Neuro-Oncology
24(S6), S33–S41, 2022 | https://doi.org/10.1093/neuonc/noac170

Updates in intraoperative strategies for enhancing intra-axial brain tumor control

Adela Wu, Janet Yuling Wu, and Michael Lim

Department of Neurosurgery, Stanford Health Care, Stanford, California, USA (A.W., M.L.); Stanford School of Medicine, Stanford, California, USA (J.Y.W.)

Corresponding Author: Michael Lim, MD, Department of Neurosurgery, Stanford Health Care, 300 Pasteur Drive, Stanford, CA 94304, USA (mklim@stanford.edu).

Abstract

To ensure excellent postoperative clinical outcomes while preserving critical neurologic function, neurosurgeons who manage patients with intra-axial brain tumors can use intraoperative technologies and tools to achieve maximal safe resection. Neurosurgical oncology revolves around safe and optimal extent of resection, which further dictates subsequent treatment regimens and patient outcomes. Various methods can be adapted for treating both primary and secondary intra-axial brain lesions. We present a review of recent advances and published research centered on different innovative tools and techniques, including fluorescence-guided surgery, new methods of drug delivery, and minimally invasive procedural options.

Keywords

glioma | intraoperative imaging | metastatic brain tumor | minimally invasive

Neurosurgical oncology revolves around safe and optimal extent of brain tumor resection, which further affects and dictates subsequent treatment regimens and patient outcomes. More than 700 000 Americans currently live with a brain tumor diagnosis.[1] Maximal safe resection has gained traction recently as the goal of brain tumor surgery. For example, previously published studies on cohorts of patients with low- and high-grade glioma point to survival benefits conferred by high degree of extent of resection.[2,3] However, intra-axial tumors, particularly diffuse and infiltrating lesions, located in eloquent areas present challenges in maximizing extent of resection.

With technological advances in intraoperative imaging, surgical tools, and other adjuncts, neurosurgeons can achieve better tumor control, with excellent clinical outcomes and safety profiles as well. With an overview of recent developments in intraoperative technologies aimed to safely increase margins of resection, this review also discusses neurosurgery's role in providing local tumor control beyond surgical resection, from minimally invasive modalities to creative drug delivery methods, such as blood-brain barrier (BBB) disruption or intracavitary treatment.

Strategies to Reduce Surgical Risk

Surgical planning and approach influence the safety of intricate operations required to remove infiltrating tumors or lesions located in eloquent regions. We present an overview and updates in research on awake craniotomies and functional brain mapping and their roles in reducing surgical complications while increasing extent of tumor resection.

Awake Craniotomies

Awake craniotomies have been one of the mainstays of intraoperative techniques for enhanced brain lesion control while maintaining patient safety. Eligible patients have supratentorial tumors located near eloquent cortical regions, involved in language, sensory or motor functions. Contraindications to offering awake craniotomies include severe neurological deficits precluding participation in intraoperative neurologic testing, large tumor volume with midline shift, anxiety disorder, and persistent cough. The

procedure itself is an orchestrated effort that involves not only the neurosurgical team but also coordinated input by anesthesiologists and neurologists.

A randomized controlled trial compared awake craniotomy and neurosurgery under general anesthesia (GA) for patients with brain lesions located within eloquent cortex (Table 1).[4,5] However, the control group had greater extent of tumor resection (>90% tumor resection: 57.2% in awake group vs 73.6% in GA group) and more neurologic improvement in the immediate postoperative period, though techniques have improved since 2007. A systematic review of seven studies published between 2001 and 2017 about patients with brain metastases demonstrated rates of gross total resection (GTR) in 61% of patients and supratotal resection in 32% of patients.[6] A series of 82 patients with eloquent glioblastoma (GBM) also demonstrated greater extent of resection with awake craniotomies and allowed for more T2-FLAIR region excision than with GA, leading to lower risks of recurrence.[7] Awake craniotomies do not lead to significant adverse events like linguistic impairments or executive dysfunction.[8] Another case series compared patients who underwent awake craniotomy against those under GA; both groups also had intraoperative MRI. There were no statistically significant differences in surgical complications between the two surgical groups, although the patients who underwent awake craniotomies had lower rates of permanent postoperative neurologic deficit (5% vs 20%) and higher rates of unchanged or enhanced neurologic status after surgery (80% vs 65%).[9]

Connectomes and Functional Pathway Maps for Surgical Planning

With increasingly sophisticated MRI, diffusion tensor imaging (DTI), and tractography, neurosurgeons can study brain lesions' relations to critical functional pathways before operating. Respecting surgical margins defined by functional tracts enhances extent of resection and preservation of functional status. However, interpretation of these tracts may be muddled by imaging quality and any inherent characteristics of parenchyma altered by the tumor, such as overlapping fibers and edema. The Human Connectome Project was a multi-institutional effort to improve diffusion imaging, ultimately resulting in an impressive map of functional tracts and connections within the human brain.[17] Even so, for practical purposes, neurosurgeons benefit from utilizing DTI, functional MRI, and connectome analysis as adjuncts to surgical planning, particularly for infiltrative tumors.

