Commentary: 5-Aminolevulinic Acid and Contrast-Enhanced Ultrasound: The Combination of the 2 Techniques to Optimize the Extent of Resection in Glioblastoma Surgery

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Recent improvement in survival for patients with glioblastoma[1] could be ascribed, in part, to technical advances permitting intraoperative visualization of what was previously *in*visible,[2] empowering the neurosurgeon to achieve maximal safe resection. In addition to the microscope, there are at least a half-dozen genres of innovation: (i) intraoperative stimulation mapping[2]; (ii) 3-dimensional (3-D) neuronavigation[2,3]; (iii) functional and intraoperative magnetic resonance imaging (MRI)[2,4]; (iv) intraoperative ultrasonography[2,4,5]; (v) fiber tractography (diffusion tensor imaging [DTI])[2,6]; and (vi) fluorescence-guided surgery (fluorescein, 5-aminolevulinic acid [5-ALA], indocyanine green [ICG]).[2,7-13] Combinatorial approaches enable neurosurgical oncologists to obtain a minimal residual volume, translating into a meaningful gain of survival.[2,11,14-17] While balancing maximal resection with neurological preservation, each individual surgeon at distinct institutions must select, refine, and master the specific technology among a growing arsenal of available tools. What is the ideal combination? Are 2 modalities superior to 1? Or none? How many imaging tools are necessary? At what cost? Can we assess the incremental value of innovative technology?

The well-illustrated, innovative, accompanying retrospective single-institution analysis of survival outcomes[18] results from outcome data gleaned by diverse surgeons employing combinations of standard navigation in addition to 1 or more adjunctive imaging techniques: (a) contrast enhanced ultrasound (CEUS) and 5-ALA; [group "0"]; (b) 5-ALA [group "1"]; (c) CEUS [group "2"]; and (d) standard techniques without either CEUS or 5-ALA [group "3"]. Using multivariate analysis, the authors demonstrate superior outcomes, measured by overall survival (OS), progression-free survival (PFS), and extent of resection (EOR), when all three modalities are combined [group "0"]. These results support the concept that EOR strongly predicts PFS and OS in glioblastoma. The best outcomes were from the multimodality approach [group "0"], which also led to the highest number of supramarginal resections, by itself translating into survival benefit.[17] Because of the retrospective nature of the study, assignment to the groups was not randomized, but, instead, reflected the personal preferences of individual surgeons. Thus, there could be a bias in selection, experience, or technical proficiency. The surgeon who uses multiple technologies could be more fastidious, or more reliant on imaging technology than on the usual visual and haptic cues. Survival, as expected, was also linked to the age of the patient, the presence of the IDH1 mutation, and the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. The authors[18] make a strong argument for the combined use of these 2 intraoperative technologies, recognizing the strengths and limitations of each modality in isolation and the synergy in combination.

Dohrmann and Rubin[19] and Chandler et al[20] 4 decades ago, introduced ultrasound into the neurosurgical theater, noting the advantages of real-time visualization, manual control, and correction for brain shift and other deformations, at a relatively low cost. Over the years, the graphic resolution of the ultrasound has improved, and can now be integrated into navigation systems.[2,4,11,21] The group in Milan, led by Francesco DiMeco,[22] has extended the use of B-mode ultrasound using contrast-enhancement to dynamically assess vascular anatomy and hemodynamics, ie, angiosonography. CEUS is a real-time, repeatable, and relatively inexpensive technology that can locate glioma nodules before and after initial resection to limit unintentional, small residuals.[22] CEUS, understandably, has its drawbacks. "A contrast-specific algorithm, present only in high-end ultrasound equipment, is mandatory to obtain the required harmonic

