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Evolving Strategies to Potentially Further Optimize Surgical Interventions in Brain Cancer

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Abstract

Purpose of Review Provide an overview, the indications for use, and a synopsis of current literature regarding two evolving neurosurgical interventions—GammaTile therapy (GTT) and laser interstitial thermal therapy (LITT).

Recent Findings GTT delivers immediate, uniform, high-dose radiation with avoidance of direct brain-to-seed contact. Innate properties of the novel carrier system and cesium-131 source may explain lower observed rate of radiation-induced necrosis (RIN) and support use in larger and previously irradiated lesions. LITT delivers focal laser energy to cause heat-generated necrosis. Case series suggest use in difficult-to-access lesions and treatment of RIN.

Summary Collaboration among subspecialties and remaining up-to-date on evolving technology is critical in developing individualized treatment plans for patients with brain cancer. While patients should be thoroughly counseled that these interventions are not standard of care, in optimal clinical scenarios, GTT and LITT could extend quantity and quality of life for patients with few remaining options. Prospective studies are needed to establish specific treatment parameters.

Keywords Brachytherapy · GammaTile · Laser interstitial thermal therapy · Primary brain cancer · Metastatic brain cancer · Glioblastoma

Introduction

Aggressive treatment for metastatic brain cancer (MBC) and for primary brain cancer (PBC) is complex, requiring a team of physicians specializing in specific therapeutic modalities. Therefore, collaboration is paramount in the development of a unique plan for each patient in hopes to achieve disease control. For this to happen, multiple factors are taken into account including a patient's age and functional status, tolerance to treatment, previous therapies, and specifics about the intracranial disease such as multifocality, location, and size. Successfully determining and implementing any treatment plan requires all collaborating medical/neuro-oncologists, radiation oncologists, and neurosurgeons to have a basic knowledge of the tools available, including those outside their field of expertise. This article will explore two evolving neurosurgical interventions that go beyond standard resection efforts—GammaTile therapy (GTT) and laser interstitial thermal therapy (LITT). Broadening knowledge of treatment options, even though that are not standard of care, will translate to expanded intra-disciplinary discussions and more patient-centric care.

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GammaTile Therapy

Treatment Overview

Brachytherapy, or treatment involving a radioactive source implanted inside or at a short distance from a tumor, has long been used in systemic cancers, most notably prostate cancer. GTT departs from traditional brachytherapy due to its innovative source carrier design [1•]. A standard GammaTile consists of a 20 × 20 × 4 mm pure collagen square tile that carries radioactive cesium-131 (Cs-131) seeds secured using vicryl sutures (Fig. 1a). These tiles can be uniquely tailored to accommodate any number of seeds, accounting for varying cavity sizes. The carrier design maintains a 10 mm distance between

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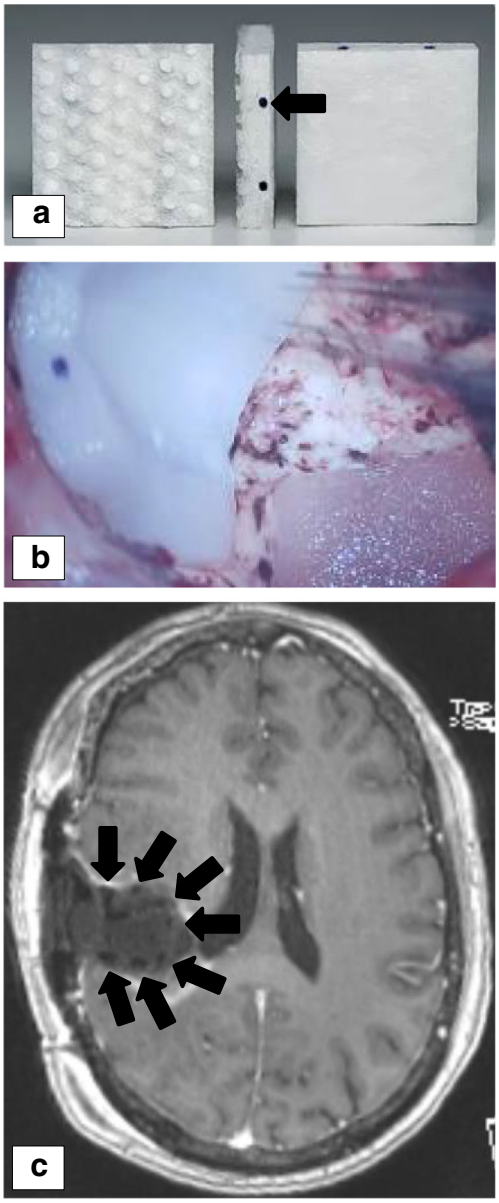