Brain mapping techniques include cortical stimulation or functional MRI, although these are limited by area. There are two major types of functional MRI, task-oriented and resting state, the latter of which is more commonly used for preoperative planning.[18] Unfortunately, gliomas may alter the reliability of functional MRI output due to blood perfusion changes. Connectome analysis encompasses both functional localization and natural brain networks. Hart et al investigated five GBM patients' resting-state function MRI scans with connectome analyses and were able to reconstruct neural connections, which were disrupted by tumor involvement.[19]

There are multiple critical white matter tracts within the human brain, such as the corticospinal tract, which is responsible for communicating signals regarding motor control. DTI visualizes white matter fibers due to their relationships with the direction of water diffusivity. Wu et al conducted a randomized controlled trial with DTI for glioma resection, which resulted in improved clinical outcomes and extent of resection in the DTI group (Table 1).[10] Patients within the DTI group also had superior Karnofsky Performance Scale scores regardless of glioma diagnosis. DTI can also decrease surgery time, particularly for awake craniotomies, and act as an additional confirmatory tool for neurosurgeons.[20] Furthermore, another study indicated that DTI planning and modeling of intact white matter fascicles can predict probability of GTR.[21] Functional brain mapping and connectomics can help neurosurgeons safely continue to push the boundaries of tumor resections.[22]

Increasing Margins of Resection

The goals of improving brain tumor control go hand in hand with safely increasing extent of resection through visualizing and possibly expanding margins of resection. Strategies, such as intraoperative MRI, are still routinely used, and newer adjunct tools, including use of fluorescing agents, can also enhance patient survival through optimizing extent of resection. This review also presents other developments in intraoperative techniques and technology, such as tubular retractors and Raman spectroscopy, which allow surgeons to access deep-seated lesions and determine residual tumors in real-time for additional resection.

Intraoperative MRI

Intraoperative MRI has been in common usage for brain tumor resection since at least 2002, when Fahlbusch et al studied the utility of intraoperative 1.5 Tesla MRI for glioma surgery.[23] Intraoperative MRI was historically regarded as an additional fail-safe should neuronavigation become increasingly unreliable due to brain shift and cerebrospinal fluid loss over the course of surgery. In 36.2% of surgeries, intraoperative MRI influenced subsequent decisions to return for further resection of visualized residual tumor, significantly reducing the final tumor volumes for both low-grade and high-grade gliomas; 41.2% of GTR were attributed to additional surgery following intraoperative MRI.[23] Intraoperative MRI has a beneficial effect of improving not only extent of tumor resection but also survival outcomes for glioma patients.[24,25] In one series, the use of intraoperative MRI was a significant predictive factor of GTR.[25] A randomized controlled trial found that more patients who underwent intraoperative MRI had GTR of their tumors compared to the control cohort (96% vs 68%, $P = .023$) (Table 1).[11] Similar findings were recapitulated in another randomized trial, with superior rates of GTR of malignant glioma with the aid of intraoperative MRI (86.4% vs 53.5%, $P < .001$) (Table 1).[12] For facilities capable of incorporating an intraoperative

Table 1 Studies With Level I Evidence for Various Intraoperative Techniques for Brain Tumor Control

Technique	Authors	Year	Experimental Arms (n)	Cohort Description	Findings
Awake craniotomies	Gupta et al.[4]	2007	Awake craniotomy(26) vs Craniotomy under general anesthesia (27)	Patients with intrinsic brain tumors in eloquent regions	*>90% tumor excision:* (Awake) 57% of cohort (Control) 73.7% of cohort *Immediate neurologic improvement* ($P = .03$): (Awake) 18.7% of cohort with motor improvement and 14.3% of cohort with speech improvement (Control) 35.7% of cohort with motor improvement and 62.5% with speech improvement
Functional pathway maps for surgical planning	Wu et al.[10]	2007	Diffusion tensor imaging (DTI) (118) vs Conventional neuronavigation (120)	Patients with gliomas	*Gross total resection for high-grade glioma* ($P < .001$): (DTI) 74.4% (Control) 33.3% *Postoperative motor deficit for entire cohort* ($P < .001$): (DTI) 15.3% (Control) 32.8% *Median survival for high-grade glioma* ($P = 0.048$): (DTI) 21.2 months (Control) 14.0 months
Intraoperative MRI	Senft et al.[11]	2011	Intraoperative MRI-guided surgery (29) vs Conventional microsurgery (29)	Patients with contrast-enhancing gliomas	*Complete tumor resection* ($P = .023$): (MRI) 90% of cohort (Control) 68% of cohort *New postoperative deficits* ($P = 1.0$): (MRI) 13% of cohort (Control) 8% of cohort
	Wu et al.[12]	2014	Intraoperative MRI-guided surgery (58) vs Conventional neuronavigation (56)	Patients with newly diagnosed WHO grade II-IV gliomas, KPS ≥70	*Gross total resection* ($P < .001$): (MRI) 86.36% of cohort (Control) 53.49% of cohort
Fluorescence-guided surgery	Stummer et al.[13]	2006	5-ALA fluorescence-guided surgery (139) vs Conventional craniotomy with white light (131)	Patients with newly diagnosed malignant glioma	*Complete resection of contrast-enhancing tumor* ($P < .0001$): (5-ALA) 65% of cohort (Control) 36% of cohort *6-month progression-free survival* ($P = .0003$): (5-ALA) 41.0% of cohort (Control) 21.1% of cohort
Brachytherapy	Laperriere et al.[14]	1998	Conventional radiation + brachytherapy boost (71) vs Conventional external RT (69)	Patients with malignant astrocytoma	*Median survival* ($P = .49$): (Brachytherapy) 13.8 months (Control) 13.2 months
	Selker et al.[15]	2002	125-iodine brachytherapy + external beam RT + BCNU (133) vs External beam RT + BCNU (137)	Patients with newly diagnosed malignant gliomas	*Median survival*: (Brachytherapy) 68.1 weeks (Control) 58.8 weeks
Convection-enhanced delivery	Kunwar et al.[16]	2010	Convection-enhanced delivery of cintredekin besudotox (183) vs Gliadel wafers (93)	Patients with recurrent GBM	*Median survival* ($P = .476$): (Convection-enhanced delivery) 36.4 weeks (Control) 35.3 weeks

Abbreviations: 5-ALA, 5-aminolevulinic acid; BCNU, β-chloro-nitrosourea/carmustine; GBM, glioblastoma; KPS, Karnofsky Performance Scale; RT, radiation therapy.
Studies included in this table are randomized controlled trials.[5]

MRI suite, it is a powerful tool for enhancing tumor control.

