The Evolving Role of Neurosurgical Intervention for Central Nervous System Tumors

Pierpaolo Peruzzi, MD, PhD[a,*], Pablo Q. Valdes, MD, PhD[a], Manish K. Aghi, MD, PhD[b], Mitchel Berger, MD[b], Ennio Antonio Chiocca, MD, PhD[a], Alexandra J. Golby, MD[a,c]

KEYWORDS

• Neurosurgery • Brain tumors • Gliomas • Innovation • Multidisciplinary approach

KEY POINTS

- Neurosurgery has evolved technically and conceptually over the years to accommodate the expanding needs of the neuro-oncology team.
- The role of neurosurgery in the management of patients with brain tumor ranges from basic clinical care to facilitation of clinical trials, tissue collection, radiological-molecular correlates, and delivery of investigational and therapeutic agents.
- Oncologic neurosurgery is progressively shaping as a self-standing surgical subspecialty, fully integrated within the larger multidisciplinary neuro-oncology team.

INTRODUCTION

Modern neuro-oncology relies on a multidisciplinary approach to the treatment of central nervous system (CNS) malignancies, integrating tumor cytoreduction, histopathologic analysis, advanced imaging, molecular and genetic profiling, administration of novel therapies, and, with increasing frequency, the acquisition of tissue for pharmacodynamics and pharmacokinetics studies of investigational agents. Furthermore, over the years, there has been a significant evolution from a minimalistic approach (ie, treating tumors when symptomatic) to a proactive approach, (ie, treating tumors based on the prediction of their behavior).[1] In addition, there has been a growing

[a] Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Hale Building for Transformative Medicine, 60 Fenwood Road, Boston, MA 02115, USA; [b] Department of Neurological Surgery, University of California San Francisco, 505 Parnassus Avenue, San Francisco, CA 94117, USA; [c] Department of Radiology, Brigham and Women's Hospital/Harvard Medical School, Hale Building for Transformative Medicine, 60 Fenwood Road, Boston, MA 02115, USA
* Corresponding author.
E-mail address: pperuzzi@bwh.harvard.edu

Hematol Oncol Clin N Am 36 (2022) 63–75
https://doi.org/10.1016/j.hoc.2021.08.003 **hemonc.theclinics.com**

need for frequent pathology reappraisals in order to guide appropriate second-tier therapies.

As a consequence, neurosurgery had to progressively evolve to meet the challenges posed by this increase in the complexity of the treatment of neuro-oncologic patients and to respond to clinical and scientific questions, while maximizing safety, functional preservation, and management of emergent/urgent scenarios.

Most of the technical and conceptual advances that have occurred in the field of neurosurgical oncology over the past decades have been catalyzed by the still unfulfilled need to cure glioblastoma, the most common and lethal of CNS malignancies in adults, and, at the same time, a paramount topic of basic and translational research interest among brain tumors.

RELIEVING SYMPTOMS AND PROVIDING TISSUE

Neurosurgeons are often the first physicians to be involved in the care of patients with brain tumors, due to the fact that usually the most crucial needs are symptomatic relief from mass effect and tissue procurement for diagnosis. These have historically been the 2 essential pillars of oncologic neurosurgery and remain its main purpose. The importance of preserving patients' functional status has long been recognized as one of the most important prognostic factors; hence, the ability to perform well-planned and well-executed surgeries remains a fundamental expectation from neurosurgeons. The growing evidence that steroids, used generously in the past as effective "fixers" for surgery-related deficits, have important undesired effects, including an association with decreased survival[2] and known immunosuppressive properties,[3] is leading many to reconsider their use only when strictly necessary. This, in turn, has pushed the evolution of safer surgical techniques, such as a more widespread use of intraoperative neurophysiological and functional monitoring (motor evoked potentials, somatosensory evoked potentials; direct cortical and subcortical stimulation; awake surgery with language and/or motor mapping), together with progressively more accurate real-time imaging systems, ranging from neuronavigation to intraoperative MRI and ultrasounds. The gain in safety offered by these techniques has also allowed neurosurgeons to become generally more aggressive with lesions that, in the past, would have not been considered amenable to surgery. As a consequence, there are presently very few regions in the brain that are not surgically accessible, if the appropriate tools (imaging, equipment, magnification, and illumination), techniques, and monitoring strategies are used.

In regard to the pillar of tissue procurement, requirements and expectations have also evolved over time. This is in response to an increased level of complexity pertaining to anatomic pathology, genomic, transcriptomic, and epitranscriptomic analysis of tissue samples. This multilayered readout of tumor markers has become extremely relevant to guide the choice of appropriate therapies and inform prognosis and is now routinely performed in most of the centers with dedicated multidisciplinary neuro-oncologic expertise. It has been established that larger tumor samples usually provide a more complete representation of tumor heterogeneity, and the concordance between specimens deriving from either needle biopsy samples or open resections has been found to be as low as 50%.[4] Moreover, the need to provide additional tissue is a frequent requirement to satisfy eligibility criteria for enrollment in many clinical trials. As a consequence, significantly larger specimens are expected from the surgeon in comparison to what was customary in the past, and this often influences the decision to perform open craniotomies as opposed to less invasive, but also less yielding, needle biopsies.