Fig. 1 **a** Photo of the 20 mm × 20 mm × 4 mm GammaTile. Arrow denotes one of the cesium-131 seeds. Photo courtesy of GT Medical Technologies (www.gtmedtech.com). **b** Intra-operative picture of multiple GammaTiles lining a surgical cavity. Photo courtesy of Dr. Clark Chen, neurosurgeon at the University of Minnesota. **c** Post-operative MRI demonstrating placement of GammaTiles (arrows)

seeds within a single tile and across multiple tiles, ensuring uniform dose delivery. Additionally, the carrier prevents direct seed-to-brain contact, limiting tissue injury [1•].

After resection of the tumor, the tiles are placed along the surgical cavity, requiring an additional 5 to 6 min on average (Fig. 1b) [1•, 2]. Upon implantation, radiation is immediately emitted within a radius of a few millimeters of the tile to target locally persisting cancer cells [2, 3•]. Post-surgically, a non-contrast computed tomography scan and magnetic resonance image (MRI) can assess seed localization and dosimetry (Fig. 1c) [1•].

Cs-131 has a short half-life of 9.7 days, with 90% of the radiation dose delivered within 33 days [1•, 4•, 5–7]. After 100 days, the GammaTile is considered inert. While the Cs-131 seeds remain in the brain, the carrier is absorbed by the surrounding tissue. Of note, while there is a correlation between the number of Cs-131 seeds implanted and surface dose rates, using the National Council on Radiation Protection guidelines, the dose equivalent from GTT maintains safe levels of exposure to family and medical personnel [1•, 8].

Indications for Use

Surgical resection alone for MBC has been shown to have recurrence rates as high as 46% [7, 9]. Moreover, 80–90% of recurring glioblastoma (GBM) is within 2 cm of the resection cavity [10]. As such, adjuvant radiotherapy has become a mainstay of treatment. However, initiation of external beam radiotherapy (EBRT) can be delayed by multiple variables ranging from post-operative recovery to lag time required for simulation and treatment planning. With a median wait time of 4–5 weeks, outcomes can be negatively impacted [6].

In July 2018, the US Food and Drug Administration (USFDA) cleared GTT for all types of recurrent brain cancers where resection remained feasible. Upon implantation, GTT delivers a large dose of radiation to the tumor bed, while sparing the surrounding tissue [6, 11]. Studies of patients with MBC, meningiomas, and GBM have shown promising results [1•, 4•, 6, 11]. Though, this emerging literature does not provide adequate evidence-based practice guidelines, and GTT is not considered standard of care for either MBC or PBC.

Aside from the medical benefits, GTT enables patients to forgo the logistical burdens of adjuvant EBRT [7]. Thus, making it a viable option when access to nearby medical centers is limited or when compliance is a concern. Furthermore, a cost analysis found that hospital charges for surgery with GTT were more cost-effective than surgery with stereotactic radiation [12]. Although GTT could be a viable option for some patients, it is important for physicians and patients to be aware that EBRT and GTT are mutually exclusive treatments for any one lesion. So, for diffusely invasive cancers, like glioblastoma, use of GTT precludes post-operative standard EBRT. This is particularly detrimental if there is early disease progression just outside the 5 mm reach of the radiation omitted from GTT.

