Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03557-x

TOPIC REVIEW

In situ vaccination with laser interstitial thermal therapy augments immunotherapy in malignant gliomas

David H. Shin[1] · Kaitlyn F. Melnick[1] · David D. Tran[1] · Ashley P. Ghiaseddin[1]

Received: 28 March 2020 / Accepted: 8 June 2020

Abstract

Introduction Laser interstitial thermal therapy (LITT) remains a promising advance in the treatment of primary central nervous system malignancies. As indications for its use continue to expand, there has been growing interest in its ability to induce prolonged blood brain barrier (BBB) permeability through hyperthermia, potentially increasing the effectiveness of current therapeutics including BBB-impermeant agents and immunotherapy platforms.

Methods In this review, we highlight the mechanism of hyperthermic BBB disruption and LITT-induced immunogenic cell death in preclinical models and humans. Additionally, we summarize ongoing clinical trials evaluating a combination approach of LITT and immunotherapy, which will likely serve as the basis for future neuro-oncologic treatment paradigms.

Results There is evidence to suggest a highly immunogenic response to laser interstitial thermal therapy through activation of both the innate and adaptive immune response. These mechanisms have been shown to potentiate standard methods of oncologic care. There are only a limited number of clinical trials are ongoing to evaluate the utility of LITT in combination with immunotherapy.

Conclusion LITT continues to be studied as a possible technique to bridge the gap between exciting preclinical results and the limited successes seen in the field of neuro-oncology. Preliminary data suggests a substantial benefit for use of LITT as a combination therapy in several clinical trials. Further investigation is required to determine whether or not this treatment paradigm can translate into long-term durable results for primary intracranial malignancies.

Keywords Magnetic resonance imaging-guided laser ablation · Laser interstitial thermal therapy · Malignant glioma · Immunotherapy · In situ vaccination · Immunogenic cell death

Introduction

Since its inception several decades ago, laser interstitial thermal therapy (LITT) has been considered a promising minimally invasive method of cytoreductive treatment for deep-seated intracranial malignancies [1–7]. While its early use was limited by an inability to accurately control its treatment field, the advent of MR thermography has allowed for much more precise use of this technology resulting in an expansion of its indications to include its use in epilepsy and radiation necrosis [8–14]. Additionally, it is currently being used as salvage therapy following failure of stereotactic radiosurgery to control intracranial metastatic disease and has been reported to augment open surgical approaches for central nervous system (CNS) neoplasms [15, 16]. This has led to an exponential increase in its use across the world in many neurosurgical practices for patients who are otherwise poor surgical candidates [17].

While the primary goal of LITT is targeted thermocoagulation of tissue resulting in necrosis, there have been interesting associated findings during the use of this therapy with implications for the treatment of primary brain tumors with chemotherapy and immunotherapy by way of blood brain barrier (BBB) disruption. Leuthardt et al. first demonstrated a temporary disruption in the BBB within the peritumoral region of recurrent glioblastoma (GBM) after treatment with LITT as measured by the vascular transfer constant of gadolinium contrast material from the tumor vasculature into the tumor interstitial space as well as the release of brain

✉ David H. Shin
david.shin@neurosurgery.ufl.edu

✉ Ashley P. Ghiaseddin
Ashley.ghiaseddin@neurosurgery.ufl.edu

[1] Department of Neurological Surgery, University of Florida, Gainesville, FL, USA

Published online: 05 August 2020

specific factors into the general circulation. By calculating these parameters at regular intervals post treatment, they demonstrated that the increased peritumoral BBB permeability was sustained for approximately 4–6 weeks after LITT in these patients [18] (Fig. 1).