Fluorescence-Guided Surgery

Several fluorophore agents, including fluorescein, indocyanine green, and 5-aminolevulinic acid (5-ALA), have been studied for fluorescence-guided surgery (FDG). 5-ALA is the only Food and Drug Administration (FDA)-approved agent for FDG for high-grade gliomas.[13] The FDA recommends administering an oral 20 mg/kg dose of 5-ALA between 2 and 4 hours before anesthesia induction. Neurosurgeons then use special filters on operating microscopes to visualize 5-ALA fluorescence to determine margins and residual tumor. Of note, potential adverse effects include photosensitivity reactions.

Overall, 5-ALA can enhance the neurosurgeon's ability to achieve better tumor resection. Stummer et al investigated outcomes of malignant glioma resection following 5-ALA administration with imaging and clinical follow-up (Table 1).[13] The 5-ALA intervention group had clinically meaningful results with 65% of patients with completely resected contrast-enhancing tumor and better 6-month progression-free survival (41% [32.8-49.2] vs 21.1% [14.0-28.2], $P = .0003$) without increase in significant adverse effects. Stummer's study also informed approval of 5-ALA in Europe and FDA guidance for 5-ALA administration timing, though other investigators have examined different timing (>4 hours) of 5-ALA administration before high-grade glioma resection.[26] In this case, clinical survival outcomes were similar to standard protocol.

Multiple case series highlight 5-ALA's utility in facilitating safe tumor resection for various patient populations.[27,28] 5-ALA has a good safety profile for pediatric patients. Labuschagne describes 19 pediatric patients with diagnoses of ependymomas or medulloblastomas.[29] Fluorescence guidance was deemed to be useful in 63% of the cases, but 5-ALA fluorescence did not correlate significantly with eventual GTR. The same surgeon also examined a cohort of eight pediatric patients diagnosed with brainstem gliomas, which are notoriously difficult to access and resect.[29] Similarly, administration of 5-ALA was safe, though substantial fluorescence was only detected in three cases. The pediatric series highlight a downside of 5-ALA use, in that the resultant fluorescence may not be strong enough for detection and tumor resection. Diffuse low-grade gliomas in particular do not exhibit reliable 5-ALA fluorescence in 24.5% of tumors, according to a systematic review of 12 studies, suggesting that low-grade gliomas convert fewer amounts of fluorescent metabolite from 5-ALA.[30]

5-ALA fluorescence combined with photodynamic therapy (PDT) is under investigation for additional antitumor cytotoxic effect. Intraoperative PDT targets residual tumor cells following FDG, as lasers activate a 5-ALA metabolite and induce local production of cytotoxic free radicals. GBM patients who underwent 5-ALA FDG and PDT experienced no significant adverse effects, and there was a 60% progression-free survival rate at 12 months (median 17.1 months).[31] A systematic review included 251 brain tumor patients with mostly high-grade gliomas who underwent interstitial PDT and 5-ALA as a photosensitizer.[32] Tumor response rate to PDT was good (92%) with temporary and permanent morbidity rates of 5% each.

Another combinatorial treatment regimen consists of 5-ALA and contrast-enhanced ultrasound (CEU). Using both 5-ALA and CEU simultaneously improved the extent of tumor resection ($P = .0003$) as well as the number of supramarginal tumor resections. CEU-guided surgical decision-making for deep tumors and lesions with irregular borders, and it could be an additional tool for enhancing intraoperative tumor control alongside 5-ALA FDG.[33]

Tubular Retractor Systems

Surgeons may use tubular retractor systems to dissect toward tumors in deep locations. This method, however, can still result in secondary surgical lesions and vascular injury. A meta-analysis of retrospective and case-control studies on patients with deep-seated brain tumors showed that GTR was achieved in 80.6% of procedures using tubular retractors.[34] Additionally, the complication rate was 10.9%, much lower than the 29% reported when using traditional retractors for resection.[34] Though available data are limited by a small sample size, there was a decrease in length of ICU stay and increase in postoperative survival.[35] Without tubular retractors, several patients' tumors would have only been treated medically, helping increase patient survival.[35] Further analyses with larger patient populations are warranted to investigate cost-effectiveness and patient outcomes.

Other analyses included comparisons of different tubular retractor systems. There were no significant differences in gross vs partial tumor resection, postoperative length of stay, complication rates, and mortality rates.[36,37] In a large, multi-institutional review, nearly 72% of surgeries achieved GTR for various brain tumors.[36] The mean depth of tumors operated on was 4.35 cm, and 9.7% of patients developed complications.[36] However, most studies are limited to individual institutions' experiences, and the field requires prospective, randomized trials to understand the true impact of tubular retraction systems on patient outcomes.[35–37]

Raman Spectroscopy

Intraoperative Raman spectroscopy detects margins of infiltrative intrinsic brain tumors, providing rapid molecular characterization of tissue based on Raman active functional groups of proteins, lipids, and nucleic acids. Though most studies on Raman spectroscopy are investigational, the method shows promise for fast, nondestructive intraoperative differentiation of neoplastic vs normal tissue.

While strategies like FDG and intraoperative imaging lack sensitivity at tumor margins, Raman spectroscopy utilizes microscopic characterization to determine residual neoplastic cells at the edges of unprocessed tissue samples. This method shows good ability to differentiate

between low-grade and high-grade gliomas as well as intracranial metastases and meningiomas from unprocessed surgical specimens.[38] Raman spectroscopy identified residual infiltrating glioma at rates comparable to immunohistochemistry and hematoxylin and eosin staining.[39] One study also found a machine-learning model based on Raman spectroscopy superior to 5-ALA-based FDG at determining GBM tissue with 0.07 sensitivity, 1.00 specificity, and 0.24 accuracy (P = .0009).[40] A recent trial compared pathologists' analyses of histologic samples with stimulated Raman histology and deep convolutional neural networks to predict diagnoses in an automated way.[41] Raman-based interpretation of fresh specimens was noninferior to conventionally processed tissue analysis (94.6% vs 93.9%). As more surgeons and centers adopt Raman spectroscopy as part of intraoperative practice, there may be additional studies investigating this imaging modality and its accuracy for diagnosing brain tumors and determining tumor margins.

