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Updates on Surgical Management and Advances for Brain Tumors

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Abstract

Purpose of Review This review summarizes the modern approach to surgical management of malignant brain tumors, highlighting new technology and multimodal treatment paradigms.

Recent Findings Outcomes in patients with glioblastoma are strongly correlated with extent of initial surgical resection. Intraoperative MRI, 5-ALA, and neuronavigation are surgical tools that can help achieve a maximal safe resection. Stereotactic radiosurgery and brachytherapy can be used to enhance local control for brain metastases in conjunction with surgery, while combinatorial approaches are increasingly employed in patients with multiple metastases. Advances in surgical techniques allow for minimally invasive approaches, including the use of tubular retractors, endoscopes, and laser interstitial thermal therapy.

Summary Primary and metastatic brain tumors require a multimodal, multidisciplinary approach to treatment. Surgical resection can be paired with radiation for metastases to maximize tumor control, expanding systemic options. Technological innovations have improved the safety of surgical resection, while expanding the surgical options and indications for treatment.

Keywords Glioma · Glioblastoma · Brain tumors · Extent of resection · Brain metastases · 5-ALA · Intraoperative MRI · Laser interstitial thermal therapy · SRS · Whole-brain radiation therapy · Endoscopic resection

Introduction

The management of central nervous system (CNS) malignancy has been fundamentally reshaped by advances in molecular characterization of tumors, allowing for exponential growth in the field of targeted therapies and immunotherapies. Even in the case of high-grade glioma, where progress has been incremental at best, our understanding of how molecular subclassification drives prognosis and treatment response has necessitated a change in the approach to these tumors. In contrast, options for the treatment of solid tumor brain metastases have increased dramatically, with a corresponding improvement in survival and overall prognosis for these patients. Furthermore, the gains in survival have been accompanied by an increasing number of patients with good functional status and systemic control at the time of recurrence or progression, necessitating a new approach to previously treated lesions.

As a result, the treatment of CNS malignancy has become increasingly complex, demanding a systematic and multimodal approach to treatment which starts with the role for surgical intervention. In this review, we will summarize guiding principles in the approach to CNS malignancy, with particular attention to the advances in surgery and radiosurgery. We will detail our center's decision-making process for determining appropriate treatment options specific to the tumor histology, and highlight innovations in neurological surgery, in particular developments in fluorescence-guided surgery, minimally invasive surgery, laser interstitial thermal therapy, and brachytherapy.

Management Paradigms for Surgical Approach to CNS Malignancy

Surgical management of CNS malignancy is founded on three basic principles: oncologic benefit, preservation and restoration of function, and quality of life. Surgical decisions are thus

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based on achieving one or more of these goals and necessitate a multidisciplinary approach to incorporate overall prognosis and functionality into treatment paradigms. At institutions where a multidisciplinary CNS tumor board is available, this resource can help to coordinate care and maximize involvement of subspecialists in treatment decisions. Figure 1 illustrates a standard approach to intracranial malignancy based on these founding principles. The specific approach to primary versus metastatic disease will be further outlined to delineate factors unique to these conditions.

High-Grade Glioma Surgery

Glioblastoma (GBM, WHO grade IV) is the most common malignant primary CNS tumor, with a dismal prognosis of only 12–16 months despite multimodal treatment consisting of maximal safe surgical resection, temozolomide, and radiation therapy [1, 2]. In the past 50 years, minimal progress has been made with regard to increasing overall survival (OS) for high-grade gliomas (WHO grades III and IV) [1]. Treatment is plagued by significant inter- and intratumoral heterogeneity, microscopic invasion, and difficulty in distinguishing tumor margins from normal brain intraoperatively [3, 4].

All glioma treatment is predicated on a tissue diagnosis, with molecular analysis supplementing histopathologic analysis. Where possible, gross total resection remains the gold standard. For lesions not amenable to gross total resection, biopsy is recommended if radiation and chemotherapy are being considered.