A major limitation in the use of chemotherapy and immunotherapy for intracranial malignancies is the poor BBB penetration of these agents [19, 20]. The BBB consists of a unique endothelial lining with tight junctions between each endothelial cell, preventing the passage of hydrophilic and large molecules into the CNS. Intracranial neoplasms have been shown to have increased BBB permeability in certain settings and regions (e.g. the enhanced rim in GBM). However, the general consensus is that the peritumoral region where the vast majority of recurrences occur, presumably from infiltrating tumor cells retaining a tight BBB, presents a major challenge in barrier penetrance and overcoming treatment resistance [21–23]. Unfortunately, the majority of standard anti-cancer agents have poor CNS penetration, severely limiting their effectiveness in CNS tumors. Even temozolomide, the mainstay chemotherapy for glioblastoma with BBB permeability is limited in this respect since its CNS concentration is only approximately 20% of the serum level. As a result, temozolomide has a suboptimal therapeutic index since achieving higher CNS concentrations often leads to excessive systemic toxicity [24].

Immune dysregulation and the impact of the BBB in immunotherapy in malignant gliomas

Increasing evidence has demonstrated striking immune dysregulation in malignant gliomas, especially GBM, including a paucity of effector T cell infiltration, excessive anergy among tumor infiltrating T cells, cytokine dysregulation, and increased inhibitory cells such as regulatory T cells and myeloid derived suppressor cells among others—all conspire to create some of the most highly immunosuppressed or "immunologically cold" tumor microenvironments observed in solid malignancies [25–27]. Unfortunately, radiotherapy, a mainstay treatment for GBM has been shown to further aggravate the local immunosuppression by inducing hypoxia, which in turn promotes production of chemokines that recruit more inhibitory cells to the tumor microenvironment [28, 29]. However, potential tumor antigens and neoantigens have been identified, and the list is continuously growing, indicating that tumor-specific recognition by immune cells is possible and thus therapeutically exploitable. To that end, methods that can convert the cold microenvironment of GBM into an immunologically hot tumor will have a significant impact on therapeutic success.

The BBB contributes substantially to many of the observed treatment failures in immunotherapy. Although there have been several case reports demonstrating promising responses in direct CNS infusion of immunotherapy [30, 31], these methods require the implantation of accessible devices, such as an Ommaya reservoir, which have their own procedurally related complications, like infection and risk of neurologic injury. The immunosuppressive effect seen in the tumor microenvironment is well documented and further aggravated by the BBB limiting ready access of tumor neoantigens to immune cells, which is a major contributor to immune escape mechanisms by tumor cells [27]. Therefore, the authors posit that the temporary post-LITT disruption of the peritumoral BBB has the potential to improve targeted delivery of immunotherapeutic agents while also promoting bilateral traffic of immune cells gaining access to an ablated and subsequently inflamed tumor microenvironment and tumor-associated neoantigens freely released into the

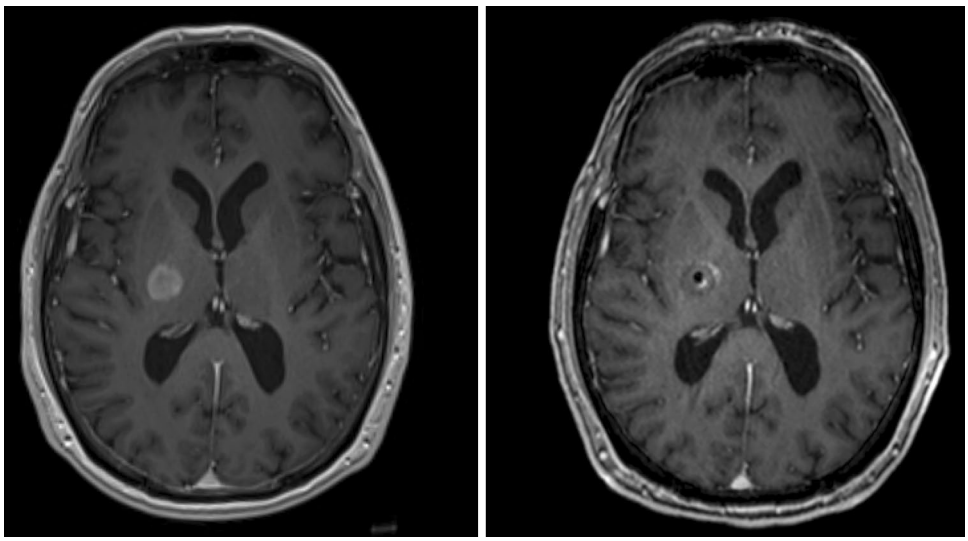

Fig. 1 Pre-LITT contrasted MRI on left demonstrating enhancing right thalamic mass. Post-LITT contrasted MRI on right demonstrating ring of contrast enhancement indicative of blood brain barrier disruption

lymphovascular circulation, leading to a successful tumor-specific immune reaction. Thus, this review seeks to discuss the mechanisms behind laser-based cell death, particularly with regard to immunogenic cell death, and highlight preliminary data behind the theory of in situ vaccination with LITT.