Treatment Delivery Beyond Surgical Resection

Neurosurgery provides opportunities for use of minimally invasive modalities and treatment delivery beyond tumor resection. For instance, carmustine wafers placed in the surgical bed are one form of local drug delivery, and other more recent technologies include convection-enhanced delivery (CED) and various methods to temporarily disrupt the BBB for improved drug permeability.[42]

Laser Interstitial Thermal Therapy

Laser interstitial thermal therapy (LITT) is a minimally invasive procedure that may allow for better access to lesions in deep or difficult locations as well as potentially decrease surgery recovery time and hospital length of stay. LITT can treat both primary and metastatic tumors, with the majority of use for patients with recurrent tumors, whose prior treatments have failed, or who suffer from radiation necrosis.[43–45]

In a phase I clinical trial, median survival was 19.8 months, and there were no recurrences of metastases within the treated zone for up to 30 months of follow-up.[46] Additionally, LITT has been proven more effective than bevacizumab when treating for radiation necrosis from brain metastases.[44] Median overall survival increased from 15.2 months with bevacizumab to 24.8 months with LITT.[44] Patients treated with LITT also had a decrease in radiation necrosis-induced lesion volume at 1-year follow-up.[44] The Laser Ablation After Stereotactic Radiosurgery (LAASR) study found that LITT helped to preserve quality of life, cognition, and Karnofsky Performance Scale score, especially since it provided treatment to patients without other viable options.[45] Unfortunately, many studies are constrained by either retrospective design or lack of comparison to open surgery treatments.[44,45] These results, particularly survival data, must also be considered in the context of systemic disease burden for patients with metastatic cancer. Thus, additional prospective observational or randomized trials are needed to truly determine the significance of the efficacy of LITT as a local therapy, particularly for brain metastases.

In the Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate system (LAANTERN) study, 9% of patients developed adverse events.[43] This statistic is much lower than those reported for open craniotomies for deeply located brain tumors and is consistent with that of biopsies alone, though further safety studies are warranted.[43]

LITT can also disrupt the BBB for up to 6 weeks postoperatively in a preliminary study.[47] This could present a unique opportunity to treat with antitumor therapeutics that do not cross the BBB. Persistent elevation of serum brain-specific enolase in 8 of the 20 patients postoperatively suggests that LITT may also enhance systemic immunological response against brain tumors for some patients, suggesting immunomodulatory potential.[47] There is currently an active phase I clinical trial investigating the role of LITT in disturbing the BBB for recurrent GBM (NCT03341806). Further studies are needed to determine whether LITT can extend quality of life, progression-free survival, and overall survival.[47]

Focused Ultrasound

Focused ultrasound (FUS) has multiple effects when applied to brain tumor cases, depending on delivered frequencies. For one, FUS at low intensities can temporarily disrupt the BBB, allowing for enhanced drug delivery to the privileged central nervous system space.[48] Several preclinical studies indicate safe and successful drug delivery with increased BBB permeability.[49–51] Furthermore, BBB permeability in a murine model can be maintained for up to 24 hours after a FUS treatment without adverse effects like edema or hemorrhage.[52] In addition, FUS-induced cavitation creates bubbles within liquids, leading to different results, such as inducing tissue necrosis within tumors, increasing coagulation volume at the focus, and promoting temporary permeability of cellular walls and blood vessels.[48]

Five high-grade glioma patients underwent low-intensity MRI-guided FUS for BBB opening along with systemic administration of doxorubicin or temozolomide.[53] Liquid chromatography-mass spectrometry analysis of resected tumor tissue from subsequent surgeries showed increased concentrations of the administered chemotherapies where the BBB was opened. Another study involved patients with recurrent GBM receiving intravenous carboplatin, demonstrating longer median progression-free survival (4.11 vs 2.73 months) and median overall survival (12.94 vs 8.64 months) in those who had evidence of BBB disruption on MRI after FUS sonication compared to patients who did not.[54]

Numerous preclinical cancer models have demonstrated immunomodulatory effects following FUS administration, which may portend improved tumor control for patients with immunotherapy. Several aspects of the immune microenvironment appear to be influenced by FUS, such as

increasing circulating populations of pro-inflammatory cytokines, activating antigen-presenting cells and macrophages, and creating tumor debris and release of tumor antigens.[55–57] Both thermal and mechanical levels of FUS ablation exerted immunomodulatory effects and promoted a pro-inflammatory microenvironment, enhancing immunotherapy action, in a murine breast cancer model.[58]

FUS has an additional role as non-invasive thermal ablation. The FDA has approved FUS within neurosurgery for patients with essential tremors or certain forms of Parkinson's disease. With intraoperative MRI guidance, FUS ablation coordinates sequential coagulation of overlapping treatment volumes with pulses of high-power sonification. Benefits of utilizing FUS in this manner include achieving precise treatment delivery while minimizing effects to surrounding parenchyma. Coluccia et al reported the first instance of MRI-guided high-intensity focused ultrasound (HIFU) used successfully and safely for a patient with recurrent GBM without causing neurologic deficits.[59] Intracavitary interstitial HIFU is another form of this technology that involves precise placement of a catheter with enhanced ability to tailor ablative heating patterns. Neurosurgeons also have the option to perform concurrent brain biopsies or deliver additional treatments with the catheters. Currently, there are no actively recruiting clinical trials involving FUS for thermal ablation of brain tumors, although one trial encompasses obtaining liquid biopsies along with HIFU for brain tumor patients (NCT04940507).

