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TOPIC REVIEW

Future directions of operative neuro-oncology

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Abstract Recent technological advancements have drastically improved the safety and surgical precision of operative neuro-oncology. These include techniques for avoiding critical functional structures through pre-operative mapping and trajectory planning, as well the development and refinement of minimally invasive surgical approaches. Innovations in intra-operative tumor mapping, and post-resection tumor ablation have further combined to improve surgical outcomes. This review highlights such advancements and discusses future directions within operative neuro-oncology.

Keywords Neuro-oncologic surgery · Minimally invasive surgery · Pre-operative mapping

Introduction

The goal of operative neuro-oncology has not changed in over 100 years: remove the mass lesion. New technologies have nonetheless transformed the field, increasing the safety and precision of neuro-oncologic surgery. These include enhanced strategies for tumor and functional mapping to augment pre-operative planning, improvements in intra-operative techniques for reaching the lesion and optimizing its removal, and the delivery of new and emerging therapies directly to the post-resection tumor bed to minimize local recurrence (Table 1). In this review we highlight recent advances in the field and preview how they may affect the future of operative neuro-oncology.

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Pre-operative planning

The first stage of any neuro-oncologic surgery is planning, which involves detailed mapping of the lesion itself, and increasingly, the structures and pathways of the surrounding normal tissues. Traditional magnetic resonance imaging (MRI) has allowed for detailed views of most lesions and their physical relation to surrounding neural structures. MRI however does not map more subtle, and variable, neural tracts and spatial functionality. MRI-based diffusion tensor imaging (DTI) and navigated transcranial magnetic stimulation (TMS) are two recently developed techniques that allow the surgeon to incorporate functional data in pre-operative surgical planning, and increasingly, into intra-operative navigation.

Fiber tract mapping

DTI utilizes the rate and direction of water diffusion in neural tissues to map major fiber tract pathways in three dimensions (3D). When coupled with state-of-the-art 3D pre-operative planning software, this technology allows surgeons to develop more advanced trajectories towards deeply located mass lesions that spare major white matter bundles.

Wakana et al. [1] described the DTI appearance and anatomic location of major white matter bundles within the brain. Standard stereotactic navigation software, such as BrainLab (Westchester, IL), can then be used to incorporate

Table 1 Strategies for the improvement of operative neuro-oncology

Pre-operative planning
MRI-based diffusion tensor imaging (DTI)
Navigated transcranial magnetic stimulation (TMS)
Technical aspects of surgical approach
Minimization of cranial approaches: "keyhole" surgery
Mini tubular retractor systems
Strategies at the lesion
MRI-guided resection
Fluorescence-guided resection
Real time molecular genetics or particulate analysis
Laser ablation
Delivery of novel therapeutic agents (e.g., viruses, nanoparticles, liposomes, micelles, and stem cells)

visualized white matter bundles into 3D planning software that is available at the time of intra-operative neuro-navigation. Given the appeal of DTI for minimizing surgical morbidity from the disruption of major white matter bundles, and the wide availability of intra-operative 3D mapping, this technique has rapidly gained favor among surgeons. However, its efficacy in reducing surgical morbidity remains to be evaluated in a controlled clinical trial. There also remain technical limits to this approach, including the alteration of DTI signal by tumor and edema, as well as navigation and registration limitations associated with dynamic intra-operative mapping based on static pre-operative images [2]. While work is being done to address these limitations, including new diffusion weighting techniques to more accurately map white matter tracts in peri-tumoral edematous tissue [3], there is a need for future improvements and standardization in both acquisition and processing techniques for DTI-based neuro-oncologic surgery.