Clinical Evidence to Date

Even though histology greatly differs between MBC and PBC, treatment standards typically include combined surgery and radiotherapy. In a majority of cases, disease recurrence is local. Cohort studies of several cancers have detailed positive outcomes when GTT is utilized as an alternative to conventional EBRT and prior methods of brachytherapy. In a 2019 Surveillance, Epidemiology, and End Results database

analysis, 362 patients with recurrent GBM had brachytherapy. Patient demographics revealed that those with more favorable characteristics, such as younger patients with tumors that were < 4 cm in size and highly accessible, were more commonly given this salvage therapy. That being said, outcome analysis did control for these variables in addition to receipt of chemotherapy and EBRT, and found a median overall survival (OS) of 16 months for patients who received brachytherapy compared with 9 months for those that did not [10]. Moreover, 17 recurrent GBM patients underwent resection with GTT, and then dose-dense adjuvant temozolomide. Results were compared with 17 closely matched historical controls, and a 3-month survival benefit was noted over chemotherapy alone [13]. Arguably, confounding factors exist; mainly the cohort that received GTT also received the potential additional therapeutic benefits of a repeat resection.

Radiation-induced necrosis (RIN) is a treatment-limiting toxicity associated with all forms of radiotherapy. More efficacious treatment modalities will limit RIN while maintaining local disease control. The traditional form of brachytherapy consists of directly implanted individual radioactive seeds. In situ, these seeds can dislodge and accumulate, resulting in non-uniform delivery of radiation and inducing tissue damage from direct seed-to-brain contact [3•]. The carrier secures Cs-131 seeds equidistant from each other, allowing for uniform dose delivery the cavity. By eliminating both the formation of "hot spots" and direct seed-to-brain contact, the incidence of RIN is reduced. Furthermore, preventing radiation "cold spots" ensures that all areas of the cavity are exposed to radiation.

Inherent biological properties of various isotopes can be advantageous. Cs-131 differs greatly from iodine-125 (I-125), a historically used isotope, and as a result, this has translated to observed differences in toxicity as exemplified by data from cohort studies in recurrent meningioma. In a study of 19 patients that underwent resection with GTT, only 11% experienced RIN, requiring only medical management [1•]. In contrast, 17 patients were treated with I-125, and 27% had RIN with 13% requiring surgery and another 27% that had wound breakdown [14]. Similarly, another study of 42 patients had a 16% RIN rate with I-125, and 12% had wound breakdown [15]. Across cancer histologies, a study of 95 patients treated for 105 brain metastases with I-125 experienced a RIN rate of 15% [16]. Conversely, in a prospective trial of 46 metastatic lesions with a pre-operative diameter of > 2 cm treated with GTT, there was no RIN [17]. To inherent biological properties can explain the differences in toxicity profiles. The half-life of I-125 is 59 days compared with 9.7 days for Cs-131 [8, 18]. The short half-life of Cs-131 means that 90% of the dose is delivered by day 33, in contrast to only 32% for I-125 at the same time point. The advantage is providing aggressive local therapy while maintaining a low incidence of RIN [1•, 5, 7]. Furthermore, contraction of the resection cavity, an anticipated post-surgical evolution, has significant effects on dose distribution and can further explain the differing rates of RIN between sources. A study-assessed dose variability follow implantation of I-125 and Cs-131. Models demonstrated a 31.8% and 30.5% increase for I-125, but only a 1.44% and 0.64% increase for Cs-131 in the minimal dose to 90% and 10% of the volume, respectively, in the peripheral target areas [19]. The fact that cavity contraction minimally effected the dose distribution of Cs-131 likely accounts for the lower rate of RIN.