Brachytherapy

For well-circumscribed brain tumors, brachytherapy could be a safe and effective strategy to establish better tumor control. Common forms of brachytherapy involve iodine-125, phosphorus-32, iridium-192, and cesium-131 seeds, which can either be injected as prescribed doses into tumors as interstitial therapy or implanted into the tumor resection bed as intracavitary therapy.[60] Benefits of intracavitary brachytherapy to limit tumor growth include prompt initiation of radiation therapy following surgery, while interstitial brachytherapy is minimally invasive and highly localized.

In a retrospective analysis, brachytherapy resulted in increased median overall survival for patients with GBM (16 months vs 9 months, $P < .001$), although the group receiving brachytherapy was younger and had smaller tumors.[61] Two randomized controlled trials compared standard high-grade glioma treatment with and without brachytherapy involving iodine-125 implants (Table 1).[14,15] Laperriere et al evaluated brachytherapy as adjunct therapy to external beam radiation therapy for patients with malignant astrocytoma and found no statistically significant difference in median survival between treatment arms.[14] Similarly, the Brain Tumor Cooperative Group NIH Trial 87-01 for patients with malignant glioma found no long-term survival benefit.[15] However, other case series have shown some promise for iodine-125-based brachytherapy. Adjuvant brachytherapy for six patients with initially large-volume or inaccessible gliomas resulted in tumor decrease, which allowed for eventual GTR for all patients.[62] Iodine-125 as either first-line or adjuvant therapy for patients with low-grade gliomas resulted in low complication rate of 16% and 5- and 10-year overall survival rates of 72% and 43%.[63]

Recent brachytherapy strategies involve cesium-131 seeds, which lead to good tumor control even as salvage treatment. No patients with recurrent brain tumors experienced local regrowth after maximally safe resection and cesium-131 brachytherapy.[64] Compared to adjuvant stereotactic radiation therapy, cesium-131 brachytherapy use also achieved lower local recurrence rates for patients with resected brain metastases.[65] The FDA has approved intracranial cesium-131 brachytherapy in the form of a collagen matrix for both new and recurrent primary and secondary brain tumors, and recent studies have shown its adequate radiation dosage for recurrent brain lesions with minimal complications.[66,67]

Convection-Enhanced Delivery of Therapeutic Agents

CED can provide higher therapeutic concentrations of drug in local tumor tissue while limiting systemic effects. Neurosurgeons place intracranial catheters, which are connected to an external infusion pump and utilize a pressure gradient. Favorable tumors have low vascular density, and ideal catheter placement avoids necrotic areas to optimize drug delivery past the BBB.

Most clinical trials involving CED have been designated for patients with GBM or diffuse infiltrating pontine glioma (DIPG). A phase III trial enrolled 276 patients with recurrent GBM and showed that there was no difference in median survival between the group treated with intracranial carmustine wafers and those treated with CED of cintredekin besudotox (Table 1).[16] Recently, phase I trials for patients with high-grade gliomas have investigated CED of carboplatin, of an oncolytic adenovirus, and of a recombinant nonpathogenic polio-rhinovirus chimera.[68–70] Those trials demonstrated acceptable safety profiles with achievement of tumor response or improved survival rate for patients who underwent CED.[69,70] A few clinical trials also exist for DIPG, with one phase I trial with IL13-*Pseudomonas* toxin indicating no improvement in patients' performance status despite transient cessation of disease progression for two out of five patients.[71] Other trials investigated the safety of CED in terms of dose tolerance and avoidance of critical cortical tracts.[72,73] One retrospective study on 13 children with DIPG, who received CED of carboplatin and sodium valproate after radiation, resulted in median overall survival of 15.3 months, median progression-free survival of 13.0 months, and tumor response in 10 patients.[74] Adverse effects included blocked infusion channels in one patient's device and cranial neuropathies in two patients that prompted drug dosage adjustments.

While CED could be a promising method to bypass the BBB for local brain tumor control, there are still several challenges inherent to the technology. The pressure gradient CED relies on can be variable throughout the tumor, resulting in unequal drug distribution.[75] Optimal intracranial catheter placement also depends on operator familiarity and can perpetuate tissue damage with subsequent loss of adequate drug delivery in addition.[75]

Phase 0 and Window of Opportunity Clinical Trials

In contrast to traditional clinical trials that primarily evaluate safety, toxicities, radiographic response, and survival rates, phase 0/window of opportunity trials incorporate molecular subtyping of tumor specimens to measure biological effects of novel therapeutic agents that are given to patients before surgery. This trial design assesses pharmacodynamics and pharmacokinetics, among other parameters, for drugs in early development.[76] Phase 0 and window of opportunity trials present opportunities for a wider variety of molecular-targeted agents to reach patients and to determine these drugs' ability to exert tumor control beyond margins of resection.

Overall, there are few published phase 0/window of opportunity trials, the majority of which involve GBM. The Response Assessment in Neuro-Oncology (RANO) working group reviewed 21 studies published up to 2020. Lack of sufficient tumor tissue to demonstrate biological effect is a particular challenge for phase 0 studies.[76,77] Small sample size is also an important consideration, especially as these trials do not include correlated control/pre-treatment tumor tissue samples and the BBB itself may confer variable drug penetrance to intracranial neoplasms in the first place.[76]

Ultimately, the RANO group recommends several criteria for phase 0/window of opportunity trials in neuro-oncology.[76] All enrolled patients should have planned tumor resection, with samples obtained from both enhancing and non-enhancing components as well as tumor margins. Obtained data should include assays of cell viability and proliferation in addition to measurements of drug targets.