IMPACTING OUTCOMES: THE QUEST FOR MAXIMAL TUMOR RESECTION AND HOW TO GET THERE

In addition to treating symptoms and providing diagnosis, surgery has a proven impact on prognosis. The first data supporting aggressive tumor resection as a favorable predictor for prolonged survival in patients with malignant glioma date back to the early 70s, but, as late as the 90s there was still debate whether this was true.[5] In the following decade, thanks to the widespread use of MRI, it has become possible to accurately measure tumor volumes and their postoperative residuals, particularly in regard to their contrast-enhancing component, and generate prognostic categories accordingly. It is now well accepted that survival in patients with high-grade glioma is positively affected if at least 70% to 80% of enhancing tumor is resected, and a progressive benefit is observed as the resection increases to the 98% to 100% range.[6] The impact of extent of resection has been found to be generally true also for low-grade gliomas.[1]

As the field continues to evolve, the concept of supratotal resection (ie, extending beyond the standard radiologically accepted tumor boundaries) has been championed by some: it has recently been proposed that younger patients (<65 year old) with glioblastoma might actually benefit from more aggressive resections extending past the contrast-enhancing component and into the fluid-attenuated inversion recovery hyperintense region.[7] Along the same line, the concept of anatomic resection, that is, a resection that is guided more by the structural and functional boundaries of specific regions of the brain affected by the tumor, rather than by the tumor itself, is progressively gaining traction, when safely feasible. For example, growing data suggest that lobectomies are superior to focused tumor resection when the lesions are localized in relatively "silent" brain regions, as the anterior temporal lobe.[8]

In the current era of tumor genomics, we are witnessing a progressive integration of molecular analysis with surgical decision making: specific biological and genetic features of the tumor, such as IDH1-R132 mutation,[9] 1p/19q codeletion,[10] and MGMT methylation,[11] have all been found to be associated with improved survival when combined with gross total or supratotal resection.

These data will need to be confirmed over time and by multiple studies before being accepted as universally true, but this has already started to change the approach to patient care, with some advocating obtaining a preresection diagnosis (either by liquid biopsy, imaging, or tissue biopsy) in order to first define the tumor's genetic features to proactively decide how radical a resection is to perform.[9]

Other important recommendations have been recently provided with regard to the role of surgery in recurrent glioblastoma. Historically, the decision to reoperate on patients with glioblastomas progression after adjuvant therapy was mainly left to surgeon preference rather than guided by data. Multiple studies now suggest that reresection confers a survival advantage (as long as it does not come at the expense of functional impairment)[12] but also only if a complete or near complete resection of the contrast-enhancing tumor is achieved, as subtotal resection has been associated with worse outcome than medical treatment only.[13] This, once more, puts the neurosurgeon in the midst of therapeutic decision-making among the neuro-oncology team, as the initial assessment on the feasibility (and safety) of an aggressive operation will determine the next steps in the treatment algorithm of this particularly challenging scenario.

The concept of safe radical resection and its therapeutic possibilities has evolved in parallel to numerous technical advancements that have significantly facilitated this goal.

- *Brain mapping*: this technique is usually reserved for tumors located in eloquent regions of the brain, such as speech areas, primary sensory/motor cortex, or

subcortical tracts. Several techniques can be used during surgery to define the exact location of these structures and thus avoid iatrogenic injury. One such option is the so-called awake craniotomy, where the patient remains conscious during the operation and kept engaged to perform tasks such as naming objects, and moving extremities to command, whereas transient currents are applied systematically with a handheld stimulator to small surfaces of the brain in a systematic fashion. These electrical pulses briefly and reversibly interfere with the function of the touched brain, and when this affects eloquent brain, it results in observable changes in the patient's ability to perform the corresponding task.[14] Alternatively, for lesions affecting the motor pathway, a direct electrical stimulation can be applied to the brain during a standard operation under general anesthesia. In this case, the readout is obtained by analyzing the presence, amplitude, and muscle specificity of motor evoked potentials triggered by the stimulation.[15] Both techniques help define a "map" of silent versus eloquent brain regions, allowing to use safe surgical corridors, and maximize resection while minimizing functional impairment.

- *Neuronavigation*: computerized, neuronavigation systems, which allow real-time localization of anatomic intracranial structures into a preoperative (or intraoperative) image set, are a relatively recent introduction, dating back to the late 80s,[16] although only gaining broad clinical adoption in the last 20 years. Substantially working as a GPS tracker for the brain, these devices allow the neurosurgeon to remain oriented within the operative field and facilitate the recognition of areas involved by tumor. Integration of preoperative advanced imaging such as functional MRI and tractography into the navigation dataset, known as functional neuronavigation, can facilitate the estimation of the location of critical cortical and subcortical areas (**Fig. 1**). Neuronavigation, however, is limited by

