# The Evolution of Laser-Induced Thermal Therapy for the Treatment of Gliomas

Purvee D. Patel, MD[a,b], Nitesh V. Patel, MD[a,b], Shabbar F. Danish, MD[a,b,*]

**KEYWORDS**

• Laser-induced thermal therapy (LITT) • High-grade gliomas • Glioblastomas • Cytoreduction

**KEY POINTS**

- Although laser-induced thermal therapy (LITT) initially was used as a salvage treatment of recurrent gliomas that had exhausted standard treatment of care, it has evolved into a first-line treatment of specific newly diagnosed high-grade gliomas.
- LITT has comparable results to surgical debulking in allowing maximal cytoreduction, minimizing new neurologic deficits, prolonging malignant transformation, and improving overall and progression-free survival.

## INTRODUCTION

As with most novel techniques, laser-induced thermal therapy (LITT) was initially met with some skepticism for its role in the treatment for intracranial pathologies. Over the last two decades, with the help of real-time monitoring, the use of LITT has expanded to a range of pathologies including intracranial metastases, gliomas, radiation necrosis, epilepsy, and so forth.[1] Initial use was typically limited—it was a salvage option for tumors, when the standard approach failed. However, as more neurosurgeons used LITT, its efficacy was obvious. With time, LITT has emerged as a favorable treatment, possibly even first line for certain pathologies. In glioma management, there has been an increasing favorability for LITT to even being considered comparable to current "standards of care" of both newly diagnosed and recurrent cases.

## NATURAL DISEASE COURSE OF GLIOMAS

Gliomas can be characterized as low grade and high grade. Diffuse low-grade gliomas (DLGGs) typically have a peak onset at the age of about 35 to 40 years. They tend to have a slow growing, "silent" phase during which they could be found incidentally on imaging. This is followed by a symptomatic phase and then a progressive phase which is often precipitated by transformation to malignant, more high-grade gliomas.[2] The median survival in patients with low-grade astrocytomas is about 5 years and death usually results due to malignant transformation.[3]

High-grade or malignant gliomas are much more aggressive in their behavior and associated with a poorer prognosis. Of note, about 80% of high-grade, or malignant, gliomas are glioblastomas (GBMs) and represent the most common primary intracranial tumor in adults.[4] There are increasing molecular data that is being reported suggesting

[a] Department of Neurosurgery, Hackensack Meridian School of Medicine, Hackensack Meridian Health - Jersey Shore University Medical Center, Nutley, NJ 07110, USA; [b] Department of Neurosurgery, Hackensack Meridian School of Medicine, Hackensack Meridian Health, Jersey Shore University Hospital, Jersey Shore University Medical Center, 19 Davis Avenue, Hope Tower 4th Floor, Neptune, NJ 07753, USA
* Corresponding author. Department of Neurosurgery, Hackensack Meridian School of Medicine, Hackensack Meridian Health, Jersey Shore University Hospital, Jersey Shore University Medical Center, 19 Davis Avenue, Hope Tower 4th Floor, Neptune, NJ 07753.
*E-mail address:* shabbar.danish@hmhn.org

Neurosurg Clin N Am 34 (2023) 199–207
https://doi.org/10.1016/j.nec.2022.12.004
1042-3680/23/Published by Elsevier Inc.

subgroups may survive longer.[5,6] The peak onset for anaplastic astrocytoma is usually at age 40 to 50 years, whereas for GBMs, it is 60 to 70 years.[3] Primary GBMs tend to occur in older patients (mean age 55), whereas for secondary GBM, it is in younger adults (<45). The medial survival, despite aggressive treatment, is approximately 3 years for anaplastic astrocytomas and 1 year for GBMs.[3]

## TREATMENT OF GLIOMAS AND THE CONCEPT OF CYTOREDUCTION

The standard of care for gliomas, especially high-grade gliomas such as GBMs, is surgical resection with adjuvant chemotherapy and radiation.[4,7] In the case of DLGGs, extensive cytoreductive surgery with removal of the anaplastic foci can delay malignant transformation, hence altering the natural history.[2,3,8] For both low-grade and high-grade gliomas, a gross total resection is associated with longer survival and improved neurologic outcomes.[3,9]

As would be expected, studies have shown that maximal resection had more benefit compared with partial resection or biopsy.[10,11] Sanai and colleagues conducted a literature search regarding extent of resection (EOR) and outcomes; for low-grade gliomas, the mean survival improved from 61.1 months to 90.5 months with a greater EOR. In high-grade gliomas, the improvement was from 64.9 to 75.2 months in World Health Organization (WHO) Grade III gliomas and 11.3 to 14.2 months in WHO grade IV gliomas.[9] Brown and colleagues[12] had similar results and concluded that patients with newly diagnosed GBMs who underwent a gross total resection were 61% more likely to survive 1 year, 19% more likely to survive 2 years and 51% more likely to be progression free at 1 year compared with those who had subtotal resection. In regard to EOR, ranges from 78% to 98% have been shown to provide a survival benefit.[13,14]