Conclusion

For brain tumor patients to experience improved survival rates without risk of adverse neurologic events, neurosurgeons must safely perform maximal tumor resection. Fortunately, various technologies and tools allow for optimal resection when possible. Preoperative and intraoperative imaging software help neurosurgeons not only plan approaches for surgery but also monitor progress and adjust surgical plans during the operation. Minimally invasive systems include FUS, laser ablation, and tubular retractors to allow surgeons to reach deep intracranial locations with limited pressure on critical structures. Furthermore, fluorophores and Raman spectroscopy provide intraoperative visualization of tumor margins. Additional future research on these intraoperative strategies for brain tumor control would benefit from prospective studies and clinical trials.

Funding

A.W. is supported by an individual fellowship from the Agency of Healthcare Research and Quality (F32HS028747).

Supplement sponsorship. This supplement is sponsored by GT Medical Technologies, Inc., the makers of GammaTile® Therapy for brain tumors. GammaTile is FDA-cleared to deliver radiation therapy in patients with newly diagnosed malignant intracranial neoplasms and recurrent intracranial neoplasms. For full product and safety information, refer to the instructions for use.

Conflicts of interest statement. M.L. has research support from Arbor, BMS, Accuray, Tocagen, Biohaven, Kyrin-Kyowa, Biohaven, Urogen. He is a consultant for VBI, InCephalo Therapeutics, Merck, Pyramid Bio, Insightec, Biohaven, Sanianoia, Hemispherian, Black Diamond Therapeutics, Novocure, Noxxon, InCando, Century Therapeutics. He is a shareholder for Egret Therapeutics. His patents include: Focused radiation + checkpoint inhibitors; Local chemotherapy + checkpoint inhibitors; Checkpoints for Neuro-Inflammation. He is a consultant for Stryker.

References

1. American Brain Tumor Association. Brain Tumor Education. https://www.abta.org/about-brain-tumors/brain-tumor-education/. Accessed November 2, 2021.
2. Wang P, Luo C, Hong PJ, Rui WT, Wu S. The role of surgery in IDH-wild-type lower-grade gliomas: threshold at a high extent of resection should be pursued. *Neurosurgery.* 2021;88(6):1136–1144.
3. 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.
4. Gupta DK, Chandra PS, Ojha BK, et al. Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex—a prospective randomised study. *Clin Neurol Neurosurg.* 2007;109(4):335–343.
5. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128(1):305–310.
6. Chua TH, See AAQ, Ang BT, King NKK. Awake craniotomy for resection of brain metastases: a systematic review. *World Neurosurg.* 2018;120:e1128–e1135. doi:10.1016/j.wneu.2018.08.243. Epub 2018 Sep 8.
7. Curzi C, Giordan E, Guerriero A, et al. The extent of resection of T2-FLAIR hyperintense area for eloquent glioblastomas: outcomes analysis between awake and general anesthesia patients. *J Neurosurg Sci.* 2021. doi:10.23736/S0390-5616.21.05342-X. Online ahead of print.
8. Bonifazi S, Passamonti C, Vecchioni S, et al. Cognitive and linguistic outcomes after awake craniotomy in patients with high-grade gliomas. *Clin Neurol Neurosurg.* 2020;198:106089. doi:10.1016/j.clineuro.2020.106089.
9. Tuominen J, Yrjänä S, Ukkonen A, Koivukangas J. Awake craniotomy may further improve neurological outcome of intraoperative MRI-guided brain tumor surgery. *Acta Neurochir (Wien).* 2013;155(10):1805–1812.
10. Wu JS, Zhou LF, Tang WJ, et al. Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts. *Neurosurgery.* 2007;61(5):935–48; discussion 948.