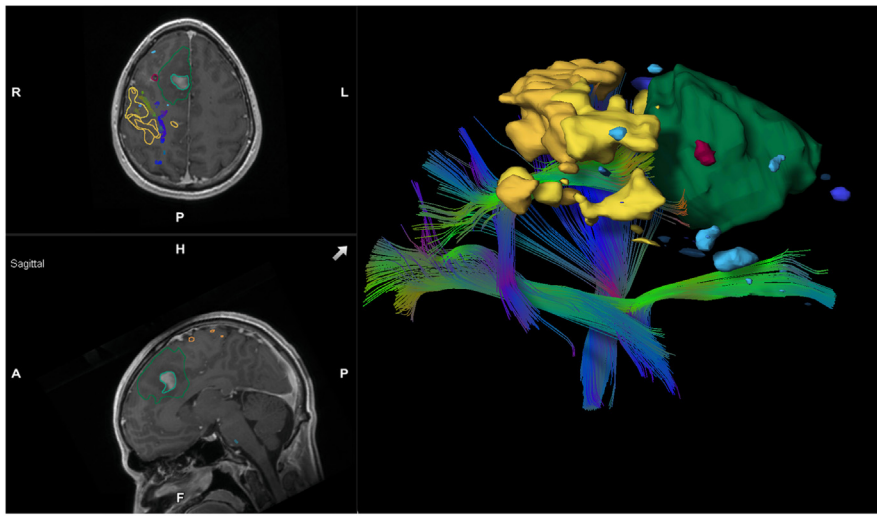

Fig. 1. Functional MRI (fMRI): in the left panels, axial and sagittal T1 sequences with gadolinium show the location of a right frontal tumor (*green lines*). The right primary motor cortex is underlined in yellow and the corticospinal tract in blue. These data can be further integrated via neuronavigation software to build 3-dimensional models (*panel on right*) that help the neurosurgeon orienting within the operative field, maximizing tumor resection and avoiding critical brain structures.

its reference to a static set of images, which renders it unable to account for tissue resection and other sources of brain shift occurring during the procedure.

- *Intraoperative MRI*: dating back to the early 1990s, intraoperative MRI (iMRI) allows to obtain detailed brain imaging during a neurosurgical operation. iMRI is used to confirm intraoperatively whether a lesion has been completely resected or if residual abnormal tissue is still present in the resection cavity. The new information provided by the updated intraoperative imaging helps the surgeon in deciding whether further resection is warranted. Its use has been consistently associated with higher frequency of gross total resections of intrinsic brain tumors.[17,18]
- *Fluorescence-guided surgery*: this strategy takes advantage of the fluorescent properties of metabolic byproducts of chemicals that can be administered orally before surgery (5′ aminolevulinic acid [5-ALA]) or chemicals that are themselves fluorescent following intravenous administration during surgery (fluorescein, indocyanine green). After administration, these chemicals are preferentially taken up by tumor cells and become visible within the operating field under appropriate lighting conditions with specialized filters (**Fig. 2**). When using 5-ALA, normal brain appears dark, whereas tumor tissue appears a red-pink color, facilitating visualization and removal.[19] Issues still remain regarding sensitivity and specificity of these methods, particularly regarding their use in low grade tumors.
- *In situ tissue optical sampling*: a novel, still experimental technology in neurosurgery, Raman spectroscopy,[20] consists of a laser-emitting probe that scans the tumor resection cavity in real time. The differences in chemical composition between the tumor and the brain can be determined by the different Raman optical spectra collected by the probe. A sophisticated analysis of these data using machine learning techniques provides a nondisruptive tissue analysis whose specificity and sensibility is comparable to standard histopathological processing[21] and can be used to inform surgical decision-making in real time.

In situations where tumors are deemed unresectable, when they have recurred beyond a reasonable control by standard means, or in patients too frail to undergo surgery, the minimally invasive option of laser interstitial thermal therapy (LITT) is a relatively new tool within the neurosurgeon's armamentarium used to delay tumor growth and/or provide symptomatic treatment of symptomatic radionecrosis.

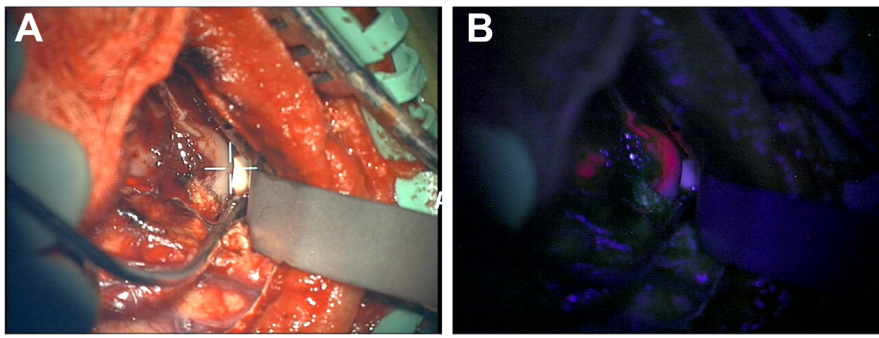

Fig. 2. *Intraoperative visualization of tumor with 5-ALA*. (*A*) Magnified view of the operating field using a Zeiss Pentero microscope shows the resection cavity with no obvious visible tumor. (*B*) Same view through a BLUE400 filter (670–710 nm wavelength) shows 2 small areas in pink that suggest residual tumor.