Eloquent motor mapping

Navigated TMS is a newer modality that relies on MRI-guided electrical targeting and electromyography (EMG) to reliably and accurately map eloquent cortical motor areas [4]. Similar to DTI, this functional information can be used for both pre-operative planning and intra-operative neuro-navigation. Recent prospective, comparative clinical data (n = 127; 34 control, 93 TMS patients) supports the addition of TMS to a clinical routine already incorporating pre-operative fiber tractography, as well as intraoperative neuro-navigation and electrophysiology. This study demonstrated a significant improvement in the extent of surgical resections in lesions near eloquent motor cortex with use of TMS (85.4 versus 75.9 % tumor resection, $p = 0.027$), without negatively impacting patient safety or long-term functional outcomes [5]. These findings are supported by similar data from previous clinical studies using historical controls [6–8]. Moreover, navigated TMS was shown to be more accurate than other existing modalities for pre-operative eloquent motor mapping, such as functional MRI (fMRI), with fewer patient restrictions [9]. Despite this promise, TMS remains limited by a reliance on pre-operative static images, which are susceptible to brainshift from dynamic lesions or intra-operative manipulation. Larger scale efficacy validation studies are thus needed prior to more widespread application.

Technical aspects of surgical approach

Once the pre-operative plan had been optimized, the intra-operative goal of neuro-oncologic surgery is to access the lesion with appropriate visualization and space for surgical manipulation, while minimizing disruption of surrounding neural structures. There are two recent progressions on this front: minimally invasive modifications of established neurosurgical approaches, and the development of low-profile tube retraction systems that facilitate atraumatic access to deeper lesions.

Minimization of cranial approaches

Since the inception of operative neuro-oncology, numerous surgical approaches have been developed to operate on lesions in critical areas of the brain, including the deep frontotemporal region and the skull base. These include the frontal, bifrontal, frontotemporal, pterional, and orbitozygomatic approaches, as well as other variations. The evolution of these approaches from Dandy's frontotemporal "macrosurgical approach", to Yasargil's microsurgical pterional approach, and finally to a supraorbital keyhole approach through an eyebrow incision, are a reflection of parallel advances in tools available to neurosurgeons (in particular the operating microscope and endoscope), and a desire to use only the minimally required exposure to safely address a given neuro-oncologic pathology. The goal of this surgical evolution and its current end product 'keyhole' surgery (a series of minimally invasive cranial approaches), was not to perform a small incision and craniotomy for the sake of a small opening, but rather, to access the target lesion while causing the least possible trauma to surrounding structures such as the skin, bone, dura, and most importantly the brain [10]. When used in the appropriate clinical setting, minimally invasive 'keyhole' techniques have similar efficacy as more invasive approaches [11]. Their future use will almost certainly increase as more comparative data on their impact on surgical complications is collected.

Mini tubular retraction systems

For any given open neurosurgical approach, there is often a need for significant brain retraction, especially to access

deep lesions. Inevitably, this places pressure on the retracted brain, and can cause local injury or hemorrhages in up to 10% of cases [12]. Malleable flat or tapered retractors are commonly used for brain retraction along a chosen trajectory, however, their rigid design prevents conformation to the shape of the retracted tissues and places uneven force distributions along delicate neural tissues. Multiple tubular retractor systems have thus been developed that better conform to circular surgical cavities and more evenly distribute outward forces on surrounding neural structures (ViewSite, Vycor Medical, Bohemia, NY; BrainPath, Nico Corp., Indianapolis, IN). These systems can be precisely placed using neuronavigation, and have demonstrated safety and efficacy in small-scale clinical studies [13–15]. While originally designed for deep lesions, these retractors can also be helpful in more superficial lesions. Future large-scale studies are needed to define the optimal operative utility of these systems.

Strategies at the lesion

In addition to improvements in pre-operative planning and technical approaches to neuro-oncologic lesions, there have also been multiple advancements in operative neuro-oncology aimed at optimizing the resection of a lesion, as well as delivering novel therapeutic agents. Such advances include the use of MRI, fluorescence, and molecular/particulate analysis to guide surgical resections, as well as laser ablation and delivery of novel therapeutic agents to the surgical site.