Extent of Resection

Of all available treatments for high-grade glioma, initial extent of tumor resection (EOR) has the greatest impact on disease control and survival [3, 5]. EOR is defined as the amount of contrast-enhancing tumor resected during surgery, evaluated by postoperative MRI. Brown et al. [5] performed a large systematic review of EOR studies involving patients with newly diagnosed glioblastoma, comparing gross total (GTR) with subtotal resection (STR), defined by extent of contrast-enhancing tumor resection. Patients with GTR were 61% more likely to survive 1 year (RR 0.62; 95% CI, 0.56–0.69; $p < 0.001$) and 19% more likely to survive at 2 years (RR 0.84; 95% CI, 0.79–0.89; $p < 0.001$) compared to patients with STR. Progression-free survival (PFS) was also significantly longer in patients undergoing GTR compared to STR. While 6-month PFS was longer in the STR compared to biopsy alone group, this benefit disappeared by 1 year, with no difference in overall survival. Notably, in this study, risk for mortality was

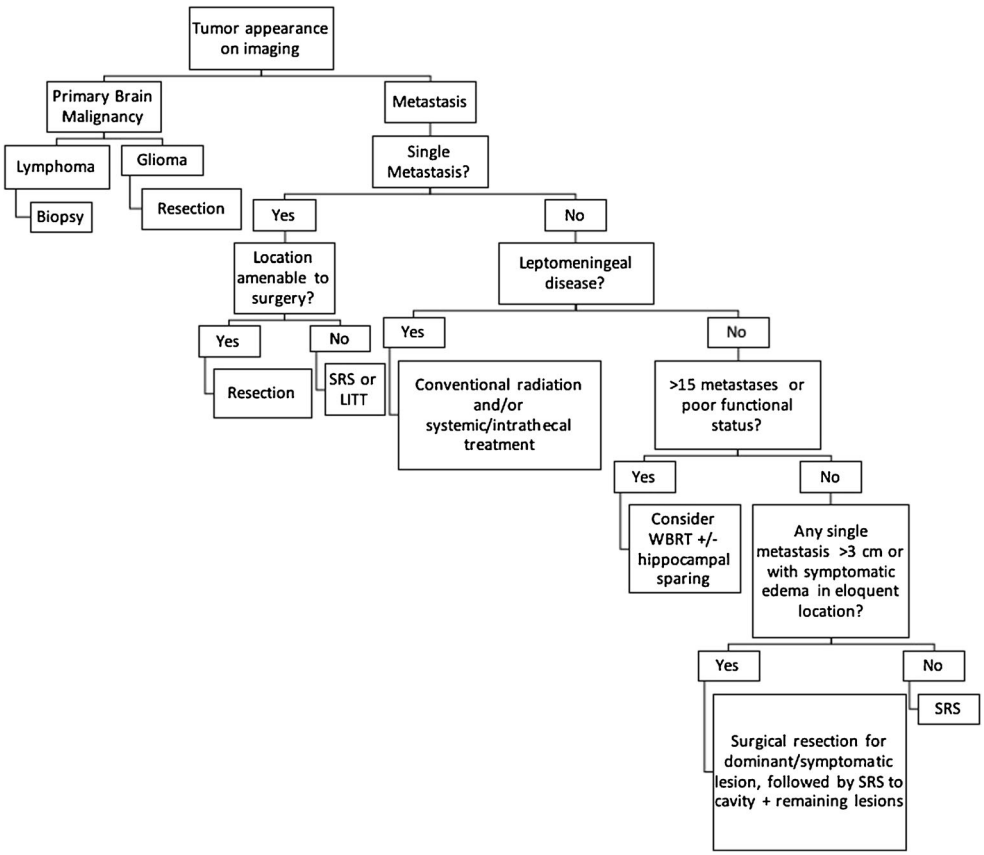

Fig. 1 Proposed management paradigm for surgical approach to intracranial malignancy. This brain tumor management workflow applies generally and is utilized in conjunction with a multidisciplinary tumor board

decreased for any degree of resection compared with biopsy at 1 year (RR, 0.77; 95% CI, 0.71–0.84 $p < .001$) [5].