LITT consists of a fiberoptic probe, which is stereotactically inserted into the tumor, and produces tumor ablation using laser thermal energy, whose delivery is controlled in real time using MR thermography and that causes coagulative necrosis of the tissue surrounding the probe as well as cell death based on the time–temperature area under the curve over a larger region up to approximately 1 cm from the probe[22] (**Fig. 3**). Major applications of LITT in neuro-oncologic patients include treatment of deep-seated lesions or radiation necrosis.[23] In the latter, it is used as a possible second-line alternative to steroids or bevacizumab in unresponsive patients or those who cannot tolerate those drugs. In recurrent glioblastoma, LITT treatment resulted in progression-free survival of 5 to 5.7 months and overall survival of 7 to 10 months.[24,25] Interesting novel use of this technique concern its reported ability to temporarily open the blood brain barrier and thus improve drug delivery[26] and also to activate both the innate and adaptive immune system by causing local inflammation and release of tumor antigens.[27]

ENABLING THERAPEUTIC AND SCIENTIFIC ADVANCEMENTS

There has been a widespread trend in the design of modern oncologic phase 0 and phase 1 clinical trials to investigate and quantify tumor pharmacokinetics and pharmacodynamics after drug administration. As a consequence, tissue procurement during experimental treatments is becoming a well-established practice, often required in robustly designed protocols, and this applies to CNS malignancies as well, which, due to the limitations imposed by the blood brain barrier (BBB), are frequently impermeable to systemic drugs unless proven otherwise. In contrast to many other cancers, which can be easily biopsied by interventional radiologists, the access to CNS malignancies is a neurosurgery prerogative. The involvement of neurosurgeons in these trials is thus crucial, particularly in circumstances where granular details, such as

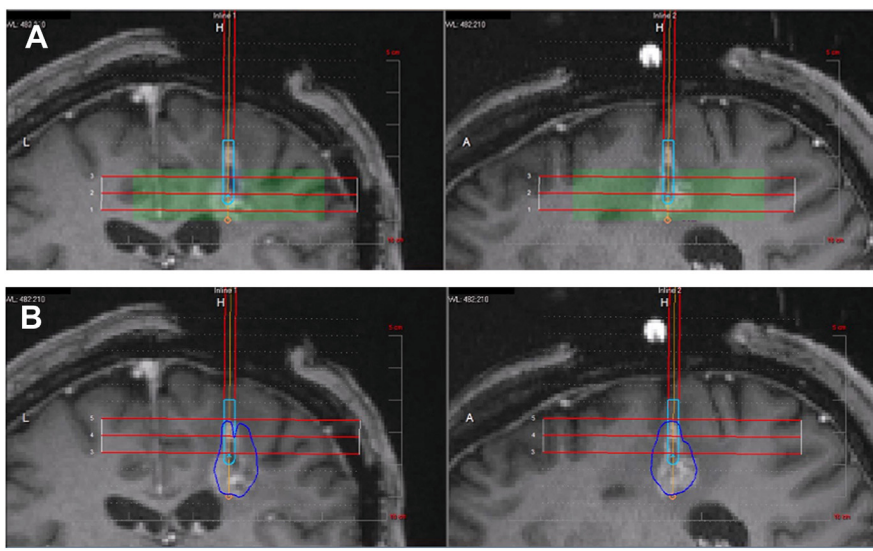

Fig. 3. *MRI-guided LITT-based ablation of a recurrent left frontoparietal GBM*. (*A*) Coronal and sagittal T1-weighted images after gadolinium administration showing placement of the electrode in the region of contrast enhancement. (*B*) Real-time MRI measurement of the area of the tumor receiving the therapeutic thermal coagulation (*blue line*).

differential drug penetration in contrast-enhancing versus nonenhancing areas of the tumor, are sought.

Targeted tissue sampling has fundamental value both for the sake of providing correct diagnoses (eg, appropriate grading of heterogeneously enhancing lesions) as well as for providing necessary tissue correlations with other experimental, less invasive diagnostic means. Targeted sampling of tumor regions that have different MRI characteristics has allowed, for example, the development of molecular-radiological correlates and the validation of MR spectroscopy and other novel MRI protocols[28,29] for noninvasive tissue profiling.

In recent years there has also been a progressive interest in using stereotactic mass spectrometry sampling as a more immediate and accurate tissue readout for intraoperative molecular diagnosis.[30] Similarly, a growing number of clinical trials nowadays resort to the use of mass spectrometry from fresh intraoperative specimens to quantify drug penetration in different parts of the tumor, analyze its pharmacodynamics, and thus help characterizing important parameters of experimental drugs, including their effective bioavailability to the tumor tissue, and the degree of their effectiveness.[31]

Another major contribution by neurosurgeons continues to be the regular collection of tumor specimens, cerebrospinal fluid, and adjacent brain samples, which over the past 20 years has allowed the thriving of consortia such as the Tumor Cancer Genome Atlas program (https://portal.gdc.cancer.gov/projects/TCGA-GBM), which have revolutionized our understanding of the genetic landscape of tumors. It is expected that neurosurgical interventions that are not immediately related to patient care, but that are vital for the optimization of new treatment or diagnostic protocols, will continue to grow in number and significance, while respecting the necessary safety requirements.

DRIVING THERAPEUTIC AND SCIENTIFIC ADVANCEMENTS

The limit imposed by the BBB to reaching CNS malignancies with therapeutic agents continues to be a major factor supporting the need to develop and perfect locoregional administration strategies. This explains why neurosurgeons, by virtue of their direct access to brain tumors, have been at the forefront in the quest for new strategies to treat these tumors.