With regard to EBRT, the risk of RIN increases with the larger lesion and delivered dose. In MBC, local control diminishes dramatically from 90% to as low as 40% as the size of the cavity increases [20]. Brachytherapy delivers high doses of radiation with a steep dose fall-off and to a well-defined target volume, ideal for large lesions [21]. In EBRT, the target volume is based on cavity size and any further cavity contraction after a planning scan means that an inaccurate dose could be delivered [6, 22, 23]. Additionally, brachytherapy offers local radiotherapy immediately upon implantation. This is in contrast to EBRT, where patients wait weeks to initiate adjuvant treatment. Furthermore, the dose of local radiation that brachytherapy delivers is higher than with EBRT. Specifically for GTT, radiation doses in the first few millimeters of the cavity can reach 80–120 Gy, 1.5–2 times greater than the 60 Gy typically achieved with EBRT [3•]. To date, several studies have compared the local control rates of GTT with that of EBRT, and results are largely equivalent [20].

From a patient-experience standpoint, GTT has demonstrated good tolerability. A study of 24 patients with MBC found sequential improvement in self-assessed quality of life per a functional assessment of cancer therapy-brain questionnaire at 12 months post-surgery [24]. That same study also found improvement in neurocognitive status, though these results were derived from a mini-mental status examination and not formal neuro-psychological testing.

Finally, any treatment plan for MBC and PBC would not be complete without a discussion on adjuvant chemotherapy. For all brain cancer, broad use of chemotherapy is large impeded by limited penetrance across the blood brain barrier (BBB). Interestingly, there is evidence that brachytherapy disrupts the BBB allowing for enhanced deliver of chemotherapy if administered shortly after seed implantation [25]. To capitalize on this therapeutic window, lacing the source-embedded carrier with chemotherapy could be investigated as studies in recurrent PBC suggested improved survival with Gliadel wafers, implantable carmustine wafers, and I-125 [26, 27].

Laser Interstitial Thermal Therapy

Treatment Overview

LITT is a minimally invasive technique available for a variety of intracranial pathologies [28]. Laser energy creates a localized rise in temperature, which results in destruction of cell membranes and DNA, activation of specific heat-sensitive proteins, and disruption of the microvasculature, if the cells are not immediately killed by the thermal exposure [29–31]. Initial introduction of this neurosurgical procedure was in 1983 and at the time was not looked upon favorably. However, evolution of this device in concordance with advances in MRI thermography has eliminated many of the technical barriers. Other improvements in laser probe technology, stereotactic surgical hardware, and computer software have further improved the ability to ablate lesions accurately and safely, while sparing nearby brain tissue (Fig. 2) [28].

Under MRI guidance, the inserted probe delivers focal laser energy into a target lesion, causing heat-generated necrosis [32, 33].The treatment temperature, duration of thermal exposure, and probe location are all monitored and calculated by a computer software program that provides the operator with a real-time predicted cell death rate with high sensitivity and specificity, 98.1% and 78.5%, respectively [34, 35]. This computer-calculated MRI thermometry feedback control will automatically abort the LITT if the temperature exceeds a certain limit. A diffusion sheath around the fiber is used to prevent overheating and tissue carbonization which can impair thermal penetration. Additionally, a constant stream of water or liquid CO2 provides a cooling mechanism to yet again, prevent probe adhesion to the tissue and minimizes carbonization [28, 34]. The technology also allows for a biopsy prior to ablation, all through a 4-mm access port.

Indications for Use

Patients with a range of intracranial pathologies including MBC, PBC, lesions serving as epileptogenic foci, and areas of RIN can derive therapeutic benefit from this procedure. LITT can be highly advantageous to patients that would otherwise be poor surgical candidates due to lesions in eloquent or difficult-to-access locations. In 2007, the USFDA approved MRI-guided LITT for use in neurosurgery, specifically for intracranial cancers. While the literature regarding LITT is expanding, adequate evidence-based practice guidelines cease to exist and LITT is not considered a standard of care for either MBC or PBC.