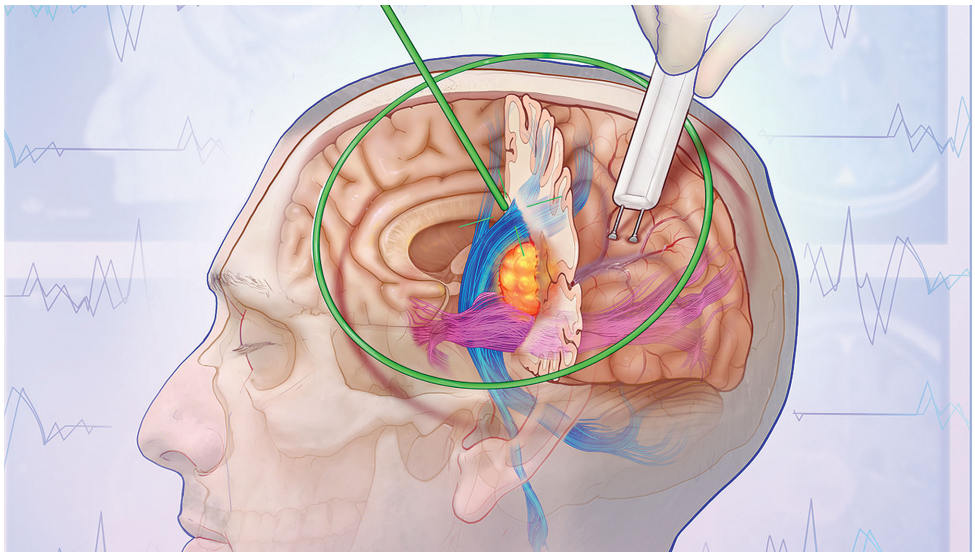

FIGURE. *Illustration of a multimodality approach to resection of an "inoperable" tumor in the left temporal-parietal area using a combination of (1) optically guided neuronavigation using a standard frameless navigation system (Curve™, Brainlab) integrated with the microscope (Pentero®, Zeiss) (green circle and probe); (2) cortical and subcortical stimulation (Ojemann electrodes); (3) DTI-tractography showing the corticospinal tracts (blue) and inferior longitudinal fasciculus/ inferior frontal-occipital fasciculus (ILF/IFOF) (lavender); and (4) ICG fluorescence (orange). Oncofunctional optimization results from the integration of innovative technology, the individual and collective experiences of dedicated neurosurgical oncologists, and the specific institutional rubric for tackling tumors affecting functional areas of the brain. [Artist: Eo Trueblood].*

imaging. Also, CEUS is operator-dependent, and therefore specific training is required to regulate the settings, such as mechanical index and ultrasound focus, as well as image interpretation".[22] The technique involves a sulfur-hexafluoride-filled, lipidic microbubble, echographic method, followed by a special contrast-tuned imaging algorithm, with dynamic display. Devascularization of the tumor by the surgeon during hemostasis ("vascular deafferentation") can also limit the value of CEUS.[18]

5-ALA is Food and Drug Administration (FDA)-approved and now widely used in glioma surgery.[2,4,7-11] Other agents, such as fluorescein[12] and ICG,[13] can also be used to directly visualize the tumor, and prevent inadvertent residual remnants. 5-ALA is based on direct tumor (cellular porphyrin) metabolism, while CEUS is predicated on density properties resulting from tumor angiogenesis, blood-brain barrier disruption, and "augmented vascularization".[18] False negatives with 5-ALA, as the authors note,[18] include tumors obscured by blood, overlapping brain tissue, or cottonoids, as well as deep tumors ("blind alleys"), or finger-like projections of amoeboid gliomas that cannot be directly visualized in orthogonal views. Satellite nodules covered by normal brain in a multifocal tumor would also go undetected. Prolonged exposure under the light from the microscope can weaken the fluorescence (photobleaching).[18]

Each institution, given individual and collective experiences, "learning curves," budgets, and culture, will develop its own rubric for oncofunctional optimization. At our institution (Figure), the neurosurgical palette offers a choice of incorporating one or more of the following 4 technologies: (i) 3-D neuronavigation integrated with the microscope tracking; (ii) ICG fluorescence[13]; (iii) intraoperative electrical stimulation (brain mapping)[2]; and (iv) fiber-tracking (DTI).[6] Taken together, to succinctly capture in a single metric the twin goals of maximizing resection while preserving function, we devised an "80/80 rule,"[23] achieving ≥80% EOR while maintaining a Karnofsky performance score (KPS) of ≥80 (or a combined oncofunctional score of ≥160); note that patients, postoperatively, generally have unchanged or improved KPS and that >20 points KPS drop is rare.[23]

Innovation never gets old. Just as ultrasound and fluorescence have moved into the operating room, emerging technologies—eg, transcranial magnetic stimulation,[2,24] connectomics,[25-27] and stimulated Raman histology with deep neural networks,[28] among others—promise to increase our ability to visualize and treat tumors within their functional contexts. By making the invisible visible, "inoperable" tumors will become operable[29] while achieving optimal oncological and functional outcomes.

Disclosures

The authors have no personal, financial, or institutional interests in any of the drugs, materials, or devices described in this article.

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