Editorial

Use of 5-aminolevulinic acid for visualization of low-grade gliomas

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Achieving gross-total resection of a brain tumor has been repeatedly shown as a significant prognostic indicator of patient survival across the spectrum of CNS neoplastic pathological entities, ranging from low-grade glioma (LGG) to highly aggressive tumors such as glioblastoma multiforme and anaplastic meningioma. Multiple surgical adjuncts have been added to neurosurgeons' armamentarium during the most recent decades so as to facilitate a greater extent of resection (EOR) in surgically treated tumors; these advancements include real-time neuronavigation, ultrasonography, and intraoperative MR imaging. Other technologies have also been introduced so as to complement the increased aggressiveness of tumor resection with avoidance of neurological morbidity; these include functional MR imaging, diffusion tensor imaging, and awake craniotomy coupled with cortical and subcortical stimulation. Few can argue with the demonstrated increases in tumor EOR afforded by these modalities; indeed, neuronavigation has found its way into the vast majority of operating theaters and has been adopted as a necessity within the US and most other countries' neurosurgical practices. Clearly, new surgical techniques that facilitate complete tumor resection, while maintaining patient safety, are always welcome additions to the field.

One relatively recent advance is the application of fluorescence-guided tumor resection. This concept is based on the observation that malignant cells preferentially accumulate fluorescent protoporphyrin IX after administration of 5-aminolevulinic acid (5-ALA), as compared to normal brain parenchyma. Protoporphyrin IX will emit red-violet light when stimulated with blue light. A 2006 study by Stummer et al reported an increase in tumor volume resection as well as a significant increase in 6-month progression-free survival in patients with glioblastoma multiforme in whom fluorescence-guided resection was performed, as compared to surgical controls. Subsequent studies have endorsed these findings, and have also shown that more aggressive pathological entities have a greater degree of fluorescence. This latter point is important, because low-grade tumors have not demonstrated an increased level of gross visual fluorescence relative to normal brain parenchyma, which renders this technology not generally applicable for WHO Grades I and II tumors.

The study by Sanai et al. in this issue of the JOURNAL OF NEUROSURGERY explores this topic by integrating 5-ALA tumor fluorescence targeting LGGs with the incorporation of intraoperative confocal microscopy. The authors surmised that the very low level of fluorescence in LGGs, although invisible to the surgeon's eye under the operating microscope, would be identified with confocal microscopy capable of magnification to 1000×. To this end, this proof-of-concept trial used intraoperative confocal technology to examine LGG tissue as well as surgical margins for assessment of EOR in 10 consecutive patients with presumed LGG. Tumor resection was facilitated by current techniques, including neuronavigation and the operating microscope in all patients, and preoperative functional MR imaging and intraoperative stimulation/awake craniotomy in a minority of patients. Intraoperative confocal microscopy was used at 3 points in the procedure: at the start of tumor resection, at midpoint, and at the time of presumed gross-total resection. Tissue examined in vivo was obtained by biopsy and analyzed ex vivo by both confocal microscopy and histological techniques; adjacent cortical and subcortical normal tissue was also assessed for fluorescence under the confocal microscope. Last, the final tumor EOR was dictated by evidence of continued confocal fluorescence at the surgical cavity periphery (in patients in whom further resection was deemed safe in terms of harming functional pathways).

The authors demonstrate a number of important concepts with this study. First, all presumed tumor tissue (at both the beginning and midpoint of the operation) did indeed fluoresce under the confocal microscope; although importantly, macroscopic fluorescence was not identified in any of these low-grade tumors. Additionally, no presumed normal tissue fluoresced in either modality. These key findings suggest a high sensitivity and specificity toward LGG/normal tissue differentiation. Second, there was a strong correlation between in vivo and ex vivo tissue analysis, emphasizing the robust nature of the portable confocal probe within the operating theater. Third, the technology added only approximately 10 minutes to the length of the total surgical procedure, suggesting ease of
use, and limiting the patient morbidity that accompanies increased operating time. Last, in a minority of patients the surgical plan was altered because of continued fluorescence at the presumed end of tumor resection (by implied visual gross-total resection), allowing for a greater tumor EOR.

There are some drawbacks to this study, although these largely relate to the small sample size and proof-of-concept nature of the investigation. The important point to understand is that this undertaking affirms further analysis of concomitant 5-ALA administration together with confocal microscopy-assisted LGG tumor resection. It is impossible to predict whether this technology will alter EOR in LGG surgery, or whether it will improve actual clinical outcomes for this patient subset. The authors note that the previous investigation of 5-ALA administration in surgery for high-grade glioma by Stummer et al. improved EOR and rates of gross-total resection; however, the study did not use so-called surgical-assist technologies such as neuronavigation and intraoperative MR imaging during tumor resection. Subsequent independent evaluations of these and other technologies, some in which 5-ALA was used, demonstrated parallel or even improved rates of resection over that seen with 5-ALA administration alone.3,6–8,11 Sanai et al. appropriately conclude that 5-ALA confocal microscopy–guided surgery may likewise improve resection rates in LGG when used independently, but any benefit may have to be evaluated in the context of the greater use of current surgical-assist technology.

As with any new surgical technique, continued improvement of the procedure protocol will optimize effectiveness and safety. Questions such as the appropriate number of peripheral surgical cavity sites to be sampled with confocal microscopy, and the correlation of confocal findings with intraoperative navigation imaging will help to refine the procedure and define its relationship to existing surgical technology. If the technology reported by Sanai et al. evolves into widespread practice for the resection of LGG, it may effectively compete with more expensive and time-consuming intraoperative adjuncts, such as intraoperative MR imaging. However, before this happens, prospective clinical trials with control groups and clinical outcome measures are needed for assessment of actual clinical effectiveness and safety. The Barrow ALA Intraoperative Confocal Evaluation (BALANCE) study, as described by the authors, will probably address many of these questions with its prospective design and use of control groups.

This preliminary study should be lauded in advancing an exciting technology that could alter current surgical intervention procedures for CNS tumors. Continued rigorous trials of safety, cost, technical feasibility, and tumor-free survival outcomes will delineate the permanence of 5-ALA confocal microscopy–guided resection. Perhaps one day we will not only define postoperative tumor burden by its radiographic presentation—achieving the "gross-total resection"—but also by the residual "microscopic tumor burden" revealed by this technology.

Disclosure
The authors report no conflict of interest.

References

Response
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ful editorial. Although our report offers only a first look at the integration of intraoperative confocal technology with 5-ALA for LGGs, we share their cautious enthusiasm. As they note, the impact of 5-ALA tumor fluorescence for high-grade glioma (HGG) resection in the absence of neuronavigation is unambiguous.1 Similar Class I evidence, however, does not exist for 5-ALA when neuronavigation, with its recognized extent of resection benefit, is incorporated. Interestingly, tumor fluorescence may be of greater value to the population with LGGs, where volumetrically complete resections are less common.1

To address these questions, the ongoing BALANCE trial includes 2 independent arms: 1) for LGGs, 5-ALA is combined with intraoperative confocal microscopy and neuronavigation; and 2) for HGGs, 5-ALA is used with neuronavigation alone. Intraoperative confocal technology remains in its infancy, yet for the neurosurgical oncolgist it may represent a critical step toward real-time cellular resolution of tumor infiltration.2

References


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