Mechanism of laser-based hyperthermic cell death

The effectiveness of LITT relies on the distribution of high energy photons emitted from the fiberoptic catheter tip into the targeted surrounding tissues [32]. Control of the emission is dependent on the emission of energy from the tip of the probe, which is generally ellipsoid in shape, although modifications to the two currently FDA-approved ablation systems (Monteris NeuroBlate and Medtronic Visualase) allow for the shape to be tailored into more specified dimensions. Additionally, the penetration of light through the tissues is highly dependent on the wavelength of the emission. As a result, the near infrared wavelengths on the commercially available systems are designed for penetration through the CNS.

Tissue absorption of delivered photons generates heat resulting in thermocoagulative damage, which correlates with the measured temperature. Temperatures greater than 50 °C will generally result in irreversible cellular damage and death through protein denaturation and direct nuclear damage [33]. Temperatures below this level have been shown to activate cellular homeostatic mechanisms to mitigate thermal injury and maintain cell viability. Temperatures near 90 °C run the risk of generating significant volumes of CO_2 due to vaporization of tissue, potentially increasing intracranial pressure. To deliver heat rapidly to achieve focal temperature elevations in the targeted tumor that can safely dissipate to adjacent normal tissue, it is critical to actively monitor and control the temperature at which the lesioning occurs. Prior to the advent of MR thermography, it was impossible to safely carry out intracranial laser thermocoagulation, limiting the early use of thermal therapy to treatment modalities where direct visualization was possible such as endoscopic ablation of gastrointestinal disease or in dermatologic conditions [34, 35].

Immunogenic cell death

Harnessing the immune system for the treatment of cancer has long been a favored approach compared to the scorched-earth methodology of targeting rapidly dividing cells with cytotoxic chemotherapy. The complex mechanisms by which innate immunity helps to prime adaptive immunity to selectively eliminate cancer cells have been rigorously studied. Specific intracellular damage associated molecular patterns (DAMPs such as ATP and heat shock proteins) of the innate immune system generated by dying tumor cells provides a critical link to the adaptive immune response, resulting in the recruitment and maturation of dendritic cells (DCs) to present tumor antigens and neoantigens to stimulate an ongoing immune response in a process known as immunogenic cell death (ICD) [36].

Chemotherapeutic agents, primarily topoisomerase II inhibitors and DNA alkylating drugs, have recently been found to upregulate expression of certain DAMPs on the surface of tumor cells, raising the possibility that they may contribute to ICD [37]. However, in a murine glioma model, the alkylating agent temozolomide induced the generation of DAMPs but failed to result in ICD. On the other hand, light emission, especially near infrared phototherapy, has been shown to produce large amounts of DAMPs and induce ICD [38]. As a result, the direct thermocoagulation of tumor by LITT provides a dual therapeutic goal of effective cytoreduction and the potentiation of a DAMP-associated ICD and immune response. Since the propagation of an adaptive immune response in the setting of DAMPs and ICD in tumors is highly dependent on the proliferation and recruitment of tumor-specific cytotoxic T-lymphocytes, increasing interest is focused on inhibition of intratumoral immune checkpoints (e.g. PD-L1) to potentiate ICD.