There remains a balance to be struck between achieving a gross total resection and preventing any new neurologic deficits. Associated technology such as intraoperative MRI, use of fluorescent 5-aminolevulinic acid, artificial intelligence, virtual/augmented reality, and more recently connectomics have improved prospects of maximal safe resection.[4,15–20] Beyond the EOR, the adjunct of standard chemotherapy and radiotherapy, that is, Stupp protocol, for GBMs, can provide a significant survival benefit.[7]

There can be microscopic residual tumor beyond the contrast enhancement and so, a significant chance of recurrence despite near 100% resection of visual tumor.[12,21] Stemming from the records of Dandy, who performed a hemispherectomy for tumor resection of low-grade gliomas in hopes to irradicate all tumor contents, the concept of supramaximal resection has gained momentum.[22] Beyond just resection of the contrast-enhancing tumor, it has been found that resection of the areas with abnormal Fluid-Attenuated Inversion Recovery (FLAIR) and T2 noncontrast enhancement surrounding the contrast-enhanced tumor is associated with improved outcomes.[23–26]

Vivas-Buitrago and colleagues conducted a study looking at 101 patients with newly diagnosed GBMs who underwent resection of their tumors. They found that supramaximal resection (SMR) was associated with improved overall survival in patients with Isocitrate Dehydrogenase (IDH)-wildtype GBMs compared with patients who underwent just gross total resection, however, that finding was true for 20% Supramaximal resection (SMR) and there was no significant effect on overall survival when that percentage exceeded 60%.[27] Although resection of T2 FLAIR hyperintense region surrounding the tumor is likely to contain microscopic infiltrative tumor cells, it also contains functional brain parenchyma. Therefore, it can be challenging to find a balance between maximal diffuse tumor resection and preservation of “normal” functional brain parenchyma. One feasible solution proposed by this group included awake craniotomies with cortical and subcortical mapping and neuropsychological testing when feasible based on tumor location and symptomology. Although the concept of supramaximal resection is believed to lead to better outcomes from the tumor burden standpoint, it is important to consider and balance this with preservation of neurologic function and minimize development of new neurologic deficits.[28]

## RADIOFREQUENCY ABLATION FOR INTRACRANIAL TUMORS/GLIOMA

Several minimally invasive techniques were introduced in efforts to achieve the cytoreductive effects of surgery without the associated, morbid complications. These include laser, cryotherapy, radiofrequency microwaves, and focused ultrasound.[29] Radiofrequency ablation is a thermal ablation method which delivers electromagnetic radiation to heat tissue leading to coagulative necrosis.[30] It could be used to treat deep-seated intracranial tumors and could be coupled with MR imaging.[31] It also has the ability to initiate a cell-mediated immune response against the tumor cells, producing a long-term immunity. Some disadvantages include formation of vascular

thrombosis, dependence on electrical and thermal tissue conductivity, subject to "heat sink" effect when near vascular structures thus sparing cancer cells close to those blood vessels and formation of a hypoxic microenvironment which could promote tumor progression. Anzai and colleagues[32] found good local control in their 14 primary and metastatic brain tumors treated with radiofrequency ablation.

## ADVANTAGES OF LASER-INDUCED THERMAL THERAPY

LITT has evolved over the past two decades as a minimally invasive technique that allows for thermal ablation of several intracranial tumors. Although its uses were initially limited and met with much skepticism, it has gained popularity over the years as it proved its efficacy and safety for several intracranial pathologies. One of the most common uses for LITT today is high-grade gliomas—both newly diagnosed and recurrent. Some of the key characteristics that allowed LITT to grow popular among the neurosurgery world include its efficacy in achieving similar cytoreduction of tumors as does standard surgical resection and allowing for real-time monitoring of tumor ablation, hence minimizing damage to nearby eloquent areas and lowering risk of developing new neurologic deficits.

Some studies suggested a benefit of LITT over surgical resection when treating deep-seated tumors. Barnett and colleagues[33] conducted a systematic review and meta-analysis specifically for high gliomas in or near eloquent area of the brain. Their extent of ablation (EOA) was 85.4% with LITT compared with an EOR of 77% with open craniotomy. In addition, the complication rate was lower for LITT compared with open craniotomy—5.7% versus 13.8%. There was a statistically significant improvement in EOR/EOA and a reduction in major neurocognitive complications with LITT compared with craniotomy. Specifically for high-grade tumors in eloquent brain regions, which are otherwise deemed inoperable or if surgery is offered, it is often limited to just open biopsy or partial resection, LITT provides an acceptable alternative with benefits that are comparable, if not, superior, to those of surgical resection.