There has been controversy surrounding the amount of resection needed to confer a survival benefit. Earlier studies suggested EOR of at least 78% or greater improved overall survival, with incremental improvement in OS with greater resection [3]. More recent studies have suggested resection of > 98% is required to significantly improve OS [6], although this predated a more nuanced understanding of molecular drivers of prognosis, and does not take into account the benefits of a partial resection on symptom palliation and preserving function during radiation.

In recent years, the concept of "supramaximal" resection, involving resection of both contrast-enhancing tumor and additional resection of the surrounding non-enhancing MR FLAIR signal, has evolved. In a study by Li et al. [6], patients with GTR and resection of greater than 53.21% of FLAIR signal had significantly longer overall survival compared to those with GTR and resection of less than 53.21% of FLAIR signal (20.7 months versus 15.5 months; $p < 0.001$). Importantly, there was no increase in risk of overall or postoperative neurological deficit with expanded resection in these cases. These results were independent of age, KPS score, preoperative contrast-enhancing tumor volume, presence of cyst, and prior treatment status [6]. Collectively, these studies demonstrate increased overall survival with increasing resection of contrast-enhancing tumor, with a further benefit of resection of FLAIR signal. More aggressive resection may be of particular benefit for IDH mutant gliomas [7••]. A new surgical adjunct that determines molecular pathology intraoperatively in a matter of minutes has the potential to guide real-time surgical decisions [8••].

There is little doubt that a maximal safe resection remains the goal in all cases, and neurosurgeons take maximal measures to achieve a GTR when possible. Resection of non-enhancing disease is recommended in cases in which it does not confer additional morbidity. Development of postoperative neurological deficits has detrimental effects on patient outcomes and survival [9]. Our institution utilizes various surgical adjuncts to achieve maximal safe surgical resection while minimizing the risk of postoperative neurological deficits. The benefits of a GTR must be balanced with the primary goal of preserving neurologic function, with an emphasis on maintaining a functional status that allows radiation and chemotherapy.

Maximizing Surgical Resection

Given the clear importance of maximizing resection in high-grade gliomas, various intraoperative adjuncts are available to increase EOR with the goal of preserving neurological function. Neuronavigation allows for real-time stereotactic localization of the tumor and vital neural structures through registration of anatomical landmarks with preoperative MRI and is standard of care. However, it is limited in utility after initial approach due to reliance on preoperative imaging, making intracranial navigation inherently inaccurate due to anatomic shift caused by edema, positioning, and fluid shifts. Intraoperative ultrasound is advocated to provide real-time feedback and is readily available at most centers.

Intraoperative MRI

Postoperative MR imaging is typically performed within 48 h of surgery to assess for EOR. If EOR is deemed to be suboptimal, performing a second resection soon after the initial surgery delays recovery and the start of chemoradiation, and confers additional morbidity. Utilization of iMRI allows for real-time assessment of EOR while the patient remains anesthetized, giving the surgeon the option of further resection if necessary. Following iMRI, the patient is repositioned and registered with the updated neuronavigation. The accuracy and precision of neuronavigation is greatly improved, as the new scan now accounts for brain shift from fluid changes, edema, and resection. While performing iMRI increases operative time, several studies demonstrate a significant improvement in EOR. Meta-analysis of recent literature by Golub et al. [10] revealed surgical resection with the guidance of iMRI was superior to resection with conventional neuronavigation alone (OR 4.99, 95% CI 2.65–9.39, $p < 0.001$). However, this does not take into account the use of intraoperative ultrasound and fluorescence-guided resection.

Fluorescence-Guided Resection

Orally administered 5-aminolevulinic acid (5-ALA) is a prodrug preferentially metabolized intracellularly by glioma and endothelial cells to form the substrate protoporphyrin IX (PpIX) through the heme synthesis pathway. PpIX produces red fluorescence (635–704-nm wavelength) when excited with blue-violet light (375–440-nm wavelength). The ability of the prodrug to cross the blood-brain barrier, and its preferential metabolism by glioma cells, allows for improved definition of the tumor margins, in some cases beyond the contrast-enhancing signal on MRI, thereby increasing EOR [11].

