion

The standard multimodal therapy for treatment of this aggressive primary brain tumor includes resection followed by chemotherapy and radiation therapy.13 With this treatment, the average survival time for patients without MGMT promoter methylation is 12–14 months. Of those patients with MGMT promoter methylation who are treated with temozolomide after resection—as was the case for the patient presented here—46% have a 2-year overall survival.5 We describe a patient who has long outlived both of these projected timelines.

This patient initially presented with subtle visual field changes. Tumor progression was marked years later by increasing transient visual field deficits. There are other descriptions of similar symptoms—described as visual seizures—in the literature associated with occipital lobe GBM.5 Preoperative MRI at the time of recurrence suggested that the patient had distant and distinct recurrent disease—that is, multicentric recurrence. However, intraoperatively, 5-ALA fluorescence confirmed that the faint subependymal FLAIR signal abnormality on MRI was, in fact, ependymal and subependymal tumor dissemination from the original site in the occipital lobe.

![Intraoperative Images](image_url)

**Fig. 3.** Intraoperative images. **A:** Intraoperative screenshots from Brainlab neuronavigation with probe at the base of the resection cavity at the level of the subependymal lining of the right lateral ventricle. The tip of the probe is pointing to the 4-mm Gd-enhancing nodule and surrounding FLAIR signal on MRI. Diffusion tensor imaging functional white matter pathways are also seen. **B and C:** Corresponding intraoperative microscope images under white light illumination (B) and under blue light (400 nm) (C). The base of the resection cavity is visualized here and shows complete resection of the nodule (B). Subependymal and ependymal tumor spread is visualized by 5-ALA in pink fluorescence under blue light illumination (C).

![Histopathology](image_url)

**Fig. 4.** Histopathology. Hematoxylin and eosin staining performed on formalin-fixed tumor resected intraoperatively. Viewed under white light at 40× (left) and 200× (right) magnification, diffuse hypercellularity, areas of necrosis with surrounding peripheral palisading cells, and multiple mitotic figures consistent with a diagnosis of WHO Grade IV GBM are noted.
Subependymal spread of glioblastoma

Goals of Surgery at Tumor Recurrence and Intraoperative Use of 5-ALA Fluorescence

It has been demonstrated in the literature that at the time of initial diagnosis, a greater extent of resection portends a better survival outcome. Specifically, if 78% of the tumor can be resected, this yields a significant increase in survival.9 Beyond that, an increasing advantage is reached from 95% to 100% extent of resection. The patient described here did undergo a radiological gross-total resection at the initial time of tumor presentation and had 7 years without recurrence, thereby supporting a goal of gross-total resection. Repeat resection for recurrent GBM has been shown to increase quality of life as well as length of survival.1,6 However, Gorlia et al.3 (2012) show that performance status is the major prognostic factor when determining overall survival and progression-free survival in patients with recurrent GBM.

At the time of recurrence, the surgical goal was initially to achieve a gross-total resection. The preoperative administration of 5-ALA has been shown to increase the success rate of gross-total resection from 36% using conventional visualization to 65% with 5-ALA fluorescence.5,12 With the assistance of 5-ALA—mediated tumor fluorescence, tumor was seen to be tracking along the subependymal and ependymal lining of the right lateral ventricle. In fact, the 3 foci seen on preoperative MRI were identified not as distinct distant areas of recurrence, but instead were contiguous distal extensions of ependymal spread of recurrent GBM. Five-ALA confirmed the FLAIR signal seen on MRI to be diffuse tumor and identified the extent of tumor burden far more completely than MRI was able to do.

Conclusions

This case illustrates the potential to distinguish distant tumor recurrence without a connection to the primary site from ependymal spread of GBM from the site of tumor origin with the intraoperative use of 5-ALA. While this use of 5-ALA may not influence the ultimate outcome, it is a useful surgical adjuvant to identify infiltrative tumor along the ependymal wall versus gliosis or radiation reaction.

Acknowledgment

The authors would like to acknowledge William Dillon, M.D., Chief of Neuroradiology at the University of California, San Francisco, for extensively reviewing the MR images for this manuscript.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Berger. Analysis and interpretation of data: Cage, Pekmezci. Drafting the article: Cage. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Berger. Study supervision: Berger.

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Manuscript submitted August 6, 2012.
Accepted January 17, 2013.
Please include this information when citing this paper: published online February 19, 2013; DOI: 10.3171/2013.1.JNS121537.