Di and colleagues calculated the EOA achieved in their series of 20 patients who underwent LITT for newly diagnosed glioblastomas. They found that in patients with greater than 70% EOA, there was significantly improved progression-free survival (PFS) and a trend toward improved overall survival. PFS was further improved when LITT was followed by early chemotherapy compared with delayed treatments.[34] A study conducted by de Groot and colleagues[35] concluded that median overall survival after LITT with subsequent chemotherapy and radiation was similar to those who had surgical resections.

Mohammadi and colleagues[36] assessed the EOA in 24 patients who underwent LITT for recurrent and newly diagnosed high-grade gliomas. They found that with greater extent of tumor coverage with laser ablation, as defined by tumor damage threshold lines, there was improved PFS. They concluded that the cytoreductive effect of hyperthermia via laser ablation was equivalent to that from surgical debulking. Similarly, Shah and colleagues[37] reported a statistically significant difference in local control when patients underwent greater than 85% EOA compared with $\leq$85% EOA. Their time to recurrence was 56 months in the greater than 85% EOA group compared with 12.3 months in the $\leq$85% group. They demonstrated that EOA was the strongest predictor of local control and greater EOA correlated with better local control for multiple types of lesions. As previously mentioned, LITT may show superiority as a treatment option for deep-seated tumors or those in areas of eloquence, when compared with open resection.[33] Although the results of these studies are interesting, it must be noted that open surgery and LITT do carry an inherent difference—the physical cytoreduction with surgery versus the ablative cytoreduction with LITT. The significance of this difference seemed intuitive in the past; however, as more studies have surfaced, it ultimately brings this question back into the spotlight.

A feature of LITT that sets it apart from other techniques and contributed to its appeal is real-time thermal monitoring. McNichols and colleagues described a computer-controlled laser thermal therapy system, which they used to produce lesions in canine and porcine brains and used MRI-based feedback to control the thermal energy and laser ablation.[38] This system was effective in regulating heat, eliminating carbonization and vaporization, and protecting the fiber optic applicators of the lasers. Ultimately, the MRI estimation of thermal dose correlated with thermal necrosis as seen in histologic evaluation. The compatibility of LITT with real-time MRI thermometry allows for safety and quality control thus adding to the efficacy of the procedure for treating intracranial lesions.[39–41]

Other benefits of LITT include ability to use multiple times without concerns for developing dose toxicity, as with radiation, or resistance, as with chemotherapy, patients tend to have shorter hospital stays compared with open craniotomies with

faster recoveries and also increased permeability of therapeutic drugs due to disruption of the blood brain barrier (BBB).[1,42–44] Muir and colleagues[45] published their cohort of patients who underwent LITT multiple times for recurrent GBMs and found that the patients tolerated the procedure well and also had a meaningful survival considering the procedure was used as a salvage treatment.

## LASER-INDUCED THERMAL THERAPY FOR GLIOMA

### *Laser-Induced Thermal Therapy for Recurrent Gliomas*

Although LITT has been proposed for multiple uses intracranially, a common use is for malignant glioma. Initially, LITT was reserved for tumors that were deemed surgically inoperable or recurrent despite having exhausted more traditional treatment methods. LITT has its own unique benefits for the treatment of recurrent gliomas. Recurrent disease is often focal and smaller as it is often found during more frequent surveillance and therefore is particularly amenable to laser ablation.[44] In addition, repeat surgery in a potentially already frail patient can lead to morbidity and wound healing issues due to prior chemotherapy and radiation. Last, salvage chemotherapy may be more effective following laser ablation.

Compared with newly diagnosed gliomas, recurrent gliomas are particular tougher to treat and have a grim prognosis. Factors found to be associated with poor postoperative survival in patients with recurrent GBMs included tumor location in eloquent brain regions, Karnofsky performance status $\leq$ 80, and tumor volume $\geq$50 $cm^3$.[46] Often times, at the time of recurrence, many patients are not as healthy to tolerate further open surgery. In fact, only about one of four patients with recurrent GBMs is candidates for reoperation.[47] Especially in those instances, LITT offers a safer alternative that can still decrease tumor burden offering comparable cytoreductive effects through ablation. Multiple studies have shown its efficacy and safety in its use for recurrent gliomas.[48–56]