Several studies have demonstrated that use of 5-ALA can result in increase in EOR in high-grade gliomas. In 2019, Gandhi et al. [12] published a systematic review and meta-analysis on the use of 5-ALA-guided surgical resection of high-grade gliomas and the effect on GTR and survival outcomes. The rate of GTR was 76.8% (95% CI, 69.1–82.9%) with 5-ALA-guided resection. When compared to

conventional surgery, the use of 5-ALA resulted in 26% higher rate of GTR. Additionally, the use of 5-ALA increased OS by 3 months, and PFS by 1 month, respectively [12]. Golub et al. [10] demonstrated 5-ALA-guided resection was superior to resection with conventional neuronavigation alone (OR 2.866, 95% CI 2.127–3.863; $p < 0.001$). Notably, some groups have reported an increase in transient neurologic deficits with more aggressive resection, and this must be weighed against the potential impact on outcome [10].

Haider et al. [13] confirmed the use of 5-ALA-guided resection to increase EOR, including increasing EOR to 100% when tumors that were preoperatively deemed to be fully resectable. In addition, coupling iMRI and 5-ALA for resection of lesions in eloquent structures increased EOR from 57.6 to 71.2% when compared to resection with iMRI alone [13]. Ultimately, surgical resection of high-grade gliomas with the assistance of various intraoperative adjuncts can lead to increased EOR with longer OS and PFS; the choice and combination of modalities is left to the discretion of surgeons. In our experience, 5-ALA and iMRI offer similar benefit individually, and 5-ALA may be a cost-effective way to achieve increased EOR in centers in which iMRI is cost or resource prohibitive.

Brain Metastases

Surgical Resection

Advances in targeted therapy and immunotherapy have resulted in an increasing number of patients with metastatic cancer acquiring good systemic disease control, often leaving the CNS as the only site of uncontrolled disease. Patients with non-small-cell lung cancers (NSCLC) harboring targetable mutations often present with isolated brain metastases [14], driving a fundamental change in our approach to patients with progressive CNS disease without systemic progression. While even therapies with CNS efficacy can have more modest results intracranially than systemically, an approach to CNS disease which leverages the role of surgery and focused radiation can allow patients to continue on otherwise effective systemic agents.

Aggressive surgical approaches to brain metastases are critical in the management of metastatic disease. At our institution, patients newly diagnosed with a single surgically accessible brain metastasis are generally recommended for resection in the appropriate clinical context. As of now, surgical resection and stereotactic radiosurgery (SRS) have individually proven to be comparably safe and efficacious for treatment of solitary metastases with respect to survival, adverse events, and quality of life. Patients with high performance score (KPS > 70) and well-controlled primary disease or disease with reasonable systemic options are carefully considered for surgical management [15] followed by adjuvant SRS. For tumors not amenable to surgery, SRS becomes a first-line therapy [16]. In the setting of multiple metastases, accessible lesions should be evaluated for the need for surgical resection. Patients with large lesions (> 3 cm), lesions resulting in neurologic deficit, and/or lesions resulting in significant radiographic mass effect or impending impairment of CSF flow are all candidates for surgical resection followed by SRS to the resection cavity. In patients with poor systemic options, surgery is reserved as a palliative option for large symptomatic lesions resulting in neurological deficit.

Radiation Therapy

With the marked improvement in survival of patients with brain metastases, WBRT is increasingly reserved for patients who are not surgical or SRS candidates. While effective in providing intracranial control, studies also showed neurocognitive deterioration associated with WBRT, affecting long-term cognitive status and quality of life [17, 18••]. Innovations in therapeutics over the past decade have driven a major paradigm shift away from the use of whole-brain radiation therapy (WBRT) for palliation treatment to high-dose targeted radiation to improve tumor control rates, with a focus on longer term oncologic benefit. Hippocampal avoidance whole-brain radiation therapy (HA-WBRT) is currently under investigation as a treatment modality to reduce neurocognitive decline [19], and as a cost-effective alternative to SRS for patients with multiple brain metastases.