A noticeable example includes the ideation of biodegradable, drug-releasing polymer wafers impregnated with the DNA alkylating agent carmustine.[32] These are applied in the tumor resection cavity at the end of a standard operation, where, over the course of the following days, while being degraded, they release high concentration of chemotherapy in the surrounding tissue, to directly kill invasive tumor cells at the tumor-brain interface. Updated iterations of such local delivery methods continue to be proposed, including hydrogel-based formulations engineered to release chemotherapeutics, nucleic acids, or engineered stem cells with antitumor properties.[33,34]

Another significant endeavor is the growing field of oncolytic virotherapy, which is based on the use of genetically engineered viruses that can selectively replicate and kill tumor cells but not normal cells.[35] Several different virus strains, including polio,[36] herpes simplex virus 1 (HSV1)[37] and adenoviruses,[38] have shown encouraging, albeit preliminary, evidence of survival benefit in subgroups of patients with recurrent high-grade glioma. In recent developments, new-generation viruses have been additionally armed with transgenes to expand their mechanisms of action and augment their antitumor efficacy: noticeable examples are the use of prodrug-activating genes such as the herpes thymidine kinase gene[39] or genes encoding immune stimulating cytokines, such as interleukin-12.[40]

Convection-enhanced delivery (CED) is another example of a neurosurgery-led effort to increase the delivery of therapeutics to brain tumors. CED is a minimally invasive technique whereby highly active but poorly penetrant antitumor agents (such as antibodies),[41] toxins,[42] large cytotoxic chemotherapeutics,[43] or virus particles,[36] which are not suitable for systemic administration, are delivered into the tumor through one or more cannulas that are stereotactically inserted into the tumor. The cannulas are then connected to a pump that generates a continuous pressure gradient, forcing the compounds to diffuse into the tumor in a way that is unaffected by the BBB.[44]

EMBRACING DIFFERENT TOOLS

The neurosurgical armamentarium extends beyond the standard invasive procedures commonly used with brain tumors (ie, open craniotomies and stereotactic biopsies). One interesting and potentially relevant strategy borrowed from vascular neurosurgeons is the use of endovascular techniques to selectively administer chemotherapy drugs directly in the arteries that are in close proximity to the tumor. Intraarterial drug delivery dates back to the 1960s and was envisioned as a tool to limit systemic toxicity derived from the common intravenous or oral administration routes.[45] Because material and technical progress has ensued in the following decades, intracranial arteries can be selectively cannulated up to the tiny branches that directly feed the tumor (superselective intraarterial infusion), thus further decreasing the amount of drug delivered to other parts of the CNS, as well as to the rest of the body.[46] This administration modality can be further combined with temporary disruption of the BBB by concurrent administration of mannitol or other hyperosmolar solutions.[47] Some evidence of clinical and radiological response has been observed with recurrent glioblastoma.[48]

Another noninvasive technique, MRI-guided focused ultrasound (MRgFUS) was borrowed from the functional neurosurgery world, where it has been successfully used for selective brain lesioning[49] and initially experimented, with little effect, as a direct antitumor strategy to induce tumor coagulative necrosis.[50] In recent advances, MRIgFUS is used to produce temporary and spatially localized permeabilization of the BBB and thus augment chemotherapy delivery.[51] Low-energy FUS is able to disrupt the BBB when combined with the intravenous delivery of microbubbles (an ultrasound contrast agent) that oscillate inside of the blood vessels to temporarily disrupt the tight junctions and likely several other mechanisms.[52] A clinical trial studying the safety and radiological response of this approach followed by systemic temozolomide administration in patients with newly diagnosed glioblastoma (GBM) is currently ongoing and has so far proved to be well tolerated with encouraging radiological correlates (NCT03551249). Future clinical trials are envisioned in recurrent GBM and low-grade glioma, also investigating permeabilization to different drugs, such as carboplatin.

TOWARD A LAB-IN-A-PATIENT REVOLUTION

Neurosurgery has a rich tradition for advancing science directly from the operating room. The understanding of brain circuitry, for example, has significantly benefitted from the collection of neuronal firing patterns during otherwise standard neurosurgical procedures such as deep brain stimulation. Adapting this approach to neuro-oncology, neurosurgeons have championed the use of intratumoral microdialysis, which entails the stereotactic insertion of specialized cannulas into the tumor. The lumen of the cannula is separated by a semipermeable membrane that allows the selective filtration and continuous collection of the tumor's interstitial fluid.[53] This strategy is used to obtain important information concerning tissue penetration of systemic chemotherapy agents across the BBB,[54] characterization of tumor metabolites,[55] and,

more recently, changes in the tumor's cytokine profile in response to immunotherapy.[56]

Finding strategies to inform effective chemotherapy in a personalized manner remains a major goal in neuro-oncology. Currently, chemotherapy selection is based on an inferential process whereby it is assumed that certain genetic mutations observed from the analysis of tumor specimens (eg, *EGFR* or *CDK4* amplification) will result in sensitivity to drugs targeting those molecules. This approach has currently not resulted in any significant therapeutic breakthrough for GBM,[57] and the only clinically relevant and generally accepted predictor of response to a specific drug (temozolomide) to date remains the methylation status of the *MGMT* gene promoter.[58] A neurosurgery-driven clinical trial is currently exploring the feasibility to test an array of many different chemotherapeutics simultaneously in situ and directly on patients, and this is done using a drug-releasing microdevice,[59] which is inserted into the tumor at the time of surgery (**Fig. 4**). The device is filled with microdoses of many different drugs, which are released into the tumor in a spatially defined fashion. After an appropriate incubation time, the device is removed together with a cuff of surrounding tumor, and the specimen is analyzed to establish which drugs have resulted in the most relevant antitumor effect and how each drug has affected the tumor microenvironment. These data can then inform the most effective compound to be used systemically for any individual patient, in an "ultrapersonalized" manner (NCT04135807).