MRI-guided resection

The use of intraoperative MRI (iMRI) to enhance neurosurgical resections has been available since the mid 1990s. Currently, iMRI is useful for optimizing the resection of primary glial neoplasms with poorly-defined borders and detecting early complications by allowing the surgeon to visualize progress and adapt the surgical plan in real time [16]. The drawbacks associated with this technique are the addition of significant surgical time, increased operating room costs, and difficulty interpreting intra-operative contrast images due to iatrogenic disruption of the blood brain barrier. When combined with the relatively poor resolution of first generation iMRI [0.5 Tesla (0.5 T)], these limitations prevented routine neuro-oncologic iMRI use outside of select centers. However, newer second-generation 1.5 and 3 T iMRI machines have increased resolution and accelerated scanning times, making them more appealing intra-operatively. Emerging data with high-resolution iMRI demonstrates its utility for safely increasing the surgical resection of glial-based tumors, with the near complete resections achieved with iMRI leading to a significant survival advantage [17, 18]. The increased magnetic strength of second-generation iMRIs nonetheless requires strict adherence to technical protocols to ensure its safe use, mandating a considerable upfront institutional investment prior to implementation.

Fluorescence-guided resection

Similar in concept to iMRI improvements in surgical resection, systems utilizing the aberrant metabolism of cancer cells to define tumor borders intra-operatively have been developed. Fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) is the most studied of these techniques, and utilizes the preferential accumulation of 5-ALA fluorescent breakdown products in tumor tissues to identify otherwise occult residual tumor cells intra-operatively [19]. When tested in a large, randomized, controlled trial ($n=322$; 161 5-ALA, 161 control patients), this approach demonstrated significantly improved complete resection rates (65 versus 36%, $p<0.0001$) and 6 month progression free survival (41.0 versus 21.1%, $p=0.0003$) as compared to standard white light microsurgical resection, without an increase in morbidity [20]. Although fluorescence-guided surgery is less expensive than iMRI, when compared directly 5-ALA was associated with inferior complete resection rates [21]. Moreover, use of 5-ALA is largely limited to higher-grade tumors possessing elevated 5-ALA metabolism beyond a diagnostic minimum [19]. The exact fluorescence level to histologic correlate, a link critical to the standardization of surgical resections, remains an ongoing area of research [19]. While approved in Europe since 2007, use of 5-ALA for intra-operative glioma surgery remains in the clinical trial phase in the United States. Other novel tumor specific fluorescent agents have been described [22], but require further study before large-scale utilization.

Real time molecular genetics or particulate analysis

Intra-operative molecular or particulate analysis is another emerging methodology for determining the true tumor margin in real-time, as well as obtaining a definitive intra-operative molecular diagnosis beyond simple frozen section histology. Published approaches include ambient mass spectroscopy based on defined tumor profiles [23, 24], genotyping for know tumor mutations such as telomerase reverse transcriptase (TERT) promoter and isocitrate dehydrogenase 1 and 2 (IDH1, IDH2) [25, 26], molecular analysis based on tumor core versus leading edge gene expression differences [27], and flow cytometry assessing cell proliferation densities [28]. These techniques have all shown promise for guiding surgical resections and improving intra-operative tumor characterization, but are largely in the proof-of-principle stage. Further clinical studies are

needed to assess their relative efficacy prior to more widespread clinical application.

Laser ablation

Explorations into techniques for tumor ablation beyond open resection are also underway. The anti-neoplastic properties of thermal energy have long been recognized by the medical community [29]. Unlike other ablative techniques such as radiation or chemotherapy that rely on a tumor cell's genetic and metabolic properties, thermal ablation functions independently of the neoplastic cell's biochemical state [29]. Neuro-oncologic ablative implantable lasers or laser induced thermal therapy (LITT) has been reported as early as 1990 with a small case series on Neodymium-doped yttrium aluminum (Nd:YAG) lasers placed under stereotactic CT guidance [30]. This was quickly followed by LITT ablation protocols that added the combination of MRI and magnetic resonance temperature imaging (MRTI) [31].