Similar to surgical resection, SRS aims to achieve local CNS control and is used in conjunction with systemic therapy to prevent overall metastatic progression. SRS is indicated in the treatment of smaller lesions (< 3 cm) with low levels of edema, or lesions located in surgically inaccessible sites [15, 20]. A recent multicentered phase 3 trial investigated cognitive outcomes and survival in patients treated with SRS versus WBRT and demonstrated improved quality of life, functional independence, and greater intracranial control with SRS [18••]. In 2019, Nguyen et al. [21] advocated a single-fractioned partitioned SRS strategy using Gamma Knife Icon (GKI-SPARE), which conferred a dosimetric advantage when compared to HA-WBRT for the treatment of 10–30 metastases in a retrospective study. As such, SRS is the preferred adjuvant therapy, with WBRT reserved for patients ineligible for SRS and/or with leptomeningeal dissemination [15, 21].

As a single modality, recent studies have shown no significant difference in local control between surgical resection or SRS [16, 22•]. However, the combination of surgical resection and radiosurgery achieves maximal local control, and the paradigms above are thus used to guide decisions regarding first-line treatment for patients with brain metastases [17]. At our institution, patients with good systemic options and functional

status are offered radiosurgery for upwards of 15 lesions, in the appropriate clinical context. The benefit of enhanced performance scores, greater local control, and decreased dependence on steroids support this combined treatment strategy [23].

While both single-fraction and multifraction (typically 3) SRS can be used, literature has increasingly supported the use of multiple fractions to increase therapeutic efficacy for brain metastases [15]. As a result, our standard practice is to deliver 27 Gy in 3 fractions to metastatic brain targets, with exceptions for proximity to critical structures such as the optic nerves or chiasm, tumors > 3 cm or with significant vasogenic edema, and brainstem lesions. In optimizing the implementation of SRS, the addition of a ~ 2-mm margin surrounding the resection cavity significantly reduces rates of local failure from 16% down to 3% at 12 months [24, 25].

Hypofractionated stereotactic radiosurgery (HF-SRS) is effective in patients who are otherwise poor candidates for SRS due to large tumor size or lesions located in eloquent cortex [26]. HF-SRS provides higher overall-dose radiation delivery by means of serial low-dose treatments and is an increasingly safe option for patients requiring high levels of radiation doses while limiting adverse neurocognitive effects [25, 26]. Typically, 30 Gy dose delivered in 5 to 6 fractions can be safe and effective for these lesions, minimizing rates of radiation necrosis with good tumor control [27•].

Stereotactic radiation may also confer an abscopal effect, which is the phenomenon observed when radiation to a primary site leads to regression of metastases at distant, secondary sites. This phenomenon is also referred to as the "distant bystander effect," since these antitumor alterations persist at the target tumor site as well as having a systemic out-of-field effect [28]. Ongoing research cites the immunomodulatory effects of radiation therapy in altering the microenvironment of the tumor and consequently reactivating the body's immune response [29]. Studies are underway investigating the effect of immunomodulation following surgical resection and radiation therapy, and increased efficacy of immunotherapy.

Innovations in Minimally Invasive Surgical Approaches

Endoscopic Approaches

Over the past 1–2 decades, the use of the endoscope in neurosurgery has evolved exponentially, offering minimally invasive methods to access CNS tumors. The endoscopic technique is most commonly utilized for endonasal approaches to the skull base and intraventricular surgery. Endonasal approaches to the anterior skull base allow for resection of pituitary metastases (most commonly from breast and lung primary sites) [30, 31], as well as malignancies of the anterior skull base [32], including malignant meningioma. The utilization of endonasal endoscopic approach is widely advocated at our institution, with increasing indications for its use, including a recent report by Shafiq et al. [33•] for endoscopically placed brachytherapy seeds at the site of recurrent skull-based meningioma.