Treatment with chemotherapy, whether that is monotherapy or combination chemotherapeutic drugs, has been studied as a potential treatment option for recurrent high-grade glioma. Food and Drug Administration (FDA) FDA-approved chemotherapeutic agents for recurrent high-grade gliomas are temozolomide, bevacizumab, lomustine, and carmustine (intravenous or wafer implants), as either single-drug treatment or in combination with other chemotherapeutic drugs, although no single regimen has proven to be superior to others for the treatment of recurrent of progressive glioblastoma.[47,57] Although no studies have directly compared the efficacy of LITT versus any chemotherapeutic regimens, individual studies have shown comparable, if not superior, results of LITT to those of chemotherapy. In a study looking at the use of lomustine and bevacizumab for recurrent glioblastoma, the overall survival was 9.1 months for the drug combination and 8.6 months when lomustine was used alone ($P > .05$) and PFS was 4.2 months in the combination group and 1.5 months in the single therapy group.[58] This can be compared with an overall survival of 11.6 months seen after 41 recurrent GBMs were treated with LITT.[56] A pooled analysis of all available literature in which LITT was used to treat recurrent GBMs, the authors found a pool overall survival of 18.6 months, a pooled post-LITT survival of 10.2 months and a pooled PFS of 6.2 months.[51] These values suggest that LITT may be favorable to chemotherapy for the treatment of recurrent, progressive glioblastomas.

### *Laser-Induced Thermal Therapy for Newly Diagnosed Gliomas*

LITT is often referred to as a salvage treatment option for recurrent gliomas that have been previously resected and exhausted adjuvant radiation and chemotherapy. However, more recently, neurosurgeons have started to offer this approach for newly diagnosed glioma as well.[48] This approach has been especially offered for gliomas which are deemed surgically inoperable due to deep-seated locations or being near eloquent regions of the brain or for patients who are deemed poor candidates for open surgery due to comorbidities or old age.[44] Some of the tumor locations ideal for upfront LITT therapy include the deep gray matter structures such as thalamus and basal ganglia, corpus callosum, or insula.

Ivan and colleagues showed their early results of 25 patients who underwent laser ablation for newly diagnosed glioma. Their cohort had a mean overall survival of 14.2 month and a complication rate of 3.4%.[59] Similarly, Muir and colleagues[60] presented their series of 20 patients with newly diagnosed, “inoperable” GBMs and concluded that those patients had similar survival times and local recurrence rates as patients who underwent surgical resection.

LITT seems to be a growing option for surgically inaccessible, deep-seated lesions such as those near the brainstem or deeper gray matter regions.[61] Shah and colleagues[62] had a mean EOA of 98.5% and mean PFS of 14.3 months in their cohort of 74 patients who underwent LITT for

deep-seated gliomas that were deemed surgically inaccessible. Ashraf and colleagues[63] presented a multi-institutional study reviewing the results of LITT for lesions within the posterior fossa. It was noted that the lesions tended to be smaller in size compared with their supratentorial counterparts. The complication rate was approximately 24% and it was advised that extra caution must be taken to prevent damage to surrounding neural structures as there is relatively more surrounding eloquent tissue in the posterior fossa compared with the supratentorial space. Dadey and colleagues[64] further demonstrated the importance of precise and accurate placement of the laser probe using stereotactic guidance to ensure effective ablation of these deep-seated lesions without major complications. Other studies also supported LITT as an effective option for posterior fossa tumors.[65,66]

## THE ROLE OF LASER-INDUCED THERMAL THERAPY IN DISRUPTION OF THE BLOOD BRAIN BARRIER

As noted earlier, LITT has been shown to increase permeability of therapeutic drugs due to disruption of the BBB. This may make it useful in salvage cases as adjuvant chemotherapy may be more effective following laser ablation. The BBB presents a unique obstacle in the physiology and treatment of intracranial brain tumors, compared with lesions elsewhere in the body. A variety of specialized cell types including endothelial cells, astrocytes, pericytes, microglia and neuron function together to regulate selective permeability and cellular transport, hence regulating homeostasis as well as cerebral blood flow. This vigilant regulation further restricts the targeted delivery of therapeutic drugs for the treatment of high-grade gliomas.[67]

Furthermore, high-grade gliomas and intracranial metastases also have the ability to generate a blood-tumor barrier (BTB). Through angiogenesis and neovascularization, a hallmark characteristic of GBMs, the tumors develop immature, dilated, and leaky vessels. These create a high interstitial pressure within the tumor itself and lead to a more malignant phenotype of tumors. In fact, the BTB is more permeable in the core of the tumor compared with the periphery and the BBB distinguishing the tumor from the normal brain parenchyma is impermeable. These characteristics allow for the malignant, aggressive nature of these high-grade tumors while also creating a barrier from the normal brain matter and vasculature to prevent any therapeutic agents to enter.[67]