Evidence to Date

Multiple single institutional reports as well as larger case series have found MR-guided LITT to be a safe treatment for a variety of intracranial pathologies, particularly those in more difficult-to-access locations and for patients that might not otherwise tolerate an open craniotomy [36]. Specific to high grade gliomas (HGG), in a study of 54 patients with GBM that underwent a combined total of 58 LITT treatments, the median OS and progression-free survival (PFS) post-LITT was 11.5 months and 6.6 months, respectively [37]. In that study, 40 of the 54 patients had cortically located tumors, however, several case series specifically detail the use of LITT as a surgical option for lesions in varying eloquent areas, such as the thalamus and insula [38]. In one study of 15 patients with GBM involving the corpus callosum, LITT was also found to be safe while providing a survival benefit comparable with subtotal surgical resection in concert with chemoradiation with a median PFS, post-LITT OS, and OS of 3.4, 7.2, and 18.2 months, respectively [39]. Another case series of 8 patients demonstrated the safety and effectiveness of LITT in lesions positioned in the posterior fossa [40]. In light of these results, the literature lacks consensus on the true efficacy of this procedure. For example, in a case series of 8 newly diagnosed GBM patients, all with either bi-frontal tumors, multifocal disease, or otherwise inoperable lesions, there was a median PFS of only 2 months and a median post-LITT OS of 8 months [41]. While discouraging, this more strongly advocates for a prospective comparison of outcome measures for biopsy plus LITT versus biopsy alone for this patient population.

LITT has been studied in difficult-to-access MBC, and an impressive degree of disease control has been demonstrated, particularly in radiotherapy-resistant lesions [21]. A case series of 15 metastatic tumors treated in 7 patients showed no evidence of recurrence within the thermal ablation zone up to 30 months post-LITT, and the median OS was 19.8 months [42]. In another single institutional series of 25 patients with MBC treated with LITT, the median OS and PFS was 13.3 and 6.3 months, respectively, and among the 19 patients that died, only in 6 could the cause of death be directly attributed to uncontrolled intracranial disease [43]. Here again, a prospective trial is needed to fully quantify treatment tolerance and any survival benefit.

As previously stated, EBRT is a mainstay in the treatment of intracranial cancers, and RIN is a not uncommon consequence. Steroids, bevacizumab, and surgery are widely used treatment options; however, LITT has demonstrated effectiveness in this setting as well [44]. In a study of 19 patients with biopsy-proven RIN, LITT was a good salvage option, with an OS of 100% at 12 weeks and 82.1% at 26 weeks [45]. Moreover, patients demonstrated a stabilization of Karnofsky Performance Scale (KPS) scores and preserved quality of life and cognition. Additionally, 30% of patients also demonstrated a reduction in steroids at 12 weeks post-LITT. Again, another cohort of 59 patients with MBC previously treated with radiosurgery underwent a combined 74 LITT procedures