Tubular Retractors

The advent of the tubular retractor systems, including the NICO BrainPath® (Nico Corp, Indianapolis, IN), has helped to re-shape the definition of what is surgically accessible. Surgery is performed via a 1.5-cm craniotomy, minimizing incision size and postoperative healing. These stereotactically guided tubular retractors are designed to offer a trans-sulcal corridor for tumors, utilizing the brain's natural corridors while providing distributed circumferential retraction, aiming to minimize injury to intervening brain. In many cases, the use of this tubular system can replace conventional forms of brain retraction, with the benefit of decreased trauma to the surrounding brain. In other cases, this trans-sulcal approach makes resection of deep-seated malignancies, such as those in the basal ganglia, an option [34, 35]. At our center, we also advocate the use of small tubular retractors to obtain tissue diagnosis in suspected primary malignancies, offering significantly more tissue than conventional needle biopsy techniques, and conferring the added benefit of direct visualization and control of intratumoral hemorrhage.

Management of Recurrent or Surgically Inaccessible Lesions

Laser Interstitial Thermal Therapy

Laser interstitial thermal therapy (LITT) involves use of a heat-delivering probe guided by MRI thermometry [36]. Coagulative necrosis is induced by heating tumor tissue to induce targeted hyperthermic injury at the subcellular level [37]. The two approved LITT systems, NeuroBlate® (Monteris Medical, Plymouth, MN) and Visualase® (Medtronic, Minneapolis, MN), support a treatment radius of 1–2 cm from the tip, with temperatures beyond this radius dropping off exponentially [36]. Monitoring of ablation temperatures is done simultaneously using real-time MRI thermometry and triggers immediate halting of treatment if temperatures increase beyond an operator-defined threshold [38•]. Ablation trajectories are mapped using digital stereotactic navigation tools, with efficacy demonstrated in treatment-refractory or deep, surgically inaccessible lesions. In the limited available literature, LITT is notable for a low intraoperative rate of complication and for short hospital stays, averaging only 1–2 days [37]. LITT may also be safe for posterior

fossa metastases without marked increase in postoperative edema [38•]. LITT has emerged as a safe and effective technology to treat patients with a spectrum of intracranial tumors [38•].

LITT is particularly appealing for the use of recurrent brain metastases, as it is equally effective for radiation-related changes (i.e., radiation necrosis) and recurrent tumor [39]. Furthermore, it allows for tissue sampling to help differentiate radiation necrosis from recurrence, helping to guide further treatment decisions postoperatively. Rao et al. [40] successfully utilized a LITT paradigm to target recurrent metastatic lesions < 5 cm, with a median progression-free survival of 37 weeks. LITT has met standards for local control in managing treatment-refractory metastases, with local tumor control rates reported as high as 77.4% [38•]. A multicenter study analyzing use of LITT on recurrent brain metastases which previously underwent SRS found no disease progression when achieving at least 80% tumor ablation [41].

LITT can also be utilized for high-grade gliomas not amenable to surgical resection. Meta-analysis by Ivan et al. [42] demonstrated an average of 82.9% tumor ablation volume resulting in OS and PFS of 14.2 and 5.1 months, respectively [38•]. Ablation volume has been roughly equated to extent of resection and can be thought of in a similar fashion with regard to efficacy. The image-guided stereotactic placement of the probe with real-time thermometry minimizes off-target damage. LITT can also be employed for solitary metastases not amenable to surgery or radiosurgery. Additionally, LITT may enhance adjuvant therapies, such as systemic chemotherapy, by disrupting the blood-brain barrier [38•, 43]. At present, inadequacy of practice guidelines and evidenced-based support for LITT has limited its widespread use; however, a number of academic centers are increasingly incorporating LITT into their treatment paradigms.

Salvage Stereotactic Radiation

Repeat SRS in a prospective study of 56 select patients by Iorio-Morin et al. [44•] was demonstrated to be safe and efficacious in patients undergoing multiple SRS treatments, without concerns for added burden of edema or radiation necrosis. Repeat SRS should be considered during clinical decision-making as an option to spare patients later WBRT. Response to initial SRS treatment can be predictive of response to secondary treatment, though lack of primary response does not preclude secondary therapeutic effect.