In the past, some of the therapeutic methods used to try to overcome these obstacles included intrathecal delivery of chemotherapy drugs through Ommaya reservoirs and direct delivery to the tumor itself using chemotherapeutic wafers.[67–72] Bregy and colleagues[73] did a literature search yielding a total of 19 studies and 795 patients who underwent glial wafer implantation. It was found that the mean overall survival time increased from 14 months to 16.2 months when Gliadel wafers were added on to standard treatment of surgery, radiation and systemic chemotherapy. Overall, although these wafers did marginally increase survival and local control, they were associated with a high complication rate, up to 42.7% in their cohort. For this reason, the group recommended against using gliadel wafers.[43,74–78]

The idea that hyperthermia can treat malignancy has been around for some time and body hyperthermia was indeed used as a means to disrupt the BBB and allow entrance of chemotherapeutic agents. However, as these methods were systemic, there was the risk of causing damage to other parts of the body as well.[67,79] This brought about the concept of targeted hyperthermia in hopes to directly provide thermal energy to the tumor site, disrupting the BBB and BTB and also treating the tumor cells themselves. In as early as the 1980s, studies were conducted in which microwave radiator/sensors were implanted into the site of GBMs or high-grade astrocytomas.[80,81]

The use of lasers to provide hyperthermia to tissues had been seen for many years prior. Although ruby and $CO_2$, lasers had been used previously for the treatment of tumors, it was the introduction of the neodymium-doped yttrium aluminum garnet (Nd-YAG) lasers that would lead to what we currently use today for laser ablation of intracranial tumors.[82,83]

Salehi and colleagues[84] used a mouse model to demonstrate the effects of LITT on the BBB and BTB and found that there was local disruption of the BBB and BTB leading to increased permeability for up to 30 days following the procedure. Specifically, the therapy decreased the integrity of the tight junctions of this molecular barrier and increased endothelial cell transcytosis. This, then, allows large molecules including human immunoglobulins to pass through the targeted area. In the mouse model, laser ablation and adjuvant chemotherapy with doxorubicin, which is normally not permeable across the BBB, led to increased survival.

Leuthardt and colleagues[43] calculated the degree and timing of BBB disruption following laser ablation in patients with recurrent GBM.

Specifically, they calculated the vascular transfer constant as an indicator of permeability as well as serum levels of neuron-specific enolase. They found that based on the values and their trends following laser ablation, there was a peak of highest permeability of the BBB, within 1 to 2 weeks of laser ablation, which declined and resolved within 4 to 6 weeks. This in turn suggested a therapeutic window during which administering earlier adjuvant chemotherapy may have maximal benefits for these patients. Multiple clinical trials are underway, showing the benefits of different chemotherapy regimens and their efficacy when used in conjunction with LITT.[85–87]

## SUMMARY

LITT has evolved over the past decade and proved its efficacy and safety for the treatment of a variety of intracranial pathologies, including gliomas. From being used solely as a salvage treatment of recurrent gliomas, it now is often used first line for certain newly diagnosed gliomas. It is comparable to the standard treatment of surgical resection in allowing maximal ablative cytoreduction while minimizing damage to surrounding eloquent brain matter and thus improved overall and PFS while maintaining a relatively low complication rate. As neurosurgeons gain more experience with the technique, it is believed that LITT will continue to progress as a first-line cytoreductive treatment for a number of intracranial pathologies.

## CLINICS CARE POINTS

- Maximal resection/ablation is associated with better outcomes in patients with high grade gliomas.
- Laser ablation shows superiority over open resection for the treatment of deep-seated, "surgically inoperable"
- LITT may enhance the effects of chemotherapeutic agents by increasing blood brain barrier permeability.

## DISCLOSURES

None of the authors above have any financial disclosures to report.