Mechanism of hyperthermic BBB disruption

The effects of hyperthermia on BBB permeability have been well studied in rats in which Kiyatkin et al. created an albumin-based temperature-dependent permeability curve [39]. This study demonstrated hyperthermia as an independent factor in BBB permeability. Furthermore, even physiologic hyperthermia such as exercise can also result in increased leakage [40]. On the microscopic level, although the exact mechanism is not well understood, hyperthermia is thought to induce disruption of the BBB through multiple potential mechanisms including, but not limited to, (1) a transcellular process as evidenced by apparent permeability of the BBB to high molecular weight particles without detectable distortion or widening of tight junctions between the endothelial cells of the BBB as well as the increased production of pinocytotic vesicles within the endothelial cells during hyperthermic states, and (2) disruption of the tight junctions due to downregulation of tight junction proteins such as claudin-5 in an in vivo heat stroke mouse model and zonula occuden-1 in an in vitro endothelial model [41–43]. More localized rodent experiments evaluating unilateral hyperthermia through carotid infusion and LITT in humans have demonstrated that this effect can be regulated to specific

regions [44]. These data suggest a novel method of localized BBB disruption to augment intracranial drug delivery which would supplement other methods under active investigation such as focused ultrasound, stereotactic radiation therapy, and electric field modulation [45].

Laser therapy and augmentation of chemotherapy

Combination therapy of hyperthermia with chemotherapeutic agents has been successful. In a liver cancer model, drug delivery via temperature-sensitive liposomes have been used to target chemotherapeutic agents specifically towards a region within the liver undergoing radiofrequency ablation thereby resulting in localized high heat distribution and release of the agent [46]. This synergistic effect has been demonstrated in extracranial malignancies where combination therapy has reduced metastases and increased survival [47]. Intracranially, this has been replicated in animal models indicating that the combination therapy with temperature-sensitive liposomes when combined with local hyperthermia serves to not only open the blood brain barrier but also to release agents from the liposomes at these targeted locations [48–50]. In patients with recurrent high grade glioma, hyperthermic ablation of the tumor by LITT induced a prolonged disruption of the peritumoral BBB lasting for up to 6 weeks as measured by the rate constant of gadolinium transfer from the tumor-associated capillary bed into the interstitial space (Ktrans) and the leakage of brain-specific factors (e.g. brain specific enolase—BSE or GFAP—Fig. 3) into the circulation, providing a window of opportunity to enhance CNS delivery of chemotherapeutic agents [18]. This concept of localized hyperthermic BBB disruption in concert with treatments can also be extended into immunotherapy, where it is theorized that this strategy would improve penetration of immunotherapeutic platforms.

Laser therapy and intracranial cancer immunotherapy

Several recent studies reported on the development of photodynamic therapy using photosensitizers and a light source including laser to generate reactive oxygen species to produce cytotoxicity in multiple extracranial solid cancer models [51, 52]. While this method can generate a sustained anti-tumor response through a combination of its direct killing of tumor cells and its disruption of tumor vasculature and immunogenic cell death [53, 54], the translation of this approach to intracranial tumors has shown some promise [55], yet comes with several logistical challenges, such as limited depth of light penetration and the resultant need for an aggressive surgical resection to allow for utilization of this therapy [56].

To eliminate the need for photosensitization, others championed an in situ autologous cancer vaccination or inCVAX in several late stage solid cancers in combination with local photothermal therapy to liberate whole cell tumor antigens with the immunoadjuvant activator *N*-dihydro-galacto-chitosan, a semi-synthetic functionalized glucosamine polymer, intended to activate antigen presenting cells in order to elicit a systemic tumor-specific immunologic response [57, 58]. Using laser to deliver intratumoral hyperthermia to induce ICD has also emerged as a potentially powerful approach to elicit tumor-specific immunity. Early attempts at applying this approach combined with the immune checkpoint CTLA-4 inhibitor in a patient with metastatic melanoma produced a durable response [59]. The authors in this case report postulated that the release of tumor associated antigens post LITT (i.e. likely through DAMP release) resulted in a therapeutic synergy with the CTLA-4 inhibitor. As a result, there has been growing evidence that LITT can improve the effectiveness of immunotherapeutics in solid tumors and is amenable to logistical adoption in primary intracranial tumors.