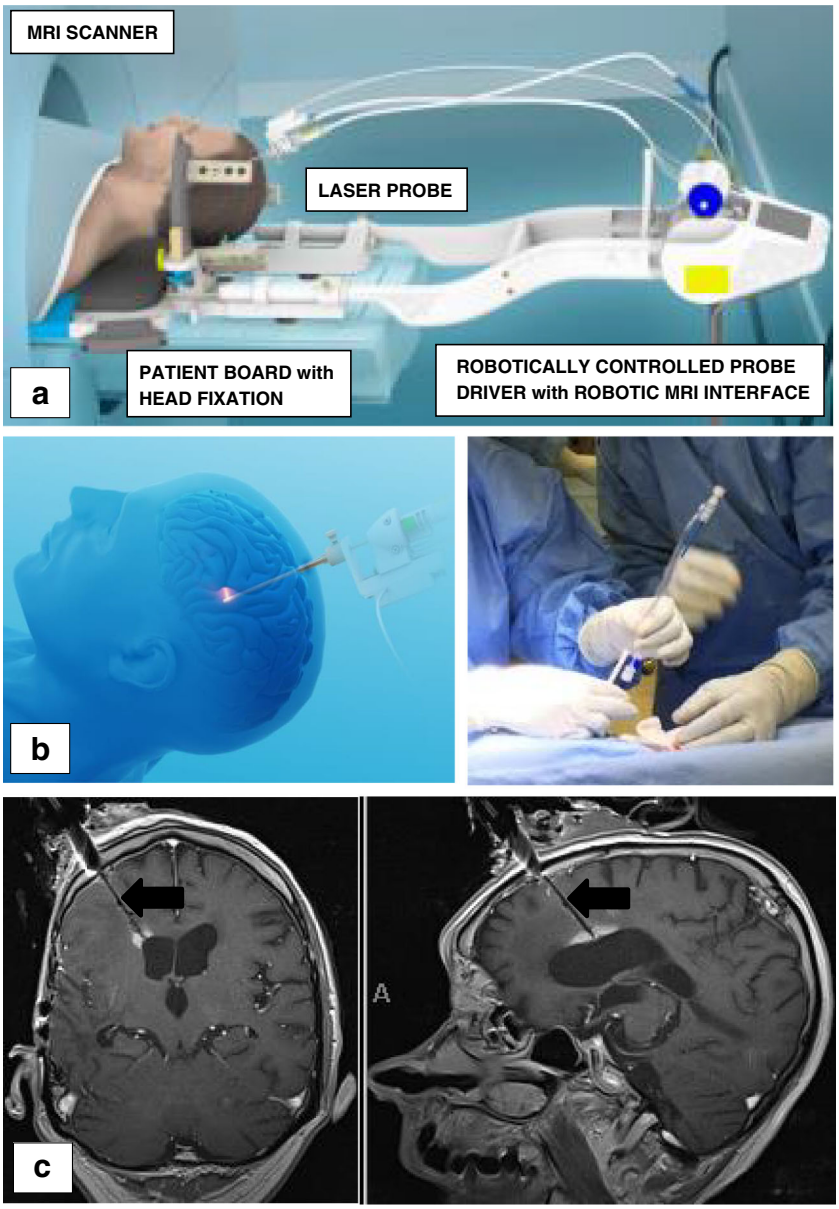

Fig. 2 **a** Laser interstitial thermal therapy (LITT) system. Graphic of the NeuroBlate System courtesy of Monteris Medical (www.monteris.com). **b** Simulated picture (left) and intra-operative photo (right) of a laser ablation procedure. Picture/photo courtesy of Monteris Medical (left) and Dr. Matthew Hunt, neurosurgeon at M Health Fairview (right). **c** Intra-operative MRI of a LITT procedure in which the trajectory track of the laser probe is seen targeting a periventricular contrast enhancing lesion in the coronal (left) and sagittal (right) planes (arrows)

and at a median follow-up of 44.6 weeks; the local control rate was 83%, and the rate of new permanent neurological deficit was 3% with most tolerating a steroid wean [46].

Specific to surgical technique, precise LITT planning of a trajectory or multiple trajectories that encompass as much tumor as feasible within the thermal damage threshold (TDT) is critical to achieve the greatest treatment benefit. As demonstrated in a study of 34 patients with malignant HGG, the more complete the coverage of the tumor by TDT lines, the longer the PFS is [47]. However, the minimally invasive advantage of LITT to accessing deep-seated targets also gives way to substantial risks. This is particularly true in cases of thermal injury to the corticospinal tracts (CST). The CST are the motor pathways that originate in the cortex and terminate in the spinal cord, and these fibers weave adjacent to many targets primed for LITT. A study investigated the predictive value of overlap between the TDT and the CST in determining post-operative motor deficit for over 140 patients [48]. Results demonstrated that even minimal overlap can cause post-LITT deficits. Consequently, precise planning to avoid critical structures as well as white matter pathways is paramount.