11. Senft C, Bink A, Franz K, et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. *Lancet Oncol.* 2011;12(11):997–1003.
12. Wu JS, Gong X, Song YY, et al. 3.0-T intraoperative magnetic resonance imaging-guided resection in cerebral glioma surgery: interim analysis of a prospective, randomized, triple-blind, parallel-controlled trial. *Neurosurgery.* 2014;61(Suppl 1):145–154.
13. Stummer W, Pichlmeier U, Meinel T, et al. 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.
14. Laperriere NJ, Leung PMK, McKenzie S, et al. Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. *Int J Radiat Oncol Biol Phys.* 1998;41(5):1005–1011.
15. Selker R, Shapiro WR, Burger PC, et al. The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery.* 2002;51(2):343–355.
16. Kunwar S, Chang S, Westphal M, et al. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. *Neuro Oncol.* 2010;12(8):871–881.
17. Briggs RG, Conner AK, Baker CM, et al. A connectomic atlas of the human cerebrum-chapter 18: the connectional anatomy of human brain networks. *Oper Neurosurg.* 2018;15(suppl_1):S470–S480.
18. Zhang S, Li X, Lv J, et al. Characterizing and differentiating task-based and resting state fMRI signals via two-stage sparse representations. *Brain Imaging Behav.* 2016;10(1):21–32.
19. Hart MG, Price SJ, Suckling J. Connectome analysis for pre-operative brain mapping in neurosurgery. *Br J Neurosurg.* 2016;30(5):506–517.
20. Bello L, Gambini A, Castellano A, et al. Motor and language DTI Fiber Tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage.* 2008;39(1):369–382.
21. Castellano A, Bello L, Michelozzi C, et al. Role of diffusion tensor magnetic resonance tractography in predicting the extent of resection in glioma surgery. *Neuro Oncol.* 2012;14(2):192–202.
22. Giammalva GR, Brunasso L, Costanzo R, et al. Brain mapping-aided SupraTotal Resection (SpTR) of brain tumors: the role of brain connectivity. *Front Oncol.* 2021;11:645854. doi:10.3389/fonc.2021.645854. eCollection 2021.
23. Nimsky C, Fujita A, Ganslandt O, Von Keller B, Fahlbusch R. Volumetric assessment of glioma removal by intraoperative high-field magnetic resonance imaging. *Neurosurgery.* 2004;55(2):358–70; discussion 370.
24. Schneider JP, Trantakis C, Rubach M, et al. Intraoperative MRI to guide the resection of primary supratentorial glioblastoma multiforme—a quantitative radiological analysis. *Neuroradiology.* 2005;47(7):489–500.
25. Shah AS, Sylvester PT, Yahanda AT, et al. Intraoperative MRI for newly diagnosed supratentorial glioblastoma: a multicenter-registry comparative study to conventional surgery. *J Neurosurg.* 2020;135(2):505–514.
26. Maragkos GA, Schüpper AJ, Lakomkin N, et al. Fluorescence-guided high-grade glioma surgery more than four hours after 5-aminolevulinic acid administration. *Front Neurol.* 2021;12:644804. doi:10.3389/fneur.2021.644804. eCollection 2021.
27. Marhold F, Mercea PA, Scheichel F, et al. Detailed analysis of 5-aminolevulinic acid induced fluorescence in different brain metastases at two specialized neurosurgical centers: experience in 157 cases. *J Neurosurg.* 2019;133(4):1032–1043.
28. Marbacher S, Klinger E, Schwyzer L, et al. Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases. *Neurosurg Focus.* 2014;36(2):E10. doi:10.3171/2013.12.FOCUS13464.
29. Labuschagne JJ. The use of 5-Aminolevulinic acid to assist gross total resection of paediatric posterior fossa tumours. *Pediatr Neurosurg.* 2020;55(5):268–279.
30. Almekkawi AK, El Ahmadieh TY, Wu EM, et al. The use of 5-Aminolevulinic acid in low-grade glioma resection: a systematic review. *Oper Neurosurg.* 2020;19(1):1–8.
31. Vermandel M, Dupont C, Lecomte F, et al. Standardized intraoperative 5-ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial. *J Neurooncol.* 2021;152(3):501–514.
32. Leroy HA, Guérin L, Lecomte F, et al. Is interstitial photodynamic therapy for brain tumors ready for clinical practice? A systematic review. *Photodiagnosis Photodyn Ther.* 2021;36:102492. doi:10.1016/j.pdpdt.2021.102492. Epub 2021 Aug 19.
33. Della Pepa GM, Ius T, Menna G, et al. "Dark corridors" in 5-ALA resection of high-grade gliomas: combining fluorescence-guided surgery and contrast-enhanced ultrasonography to better explore the surgical field. *J Neurosurg Sci.* 2019;63(6):688–696.
34. Mansour S, Echeverry N, Shapiro S, Snelling B. The use of brainpath tubular retractors in the management of deep brain lesions: a review of current studies. *World Neurosurg.* 2020;134:155–163. doi:10.1016/j.wneu.2019.08.218. Epub 2019 Sep 9.
35. Norton SP, Dickerson EM, Kulwin CG, Shah MV. Technology that achieves the Triple Aim: an economic analysis of the BrainPath™ approach in neurosurgery. *Clinicoecon Outcomes Res.* 2017;9:519–523. doi:10.2147/CEOR.S133623. eCollection 2017.
36. Eichberg DG, Di L, Shah AH, et al. Minimally invasive resection of intracranial lesions using tubular retractors: a large, multi-surgeon, multi-institutional series. *J Neurooncol.* 2020;149(1):35–44.
37. Marenco-Hillembrand L, Wijesekera O, Suarez-Meade P, et al. Trends in glioblastoma: outcomes over time and type of intervention: a systematic evidence based analysis. *J Neurooncol.* 2020;147(2):297–307.
38. Galli R, Meinhardt M, Koch E, et al. Rapid label-free analysis of brain tumor biopsies by near infrared Raman and fluorescence spectroscopy-a study of 209 patients. *Front Oncol.* 2019;9:1165. doi:10.3389/fonc.2019.01165. eCollection 2019.
39. Pekmezci M, Morshed RA, Chunduru P, et al. Detection of glioma infiltration at the tumor margin using quantitative stimulated Raman scattering histology. *Sci Rep.* 2021;11(1):12162. doi:10.1038/s41598-021-91648-8.
40. Livermore LJ, Isabelle M, Bell IM, et al. Raman spectroscopy to differentiate between fresh tissue samples of glioma and normal brain: a comparison with 5-ALA-induced fluorescence-guided surgery. *J Neurosurg.* 2020;135(2):469–479.
41. Hollon TC, Pandian B, Adapa AR, et al. Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks. *Nat Med.* 2020;26(1):52–58.
42. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. *Lancet.* 1995;345(8956):1008–1012.
43. Rennert RC, Khan U, Bartek J, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic Neuroblate System (LAANTERN): procedural safety and hospitalization. *Neurosurgery.* 2020;86(4):538–547.
44. Sujijantarat N, Hong CS, Owusu KA, et al. Laser interstitial thermal therapy (LITT) vs. bevacizumab for radiation necrosis in previously irradiated brain metastases. *J Neurooncol.* 2020;148(3):641–649.
45. Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg.* 2018;130(3):804–811.