## REFERENCES


1. Patel P, Patel NV, Danish SF. Intracranial MR-guided laser-induced thermal therapy: single-center experience with the Visualase thermal therapy system. J Neurosurg 2016;1–8. https://doi.org/10.3171/2015.7.JNS15244.
2. Smits A, Jakola AS. Clinical presentation, natural history, and prognosis of diffuse low-grade gliomas. Neurosurg Clin N Am 2019;30(1):35–42.
3. DeAngelis LM. Brain tumors. N Engl J Med 2001;344(2):114–23.
4. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol 2020;22(8):1073–113.
5. Berger TR, Wen PY, Lang-Orsini M, et al. World Health Organization 2021 classification of central nervous system tumors and implications for therapy for adult-type gliomas: a review. JAMA Oncol 2022;8(10):1493–501.
6. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 2021;23(8):1231–51.
7. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987–96.
8. Jakola AS, Myrmel KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA 2012;308(18):1881–8.
9. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008;62(4):753–64 [discussion: 264–6].
10. Stummer W, Reulen HJ, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008;62(3):564–76 [discussion: 564–76].
11. Vuorinen V, Hinkka S, Farkkila M, et al. Debulking or biopsy of malignant glioma in elderly people - a randomised study. Acta Neurochir (Wien) 2003;145(1):5–10.
12. Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol 2016;2(11):1460–9.
13. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95(2):190–8.
14. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115(1):3–8.
15. Hardesty DA, Sanai N. The value of glioma extent of resection in the modern neurosurgical era. Front Neurol 2012;3:140.
16. 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.
17. Eatz TA, Eichberg DG, Lu VM, et al. Intraoperative 5-ALA fluorescence-guided resection of high-grade glioma leads to greater extent of resection with better outcomes: a systematic review. J Neurooncol 2022;156(2):233–56.
18. Satoh M, Nakajima T, Yamaguchi T, et al. Evaluation of augmented-reality based navigation for brain tumor surgery. J Clin Neurosci 2021;94:305–14.
19. Henderson F, Abdullah KG, Verma R, et al. Tractography and the connectome in neurosurgical treatment of gliomas: the premise, the progress, and the potential. Neurosurg Focus 2020;48(2):E6.
20. Duffau H. Brain connectomics applied to oncological neuroscience: from a traditional surgical strategy focusing on glioma topography to a meta-network approach. Acta Neurochir (Wien) 2021;163(4):905–17.
21. Hirono S, Ozaki K, Kobayashi M, et al. Oncological and functional outcomes of supratotal resection of IDH1 wild-type glioblastoma based on (11)C-methionine PET: a retrospective, single-center study. Sci Rep 2021;11(1):14554.
22. Bell E Jr, Karnosh LJ. Cerebral hemispherectomy; report of a case 10 years after operation. J Neurosurg 1949;6(4):285–93.
23. Li YM, Suki D, Hess K, et al. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg 2016;124(4):977–88.
24. de Leeuw CN, Vogelbaum MA. Supratotal resection in glioma: a systematic review. Neuro Oncol 2019;21(2):179–88.
25. D'Amico RS, Englander ZK, Canoll P, et al. Extent of resection in glioma-a review of the cutting edge. World Neurosurg 2017;103:538–49.
26. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26(8):1338–45.
27. Vivas-Buitrago T, Domingo RA, Tripathi S, et al. Influence of supramarginal resection on survival outcomes after gross-total resection of IDH-wild-type glioblastoma. J Neurosurg 2022;136(1):1–8.
28. Guerrini F, Roca E, Spena G. Supramarginal resection for glioblastoma: it is time to set boundaries! A critical review on a hot topic. Brain Sci 2022;(5):12. https://doi.org/10.3390/brainsci12050652.
29. Merkle EM, Shonk JR, Zheng L, et al. MR imaging-guided radiofrequency thermal ablation in the porcine brain at 0.2 T. Eur Radiol 2001;11(5):884–92.
30. Partridge B, Rossmeisl JH, Kaloss AM, et al. Novel ablation methods for treatment of gliomas. J Neurosci Methods 2020;336:108630.
31. Franzini A, Moosa S, Servello D, et al. Ablative brain surgery: an overview. Int J Hyperthermia 2019;36(2):64–80.
32. Anzai Y, Lufkin R, DeSalles A, et al. Preliminary experience with MR-guided thermal ablation of brain tumors. AJNR Am J Neuroradiol 1995;16(1):39–48 [discussion: 49–52].
33. Barnett GH, Voigt JD, Alhuwalia MS. A systematic review and meta-analysis of studies examining the use of brain laser interstitial thermal therapy versus craniotomy for the treatment of high-grade tumors in or near areas of eloquence: an examination of the extent of resection and major complication rates associated with each type of surgery. Stereotact Funct Neurosurg 2016;94(3):164–73.
34. Di L, Wang CP, Shah AH, et al. A cohort study on prognostic factors for laser interstitial thermal therapy success in newly diagnosed glioblastoma. Neurosurgery 2021;89(3):496–503.
35. de Groot JF, Kim AH, Prabhu S, et al. Efficacy of laser interstitial thermal therapy (LITT) for newly diagnosed and recurrent IDH wild-type glioblastoma. Neurooncol Adv 2022;4(1):vdac040.
36. Mohammadi AM, Hawasli AH, Rodriguez A, et al. The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. Cancer Med 2014;3(4):971–9.
37. Shah AH, Semonche A, Eichberg DG, et al. The role of laser interstitial thermal therapy in surgical neuro-oncology: series of 100 consecutive patients. Neurosurgery 2020;87(2):266–75.
38. McNichols RJ, Gowda A, Kangasniemi M, et al. MR thermometry-based feedback control of laser interstitial thermal therapy at 980 nm. Lasers Surg Med 2004;34(1):48–55.
39. 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):943–50.
40. Carpentier A, McNichols RJ, Stafford RJ, et al. Real-time magnetic resonance-guided laser thermal therapy for focal metastatic brain tumors. Neurosurgery 2008;63(1 Suppl 1):ONS21–8 [discussion: ONS28-9].
41. Missios S, Bekelis K, Barnett GH. Renaissance of laser interstitial thermal ablation. Neurosurg Focus 2015;38(3):E13.
42. Viozzi I, Guberinic A, Overduin CG, et al. Laser interstitial thermal therapy in patients with newly diagnosed glioblastoma: a systematic review. J Clin Med 2021;(2):10. https://doi.org/10.3390/jcm10020355.
43. 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.
44. Hawasli AH, Kim AH, Dunn GP, et al. Stereotactic laser ablation of high-grade gliomas. Neurosurg Focus 2014;37(6):E1.