Another deleterious outcome detailed in the literature is LITT-associated edema, which is largely dependent on intracranial disease burden and the volume of tumor targeted for treatment. To exemplify this, one case series noted a 430% increase in peritumoral edema volume at 14 days post-LITT, which then decreased to 69% of the initial volume after 6 months [49]. For optimal aggressive treatment, PBC and MBC patients may undergo pre- or post-LITT EBRT. Since these procedures independently increase cerebral edema, the

combination in close succession can cause intolerable toxicity. This was demonstrated in a study of 8 patients with various malignant intracranial pathologies and all experienced treatment-associated edema following LITT and EBRT [50]. In this case series, patients had symptoms controlled with steroids, but others required more aggressive management with bevacizumab. An aggressive surgical intervention documented in the literature involves a post-LITT resection of amendable ablated tissue as well as resectable regions of the tumor by way of an invasive craniotomy [51]. This has shown to be beneficial as the newly created cavity accommodates edema-associated mass effect, optimizes maximum safe resection capabilities, and improves treatment tolerability.

Finally, similar to brachytherapy, data supports that LITT-induced hyperthemia also disrupts the peritumoral BBB with the peak permeability occurring within 1–2 weeks following the procedure and resolving by 4–6 weeks [52]. This provides an advantageous therapeutic window of opportunity for the use of chemotherapy following LITT.

Conclusion

A combined salvage treatment plan that optimize the advantages of surgery, radiation, and chemotherapy will likely provide the greatest survival benefit for patients with MBC and PBC. Technologies adapting the use of brachytherapy and thermal ablation for treating intra-cranial pathologies are a rapidly evolving field. While initially promising, most of the studies we reviewed were weakened by low enrollment numbers, limited follow-up, and confounded by varying adjuvant therapies. The role of GTT or LITT as an alternative to conventional treatment standard or within a complex multifaceted treatment plan is poorly defined, and only a few centers worldwide apply GTT or LITT in clinical practice. Additional studies are necessary to delineate benefits and establish correct patient selection criteria, standardized surgical technique, and treatment parameters. To exemplify this, a literature review found a comparable median OS from diagnosis of recurrence with the use of either LITT, brachytherapy, and repeat craniotomy, 20.9 months, 18.9 months, and 24.4 months, respectively [53]. The same review found the rate of severe complications for LITT to be ~ 14%, which was comparable with 11% found with open surgery. Currently, there are 8 recruiting clinical trials for LITT on Clinicaltrials.gov, not including a multi-center registry for prospective data collection. There are no recruiting clinical trials listed involving GTT.

The need for prospective trials has been addressed; however, our knowledge should not only be gained by conducting more trials, but by learning from previously failed trials and technology. A study randomized 270 patients with HGG to surgery, EBRT, and carmustine plus minus interstitial radiotherapy boost with I-125 seeds [54]. There was no significant improvement found in median OS for patients receiving the additional therapy. Fully analyzing the demographics of those enrolled in this trial, the toxicity profile, and the points of treatment success as well as failure can lead the development of more thoughtful future trials. From there, parameters for correct patient selection, optimal sequencing and timing of a multifaceted treatment approach, anticipated toxicities, and identifying the most pertinent outcome measures can be best implemented in future clinical trials. Other examples to gain valuable insight from include such technologies as GliaSite, liquid radiation delivered to the tumor bed through an inflatable balloon catheter placed in the resection cavity, and Gliadel wafers.

The aim of this review was to provide an understanding of these two treatments, the indications for use, and to discuss available clinical data. Such updates on evolving technology can further intra-disciplinary collaboration and increase the scope of treatment options considered for each patient. Since either GTT or LITT are considered standard of care, patients should be thoroughly counseled on the risks of either intervention, especially if being utilized in place of evidence-based treatment approaches. That being said, GTT and LITT could be considered given the current data demonstrating reasonable efficacy with low risk of complications and good patient tolerability. Until we learn more about the specific parameters in which this technologies can increase disease control when encompassed in a multimodal treatment plan, when applied to an optimal clinical scenario, both could serve to extend quantity and quality of life for patients that have few remaining treatment options.

Compliance with Ethical Standards

Conflict of Interest Bindi B. Parikh declares that she has no conflict of interest.

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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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