FINAL CONSIDERATIONS

Since its inception, greater than a century ago, neurosurgery has represented the fundamental trait-d'union between clinical management, scientific investigation, and

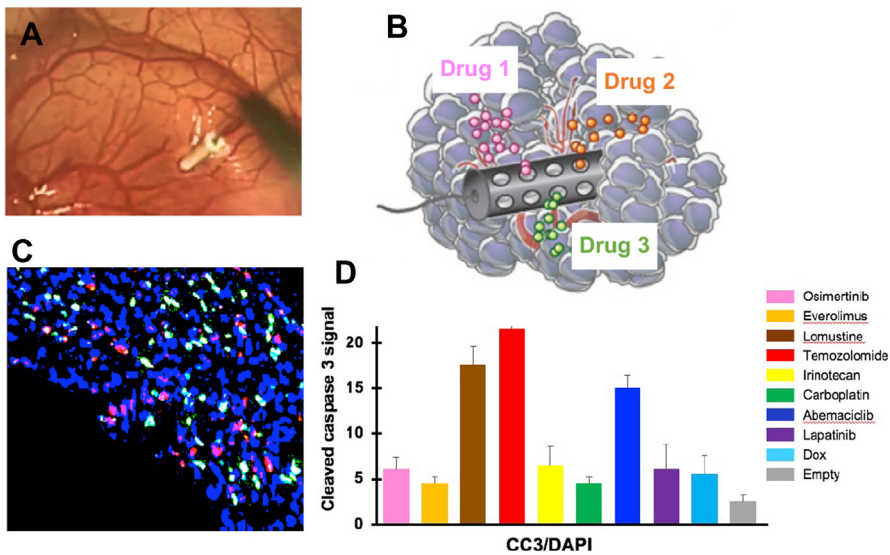

Fig. 4. *Intraoperative comparison of chemotherapy efficacy by implanted microdevices.* (*A*) Small microdevices filled with different drugs are inserted into the tumor. (*B*) Microdevices release their drug content in a locoregional fashion within the tumor. (*C*) The recovered specimen at the end of surgery is processed, and markers of cell death are analyzed (pink = activated caspase 3; blue = cell nuclei; green = Ki-67). (*D*) Comparison chart with relative antitumor efficacy among 8 different drugs tested in the same tumor specimen. CC3, cleaved caspase 3.

therapeutic advancements in the field of brain tumors. During the years, oncological neurosurgery has evolved as a self-standing subspecialty, due to technical progress, equipment improvement, evolution of therapeutic paradigms, and the progressively crucial role that it plays in the execution of complex therapeutic strategies and modern clinical trials.

CLINICS CARE POINTS

- Extent of tumor resection is associated with improved survival in patients with brain tumor.
- Emerging technologies have significantly improved safety of surgical resection and functional outcomes.
- Ad-hoc, guided tumor sampling has significantly facilitated the molecular characterization of brain tumors.
- Neurosurgeons continue to be fundamental to the advancement of new therapies for brain tumors.

DISCLOSURE

P. Peruzzi has received research support from NIH, Neurosurgery Research and Education Foundation, and The Sontag Foundation. He is named inventor on patents related to noncoding RNA technology. E.A. Chiocca is currently an advisor to Advantagene Inc., Alcyone Biosciences, Insightec, Inc., DNAtrix Inc, Immunomic Therapeutics, Seneca Therapeutics, GSK, and Voyager Therapeutics and has equity interest in DNAtrix, Immunomic Therapeutics, and Seneca Therapeutics; he has also advised Oncorus, Merck, Tocagen, Ziopharm, Stemgen, NanoTx., Ziopharm Oncology, Cerebral Therapeutics, Genenta. Merck, Janssen, Karcinolysis, Shanghai Biotech, and Sangamo Therapeutics. He has received research support from NIH, US Department of Defense, American Brain Tumor Association, National Brain Tumor Society, Alliance for Cancer Gene Therapy, Neurosurgical Research Education Foundation, Advantagene, NewLink Genetics, and Amgen. He also is a named inventor on patents related to oncolytic HSV1 and noncoding RNAs.

REFERENCES

1. Lima GL, Zanello M, Mandonnet E, et al. Incidental diffuse low-grade gliomas: from early detection to preventive neuro-oncological surgery. Neurosurg Rev 2016;39(3):377–84.
2. Pitter KL, Tamagno I, Alikhanyan K, et al. Corticosteroids compromise survival in glioblastoma. Brain 2016;139(Pt 5):1458–71.
3. Dixit KS, Kumthekar PU. Optimal Management of Corticosteroids in Patients with Intracranial Malignancies. Curr Treat Options Oncol 2020;21(9):77.
4. Jackson RJ, Fuller GN, Abi-Said D, et al. Limitations of stereotactic biopsy in the initial management of gliomas. Neuro Oncol 2001;3(3):193–200.
5. Quigley MR, Maroon JC. The relationship between survival and the extent of the resection in patients with supratentorial malignant gliomas. Neurosurgery 1991; 29(3):385–8 [discussion: 388–9].
6. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115(1):3–8.
7. Molinaro AM, Hervey-Jumper S, Morshed RA, et al. Association of Maximal Extent of Resection of Contrast-Enhanced and Non-Contrast-Enhanced Tumor With

Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma. JAMA Oncol 2020;6(4):495–503.
8. Schneider M, Potthoff AL, Keil VC, et al. Surgery for temporal glioblastoma: lobectomy outranks oncosurgical-based gross-total resection. J Neurooncol 2019;145(1):143–50.
9. Beiko J, Suki D, Hess KR, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol 2014;16(1):81–91.
10. Garton ALA, Kinslow CJ, Rae AI, et al. Extent of resection, molecular signature, and survival in 1p19q-codeleted gliomas. J Neurosurg 2020;134(5):1357–67.
11. Incekara F, Smits M, van der Voort SR, et al. The Association Between the Extent of Glioblastoma Resection and Survival in Light of MGMT Promoter Methylation in 326 Patients With Newly Diagnosed IDH-Wildtype Glioblastoma. Front Oncol 2020;10:1087.
12. Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 2014;120(4):846–53.
13. Suchorska B, Weller M, Tabatabai G, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro Oncol 2016;18(4):549–56.
14. Kim SS, McCutcheon IE, Suki D, et al. Awake craniotomy for brain tumors near eloquent cortex: correlation of intraoperative cortical mapping with neurological outcomes in 309 consecutive patients. Neurosurgery 2009;64(5):836–45 [discussion: 345–6].
15. Suarez-Meade P, Marenco-Hillembrand L, Prevatt C, et al. Awake vs. asleep motor mapping for glioma resection: a systematic review and meta-analysis. Acta Neurochir (Wien) 2020;162(7):1709–20.
16. Watanabe E, Watanabe T, Manaka S, et al. Three-dimensional digitizer (neuronavigator): new equipment for computed tomography-guided stereotaxic surgery. Surg Neurol 1987;27(6):543–7.
17. Mislow JM, Golby AJ, Black PM. Origins of intraoperative MRI. Neurosurg Clin N Am 2009;20(2):137–46.
18. Masuda Y, Akutsu H, Ishikawa E, et al. Evaluation of the extent of resection and detection of ischemic lesions with intraoperative MRI in glioma surgery: is intraoperative MRI superior to early postoperative MRI? J Neurosurg 2018;131(1):209–16.
19. Stummer W, Pichlmeier U, Meinel T, et al, ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7(5):392–401.
20. Desroches J, Jermyn M, Pinto M, et al. A new method using Raman spectroscopy for in vivo targeted brain cancer tissue biopsy. Sci Rep 2018;8(1):1792.
21. Hollon T, Lewis S, Freudiger CW, et al. Improving the accuracy of brain tumor surgery via Raman-based technology. Neurosurg Focus 2016;40(3):E9.
22. Hawasli AH, Kim AH, Dunn GP, et al. Stereotactic laser ablation of high-grade gliomas. Neurosurg Focus 2014;37(6):E1.
23. Hong CS, Deng D, Vera A, et al. Laser-interstitial thermal therapy compared to craniotomy for treatment of radiation necrosis or recurrent tumor in brain metastases failing radiosurgery. J Neurooncol 2019;142(2):309–17.

24. Montemurro N, Anania Y, Cagnazzo F, et al. Survival outcomes in patients with recurrent glioblastoma treated with Laser Interstitial Thermal Therapy (LITT): A systematic review. Clin Neurol Neurosurg 2020;195:105942.
25. Thomas JG, Rao G, Kew Y, et al. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. Neurosurg Focus 2016;41(4):E12.
26. Leuthardt EC, Duan C, Kim MJ, et al. Hyperthermic Laser Ablation of Recurrent Glioblastoma Leads to Temporary Disruption of the Peritumoral Blood Brain Barrier. PLoS One 2016;11(2):e0148613.
27. Shin DH, Melnick KF, Tran DD, et al. In situ vaccination with laser interstitial thermal therapy augments immunotherapy in malignant gliomas. J Neurooncol 2021;151(1):85–92.
28. Barajas RF Jr, Phillips JJ, Parvataneni R, et al. Regional variation in histopathologic features of tumor specimens from treatment-naive glioblastoma correlates with anatomic and physiologic MR Imaging. Neuro Oncol 2012;14(7):942–54.
29. Croteau D, Scarpace L, Hearshen D, et al. Correlation between magnetic resonance spectroscopy imaging and image-guided biopsies: semiquantitative and qualitative histopathological analyses of patients with untreated glioma. Neurosurgery 2001;49(4):823–9.
30. Eberlin LS, Norton I, Orringer D, et al. Ambient mass spectrometry for the intraoperative molecular diagnosis of human brain tumors. Proc Natl Acad Sci U S A 2013;110(5):1611–6.
31. Randall EC, Lopez BGC, Peng S, et al. Localized Metabolomic Gradients in Patient-Derived Xenograft Models of Glioblastoma. Cancer Res 2020;80(6):1258–67.
32. Brem H, Mahaley MS Jr, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. J Neurosurg 1991;74(3):441–6.
33. Erthal LCS, Gobbo OL, Ruiz-Hernandez E. Biocompatible copolymer formulations to treat glioblastoma multiforme. Acta Biomater 2021;121:89–102.
34. Li Q, Wijesekera O, Salas SJ, et al. Mesenchymal stem cells from human fat engineered to secrete BMP4 are nononcogenic, suppress brain cancer, and prolong survival. Clin Cancer Res 2014;20(9):2375–87.
35. Martuza RL, Malick A, Markert JM, et al. Experimental therapy of human glioma by means of a genetically engineered virus mutant. Science 1991;252(5007):854–6.
36. Desjardins A, Gromeier M, Herndon JE 2nd, et al. Recurrent Glioblastoma Treated with Recombinant Poliovirus. N Engl J Med 2018;379(2):150–61.
37. Markert JM, Razdan SN, Kuo HC, et al. A phase 1 trial of oncolytic HSV-1, G207, given in combination with radiation for recurrent GBM demonstrates safety and radiographic responses. Mol Ther 2014;22(5):1048–55.
38. Lang FF, Conrad C, Gomez-Manzano C, et al. Phase I Study of DNX-2401 (Delta-24-RGD) Oncolytic Adenovirus: Replication and Immunotherapeutic Effects in Recurrent Malignant Glioma. J Clin Oncol 2018;36(14):1419–27.
39. Chiocca EA, Aguilar LK, Bell SD, et al. Phase IB study of gene-mediated cytotoxic immunotherapy adjuvant to up-front surgery and intensive timing radiation for malignant glioma. J Clin Oncol 2011;29(27):3611–9.
40. Chiocca EA, Yu JS, Lukas RV, et al. Regulatable interleukin-12 gene therapy in patients with recurrent high-grade glioma: Results of a phase 1 trial. Sci Transl Med 2019;11(505):eaaw5680.
41. ouweidane MM, Kramer K, Pandit-Taskar N, et al. Convection-enhanced delivery for diffuse intrinsic pontine glioma: a single-centre, dose-escalation, phase 1 trial. Lancet Oncol 2018;19(8):1040–50.