45. Muir M, Traylor JI, Gadot R, et al. Repeat laser interstitial thermal therapy for recurrent primary and metastatic intracranial tumors. Surg Neurol Int 2022;13:311.
46. Park JK, Hodges T, Arko L, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol 2010;28(24):3838–43.
47. Weller M, Cloughesy T, Perry JR, et al. Standards of care for treatment of recurrent glioblastoma–are we there yet? Neuro Oncol 2013;15(1):4–27.
48. Thomas JG, Rao G, Kew Y, et al. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. Neurosurg Focus 2016;41(4):E12.
49. Lee I, Kalkanis S, Hadjipanayis CG. Stereotactic laser interstitial thermal therapy for recurrent high-grade gliomas. Neurosurgery 2016;79(Suppl 1):S24–34.
50. Rodriguez A, Tatter SB. Laser ablation of recurrent malignant gliomas: current status and future perspective. Neurosurgery 2016;79(Suppl 1):S35–9.
51. Munoz-Casabella A, Alvi MA, Rahman M, et al. Laser interstitial thermal therapy for recurrent glioblastoma: pooled analyses of available literature. World Neurosurg 2021;153:91–7.e1.
52. Schwarzmaier HJ, Eickmeyer F, von Tempelhoff W, et al. MR-guided laser-induced interstitial thermotherapy of recurrent glioblastoma multiforme: preliminary results in 16 patients. Eur J Radiol 2006;59(2):208–15.
53. Sloan AE, Ahluwalia MS, Valerio-Pascua J, et al. Results of the NeuroBlate system first-in-humans Phase I clinical trial for recurrent glioblastoma: clinical article. J Neurosurg 2013;118(6):1202–19.
54. Carpentier A, Chauvet D, Reina V, et al. MR-guided laser-induced thermal therapy (LITT) for recurrent glioblastomas. Lasers Surg Med 2012;44(5):361–8.
55. Montemurro N, Anania Y, Cagnazzo F, et al. Survival outcomes in patients with recurrent glioblastoma treated with Laser Interstitial Thermal Therapy (LITT): a systematic review. Clin Neurol Neurosurg 2020;195:105942.
56. Kamath AA, Friedman DD, Akbari SHA, et al. Glioblastoma treated with magnetic resonance imaging-guided laser interstitial thermal therapy: safety, efficacy, and outcomes. Neurosurgery 2019;84(4):836–43.
57. Fisher JP, Adamson DC. Current FDA-approved therapies for high-grade malignant gliomas. Biomedicines 2021;(3):9. https://doi.org/10.3390/biomedicines9030324.
58. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017;377(20):1954–63.
59. Ivan ME, Mohammadi AM, De Deugd N, et al. Laser ablation of newly diagnosed malignant gliomas: a meta-analysis. Neurosurgery 2016;79(Suppl 1):S17–23.
60. Muir M, Patel R, Traylor JI, et al. Laser interstitial thermal therapy for newly diagnosed glioblastoma. Lasers Med Sci 2022;37(3):1811–20.
61. Silva D, Sharma M, Barnett GH. Laser ablation vs open resection for deep-seated tumors: evidence for laser ablation. Neurosurgery 2016;63(Suppl 1):15–26.
62. Shah AH, Burks JD, Buttrick SS, et al. Laser interstitial thermal therapy as a primary treatment for deep inaccessible gliomas. Neurosurgery 2019;84(3):768–77.
63. Ashraf O, Arzumanov G, Luther E, et al. Magnetic resonance-guided laser interstitial thermal therapy for posterior fossa neoplasms. J Neurooncol 2020;149(3):533–42.
64. Dadey DY, Kamath AA, Smyth MD, et al. Utilizing personalized stereotactic frames for laser interstitial thermal ablation of posterior fossa and mesiotemporal brain lesions: a single-institution series. Neurosurg Focus 2016;41(4):E4.
65. Borghei-Razavi H, Koech H, Sharma M, et al. Laser interstitial thermal therapy for posterior fossa lesions: an initial experience. World Neurosurg 2018;117:e146–53.
66. Sabahi M, Bordes SJ, Najera E, et al. Laser interstitial thermal therapy for posterior fossa lesions: a systematic review and analysis of multi-institutional outcomes. Cancers (Basel) 2022;14(2). https://doi.org/10.3390/cancers14020456.
67. Patel B, Yang PH, Kim AH. The effect of thermal therapy on the blood-brain barrier and blood-tumor barrier. Int J Hyperthermia 2020;37(2):35–43.
68. Kennedy BC, Brown LT, Komotar RJ, et al. Stereotactic catheter placement for Ommaya reservoirs. J Clin Neurosci 2016;27:44–7.
69. Sandberg DI, Bilsky MH, Souweidane MM, et al. Ommaya reservoirs for the treatment of leptomeningeal metastases. Neurosurgery 2000;47(1):49–54 [discussion: 54–5].
70. Hart MG, Grant R, Garside R, et al. Chemotherapeutic wafers for high grade glioma. Cochrane Database Syst Rev 2008;(3):CD007294.
71. Perry J, Chambers A, Spithoff K, et al. Gliadel wafers in the treatment of malignant glioma: a systematic review. Curr Oncol 2007;14(5):189–94.
72. Ashby LS, Smith KA, Stea B. Gliadel wafer implantation combined with standard radiotherapy and concurrent followed by adjuvant temozolomide for treatment of newly diagnosed high-grade glioma: a systematic literature review. World J Surg Oncol 2016;14(1):225.
73. Bregy A, Shah AH, Diaz MV, et al. The role of Gliadel wafers in the treatment of high-grade gliomas. Expert Rev Anticancer Ther 2013;13(12):1453–61.
74. Westphal M, Ram Z, Riddle V, et al, Executive Committee of the Gliadel Study G. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of