46. Carpentier A, McNichols RJ, Stafford RJ, et al. Laser thermal therapy: real-time MRI-guided and computer-controlled procedures for metastatic brain tumors. *Lasers Surg Med.* 2011;43(10):943–950.
47. 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.
48. Bunevicius A, McDannold NJ, Golby AJ. Focused ultrasound strategies for brain tumor therapy. *Oper Neurosurg.* 2020;19(1):9–18.
49. 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. doi:10.1038/s41598-020-65617-6.
50. Wei HJ, Upadhyayula PS, Pouliopoulos AN, et al. Focused ultrasound-mediated blood-brain barrier opening increases delivery and efficacy of etoposide for glioblastoma treatment. *Int J Radiat Oncol Biol Phys.* 2021;110(2):539–550.
51. Dong Q, He L, Chen L, Deng Q. Opening the blood-brain barrier and improving the efficacy of temozolomide treatments of glioblastoma using pulsed, focused ultrasound with a microbubble contrast agent. *Biomed Res Int.* 2018;2018:6501508. doi:10.1155/2018/6501508. eCollection 2018.
52. Marty B, Larrat B, Van Landeghem M, et al. Dynamic study of blood-brain barrier closure after its disruption using ultrasound: a quantitative analysis. *J Cereb Blood Flow Metab.* 2012;32(10):1948–1958.
53. Mainprize T, Lipsman N, Huang Y, et al. Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: a clinical safety and feasibility study. *Sci Rep.* 2019;9(1):321. doi:10.1038/s41598-018-36340-0.
54. Idbaih A, Canney M, Belin L, et al. Safety and feasibility of repeated and transient blood-brain barrier disruption by pulsed ultrasound in patients with recurrent glioblastoma. *Clin Cancer Res.* 2019;25(13):3793–3801.
55. Wu F. Heat-based tumor ablation: role of the immune response. *Adv Exp Med Biol.* 2016;880:131–153. doi:10.1007/978-3-319-22536-4_8.
56. Xu ZL, Zhu XQ, Lu P, et al. Activation of tumor-infiltrating antigen presenting cells by high intensity focused ultrasound ablation of human breast cancer. *Ultrasound Med Biol.* 2009;35(1):50–57.
57. Liu F, Hu Z, Qiu L, et al. Boosting high-intensity focused ultrasound-induced anti-tumor immunity using a sparse-scan strategy that can more effectively promote dendritic cell maturation. *J Transl Med.* 2010;8:7. doi:10.1186/1479-5876-8-7.
58. Fite BZ, Wang J, Kare AJ, et al. Immune modulation resulting from MR-guided high intensity focused ultrasound in a model of murine breast cancer. *Sci Rep.* 2021;11(1):927. doi:10.1038/s41598-020-80135-1.
59. Coluccia D, Fandino J, Schwyzer L, et al. First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound. *J Ther Ultrasound.* 2014;2:17. doi:10.1186/2050-5736-2-17. eCollection 2014.
60. Choi M, Zabramski JM. Re-irradiation using brachytherapy for recurrent intracranial tumors: a systematic review and meta-analysis of the literature. *Cureus* 2020;12(8):e9666. doi:10.7759/cureus.9666.
61. Bartek J, Alattar AA, Dhawan S, et al. Receipt of brachytherapy is an independent predictor of survival in glioblastoma in the Surveillance, Epidemiology, and End Results database. *J Neurooncol.* 2019;145(1):75–83.
62. Wang C, Liu C, Chen J, et al. Effect of neoadjuvant iodine-125 brachytherapy upon resection of glioma. *BMC Cancer.* 2022;22(1):397.
63. Watson J, Romagna A, Ballhausen H, et al. Long-term outcome of stereotactic brachytherapy with temporary iodine-125 seeds in patients with WHO grade II gliomas. *Radiat Oncol.* 2020;15(1):275. doi:10.1186/s13014-020-01719-9.
64. Chen WC, Lafreniere M, Phuong C, et al. Resection with intraoperative cesium-131 brachytherapy as salvage therapy for recurrent brain tumors. *J Neurosurg.* 2022:1–7. doi:10.3171/2021.10.JNS211886. Online ahead of print.
65. Julie DA, Lazow SP, Vanderbilt DB, et al. A matched-pair analysis of clinical outcomes after intracavitary cesium-131 brachytherapy versus stereotactic radiosurgery for resected brain metastases. *J Neurosurg.* 2020;134(5):1447–1454.
66. Budnick HC, Richardson AM, Shiue K, et al. Gammatile for gliomas: a single-center case series. *Cureus.* 2021;13(11):e19390. doi:10.7759/cureus.19390. eCollection 2021 Nov.
67. Warren KT, Boucher A, Bray DP, et al. Surgical outcomes of novel collagen tile cesium brachytherapy for recurrent intracranial tumors at a tertiary referral center. *Cureus.* 2021;13(11):e19777. doi:10.7759/cureus.19777. eCollection 2021 Nov.
68. 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.
69. Van Putten EHP, Kleijn A, van Beusechem VW, et al. Convection enhanced delivery of the oncolytic adenovirus Delta24-RGD in patients with recurrent GBM: a phase I clinical trial including correlative studies. *Clin Cancer Res.* 2022;28(8):1572–1585. doi:10.1158/1078-0432.CCR-21-3324.
70. Desjardins A, Gromeier M, Herndon JE, et al. Recurrent glioblastoma treated with recombinant poliovirus. *N Engl J Med.* 2018;379(2):150–161.
71. 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):333–342.
72. Morgenstern PF, Zhou Z, Wembacher-Schröder E, et al. Clinical tolerance of corticospinal tracts in convection-enhanced delivery to the brainstem. *J Neurosurg.* 2018;131(6):1812–1818.
73. Souweidane 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):1040–1050.
74. Szychot E, Walker D, Collins P, et al. Clinical experience of convection-enhanced delivery (CED) of carboplatin and sodium valproate into the pons for the treatment of diffuse intrinsic pontine glioma (DIPG) in children and young adults after radiotherapy. *Int J Clin Oncol.* 2021;26(4):647–658.
75. Bidros DS, Vogelbaum MA. Novel drug delivery strategies in neuro-oncology. *Neurotherapeutics.* 2009;6(3):539–546.
76. Vogelbaum MA, Krivosheya D, Borghei-Razavi H, et al. Phase 0 and window of opportunity clinical trial design in neuro-oncology: a RANO review. *Neuro Oncol.* 2020;22(11):1568–1579.
77. Wen PY, Chang SM, Lamborn KR, et al. Phase I/II study of erlotinib and temsirolimus for patients with recurrent malignant gliomas: North American brain tumor consortium trial 04-02. *Neuro Oncol.* 2014;16(4):567–578.