Brachytherapy

Brachytherapy uses implanted radioactive sources deposited inside the tumor resection cavity to treat locally infiltrating tumor cells. Early utilization of brachytherapy at non-neural sites of malignancy highlights its potential in the treatment of metastatic brain cancers. However, concerns over the historically employed iodine-125 (I-125)—due to its long half-life and associations with radiation necrosis, infections, hydrocephalus, and other complications—have limited the widespread implementation of brachytherapy in the brain until recently [33•,45]. Cs-131, with a short half-life of 9.7 days, compared to that of I-125 (59.5 days), can deliver aggressive radiation therapy while reducing the incidence of radiation-induced necrosis [46].

The use of Cs-131 has brought renewed attention to surgical resection followed by brachytherapy as a therapeutic strategy, particularly for recurrent lesions that have failed prior resection or radiosurgical treatment. Brachytherapy with Cs-131 permits radiation treatment to the tumor resection cavity immediately upon placement, eliminating the lag-time in initial radiotherapy or other interventions that require return hospital visits and additional procedures following resection surgery [45]. Recent studies demonstrate brachytherapy to be a safe and effective tool in managing patients with recurrent metastatic disease due to dissipation of radioactivity after 1 month, with 90% of the therapeutic dose delivered within this time [33•]. Furthermore, brachytherapy achieves local control while sparing normal surrounding tissues due to the steep falloff in dosing [33•]. Additional radiation to lesions following prior failed radiotherapy can carry risks of radiation necrosis and exceed the threshold of radiation tolerance in the brain. In these cases, brachytherapy presents an alternative method to achieve local control without compromising critical surrounding structures in the brain [33•].

GammaTile therapy (GTT) is a unique type of brachytherapy, utilizing implanted sources of radioactivity within a 10 mm distance from a tumor site. The therapy involves a collagen square embedded with radioactive Cs-131 seeds, placed in the tumor resection cavity. This technique delivers direct and uniform radiation while avoiding seed-to-brain contact, thus lessening undue tissue injury [45]. Brachytherapy may also have an added benefit of enhancing blood-brain barrier permeability to facilitate adjuvant chemotherapy delivery.

SRS Prior to Surgery

As mentioned above, SRS is typically provided as a postoperative adjuvant to improve local control of brain metastases following surgical resection. However, risks of local tumor recurrence or leptomeningeal disease remain relatively high. Preoperative SRS is an exciting prospect as a means to improve tumor control and potentially avoid leptomeningeal seeding in select cases, without increasing the total radiation [47, 48]. Preoperative SRS also allows physicians to contour metastatic sites, preventing creation of an irregularly shaped cavity following resection only. The so-called sterilizing effect may contribute to improved tumor control by limiting the

potential for tumor cells to successfully seed outside the cavity during surgery [47]. Furthermore, this treatment method could help reduce risks of radiation necrosis, as the bulk of the susceptible tissue will be resected shortly thereafter with no need to treat the surrounding brain during preoperative SRS [47]. Clinical trials investigating the efficacy of preoperative SRS are currently underway [49].

Conclusions

Current treatment options for CNS malignancy include surgical resection, minimally invasive surgery, SRS/HF-SRS, LITT, and brachytherapy. Multimodal treatment paradigms and multidisciplinary approaches are critical to continue to integrate promising new therapies. The surgical approach to intracranial malignancy must take into account the primary principles of diagnosis, oncologic control, neurologic preservation, and palliation. Innovations in treatment paradigms, including combinatorial strategies pairing radiation and surgery, are essential to progress in the treatment of CNS malignancy. Treatment decisions rely heavily on pathologic analysis and molecular characterization, and advances in intraoperative pathology may help guide surgical decisions for glioma in particular [8••]. Surgical advances have improved extent of resection, and expanded the breadth of tumors that may safely benefit from surgical intervention. We advocate a multidisciplinary, personalized approach to patient care with an ongoing drive to innovate and improve survival and quality of life.

Compliance with Ethical Standards

Conflict of Interest None of the authors has any potential conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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