a multicenter controlled trial. Acta Neurochir (Wien) 2006;148(3):269–75 [discussion: 275].
75. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003; 5(2):79–88.
76. Nagpal S. The role of BCNU polymer wafers (Gliadel) in the treatment of malignant glioma. Neurosurg Clin N Am 2012;23(2):289–95, ix.
77. 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):1008–12.
78. Attenello FJ, Mukherjee D, Datoo G, et al. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. Ann Surg Oncol 2008;15(10):2887–93.
79. Salcman M, Samaras GM. Hyperthermia for brain tumors: biophysical rationale. Neurosurgery 1981; 9(3):327–35.
80. Salcman M, Samaras GM. Interstitial microwave hyperthermia for brain tumors. Results of a phase-1 clinical trial. J Neurooncol 1983;1(3):225–36.
81. Stea B, Cetas TC, Cassady JR, et al. Interstitial thermoradiotherapy of brain tumors: preliminary results of a phase I clinical trial. Int J Radiat Oncol Biol Phys 1990;19(6):1463–71.
82. Schupper AJ, Chanenchuk T, Racanelli A, et al. Laser hyperthermia: past, present, and future. Neuro Oncol 2022;24(Suppl 6):S42–51.
83. Bown SG. Phototherapy in tumors. World J Surg 1983;7(6):700–9.
84. Salehi A, Paturu MR, Patel B, et al. Therapeutic enhancement of blood-brain and blood-tumor barriers permeability by laser interstitial thermal therapy. Neurooncol Adv 2020;2(1):vdaa071.
85. Butt OH, Zhou AY, Huang J, et al. A phase II study of laser interstitial thermal therapy combined with doxorubicin in patients with recurrent glioblastoma. Neurooncol Adv 2021;3(1):vdab164.
86. Hormigo A, Mandeli J, Hadjipanayis C, et al. Phase I study of PD-L1 inhibition with avelumab and laser interstitial thermal therapy in patients with recurrent glioblastoma. J Clin Oncol 2019;37(15).
87. Hwang H, Huang J, Khaddour K, et al. Prolonged response of recurrent IDH-wild-type glioblastoma to laser interstitial thermal therapy with pembrolizumab. CNS Oncol 2022;11(1):CNS81.