Currently, there are two commercially available MR-guided laser-induced thermal therapy (MRgLITT) platforms available, the Neuroblate® system (Monteris Medical Corporation, Plymouth, MN) and the Visualase® system (Medtronic, Minneapolis, MN). While the technical nuances behind these two proprietary platforms are beyond the scope of this paper, the fundamental therapeutic mechanisms are similar. Both systems use MRI compatible implantable laser catheters that can be monitored in real-time for placement and functionality. The addition of MRTI and cooling mechanisms allow the surgeon to achieve the desired tumor ablation profile while maximizing the preservation of surrounding normal brain tissue. To date, the literature concerning MRgLITT is limited and there are no prospective randomized clinical trials that have been completed. One of the largest retrospective series, with over one hundred patients, reported their experience with the Visualase® MRgLITT system, in which the total complication rate was 26.5 % [32]. As with any new surgical technology they observed a learning curve that was overcome after the first twenty consecutive patients [32]. The average ICU stay for the first twenty patients was 3.5 ± 6.2 days compared to the subsequent eighty-two patients who had an average ICU stay of 1.4 ± 2.2 days. The group observed a 13.7 % rate of new neurologic deficits, a 2.9 % rate of hemorrhage, and a 4.9 % rate of refractory edema [32]. Ablation related edema is an important potential complication of thermal coagulation, as significant life-threatening mass effect can ensue. This is of particular importance when considering ablation of tumors in the posterior fossa. Overall, LITT is a promising minimally invasive therapeutic modality, but future prospective randomized data is needed to better define its clinical role.

Delivery of novel agents

Novel ablative agents delivered directly to a tumor or to the surgical resection bed have also been developed. Gene therapy systems are the most common modality employing this approach. Multiple gene therapy strategies for neuro-oncology have been described, including the selective delivery of suicide genes to tumor cells, local augmentation of tumor suppressor genes, and the modulation of immune-response related genes [33]. These therapies often rely on non-replicating viral vectors for gene delivery, with the goal of limiting exogenous gene expression to tumor and peri-tumoral tissues. They can be used alone or in combination with the delivery of replicating oncolytic viruses directly to tumor cells [33].

Examples of suicide gene systems include targeted herpes simplex virus 1 (HSV-1) delivery of thymidine kinase or cytosine deaminase genes to tumor cells, which subsequently convert a systemically delivered prodrug (ganciclovir or 5-fluorocytosine) into a chemotherapeutic agent for selective tumor destruction [34]. Described tumor-suppressor and immunomodulatory strategies include viral delivery of the p53 tumor suppressor gene, and immunoactive genes such as interferon beta (IFN-β) [35]. These approaches have progressed from the pre-clinical to clinical stage, and while multiple trials have demonstrated safety, definitive clinical efficacy has yet to be established due to small trial sizes and limited transgene expression with non-replicating vectors [35].

Strategies employing replication competent viruses to increase transgene expression by selectively infecting (due to defects in anti-viral pathways unique to tumor cells), proliferating within, and destroying tumor cells address some of these shortcomings. Examples of replicating viral approaches include the selective delivery of enzymes for the conversion of systemically delivered cytotoxic pro-drugs with retroviruses such as Toca 511 [36], or direct oncolysis via induction of the host immune response with recombinant HSV or reovirus [35, 37, 38]. Multiple early phase clinical trials have confirmed the safety of viral oncolytic approaches, with efficacy trials currently ongoing [35].

Non-viral strategies that take advantage of unique peri-tumoral microenvironment alterations are also in development, and include the use of nanoparticles, liposomes, micelles, and stem cells for targeted tumor destruction [33]. Therapies using either neural or mesenchymal stem cells are a particularly appealing emerging strategy for selective transgene delivery due to their natural tumor tropism and high safety profile, especially with the use ex-vivo manipulated autologous cells. Based on promising pre-clinical data with such techniques [39–42], future clinical trials are warranted.

Conclusion and future directions

Researchers and clinicians have leveraged technological developments across multiple fields to increase the safety and efficacy of operative neuro-oncology. Recent improvements in pre-operative functional planning and minimally invasive approaches to avoid disruption of critical neural structures, as well as intra-operative strategies to enhance tumor resections have already been incorporated into routine surgical care. Future advancements are likely to be in the form of tumor- and patient-specific therapies, wherein real-time intra-operative genetic or molecular analyses for increasingly refined tumor subtyping could be used to guide more aggressive tumor resections, and/or match a tumor subtype with the most appropriate intra- or post-operative ablative therapy. As new neuro-oncologic strategies emerge, efficacy assessments through properly designed clinical trials will play a critical role in directing future neurosurgical practices.

Compliance with ethical standards

Conflict of interest R.C.R., D.R.S.D., J.F., N.S., and B.S.C. have no conflict of interest to report.

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