42. Heiss JD, Jamshidi A, Shah S, et al. Phase I trial of convection-enhanced delivery of IL13-Pseudomonas toxin in children with diffuse intrinsic pontine glioma. J Neurosurg Pediatr 2018;23(3):333–42.
43. Wang JL, Barth RF, Cavaliere R, et al. Phase I trial of intracerebral convection-enhanced delivery of carboplatin for treatment of recurrent high-grade gliomas. PLoS One 2020;15(12):e0244383.
44. Jahangiri A, Chin AT, Flanigan PM, et al. Convection-enhanced delivery in glioblastoma: a review of preclinical and clinical studies. J Neurosurg 2017;126(1):191–200.
45. Owens G, Javid R, Belmusto L, et al. Intra-Arterial vincristine therapy of primary gliomas. Cancer 1965;18:756–60.
46. D'Amico RS, Khatri D, Reichman N, et al. Super selective intra-arterial cerebral infusion of modern chemotherapeutics after blood-brain barrier disruption: where are we now, and where we are going. J Neurooncol 2020;147(2):261–78.
47. Rapoport SI. Osmotic opening of the blood-brain barrier: principles, mechanism, and therapeutic applications. Cell Mol Neurobiol 2000;20(2):217–30.
48. Chakraborty S, Filippi CG, Burkhardt JK, et al. Durability of single dose intra-arterial bevacizumab after blood/brain barrier disruption for recurrent glioblastoma. J Exp Ther Oncol 2016;11(4):261–7.
49. Fiani B, Lissak IA, Soula M, et al. The Emerging Role of Magnetic Resonance Imaging-Guided Focused Ultrasound in Functional Neurosurgery. Cureus 2020;12(8):e9820.
50. Ram Z, Cohen ZR, Harnof S, et al. Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. Neurosurgery 2006;59(5):949–55 [discussion: 955–6].
51. McDannold N, Zhang Y, Supko JG, et al. Blood-brain barrier disruption and delivery of irinotecan in a rat model using a clinical transcranial MRI-guided focused ultrasound system. Sci Rep 2020;10(1):8766.
52. Arvanitis CD, Askoxylakis V, Guo Y, et al. Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood-tumor barrier disruption. Proc Natl Acad Sci U S A 2018;115(37):E8717–26.
53. Pierce CF, Kwasnicki A, Lakka SS, et al. Cerebral Microdialysis as a Tool for Assessing the Delivery of Chemotherapy in Brain Tumor Patients. World Neurosurg 2021;145:187–96.
54. Lin YL, Wu MT, Yang FY. Pharmacokinetics of doxorubicin in glioblastoma multiforme following ultrasound-Induced blood-brain barrier disruption as determined by microdialysis. J Pharm Biomed Anal 2018;149:482–7.
55. Roslin M, Henriksson R, Bergström P, et al. Baseline levels of glucose metabolites, glutamate and glycerol in malignant glioma assessed by stereotactic microdialysis. J Neurooncol 2003;61(2):151–60.
56. Lynes J, Jackson S, Sanchez V, et al. Cytokine Microdialysis for Real-Time Immune Monitoring in Glioblastoma Patients Undergoing Checkpoint Blockade. Neurosurgery 2019;84(4):945–53.
57. Taylor JW, Parikh M, Phillips JJ, et al. Phase-2 trial of palbociclib in adult patients with recurrent RB1-positive glioblastoma. J Neurooncol 2018;140(2):477–83.
58. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003.
59. Jonas O, Landry HM, Fuller JE, et al. An implantable microdevice to perform high-throughput in vivo drug sensitivity testing in tumors. Sci Transl Med 2015;7(284):284ra57.