CNS-derived antigen presentation is thought to occur in the ipsilateral cervical lymph node chain. Whether this structural interaction is as robust for antigen presentation as in other organs with resident lymphoid components remains unclear [60]. The local BBB disruption caused by LITT and the subsequent release of CNS antigens into the lymphovascular system may result in a more vigorous release of tumor antigens and improve delivery of tumor antigens into the cervical lymph nodes, thereby triggering a tumor-specific immune response. To test this hypothesis, we generated DCs ex vivo from monocytes isolated from circulating peripheral blood mononuclear cells (PBMCs) in patients with recurrent GBM prior to LITT. These monocyte-derived DCs were subsequently primed with whole tumor lysate from a biopsy obtained at the time of the LITT procedure. After LITT, these primed DCs were cocultured with autologous PBMCs isolated before and at defined intervals after LITT to assess for the emergence of tumor-specific T cell activation as measured by interferon gamma production. The data in Fig. 2 from two patients with recurrent GBM treated with LITT demonstrates a significant increase in interferon gamma production starting between 2 to 4 weeks and rising further at 6 weeks after LITT. Importantly, the kinetics of immune activation coincides with the post-LITT release of CNS antigens [18, 61] (Fig. 3). These data indicate that a tumor-specific immune response is detectable in the peripheral environment after LITT and further supports the notion that LITT, through its local disruption of peritumoral BBB leading to release of tumor antigens into the periphery, can induce tumor-specific immunity akin to an in situ vaccination phenomenon.

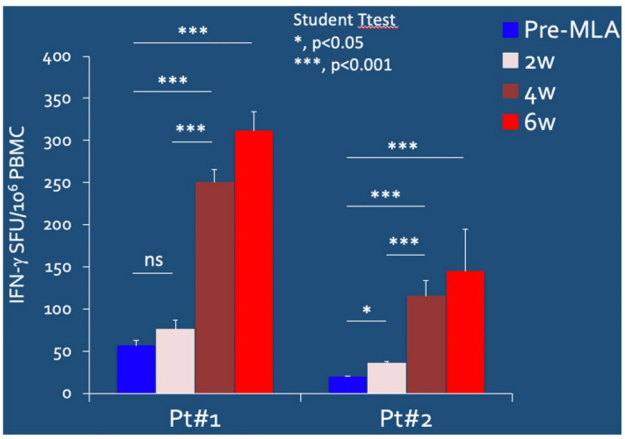

Fig. 2 Interferon gamma production detected by co-culturing tumor lysate-pulsed dendritic cells isolated pre-LITT with PBMCs taken at specified time points in relation to LITT in two selected patients. This demonstrates a dramatic increase of interferon gamma production in a temporal fashion in a glioma-specific manner

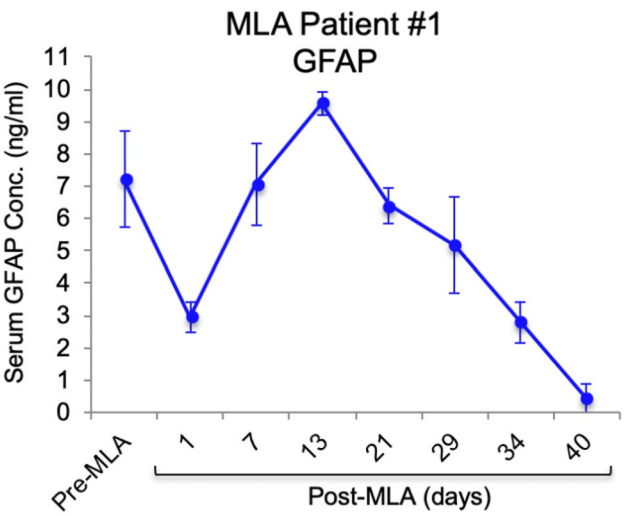

Fig. 3 Serum glial fibrillary acidic protein detected at specific time points post-LITT. There is a clear peak in detection at 2 weeks post-LITT serving as a physiologic indicator of blood brain barrier disruption

Institutional experience

To date, there are several ongoing early phase clinical trials seeking to evaluate the clinical outcomes of patients undergoing a variety of LITT-related combination therapies (Table 1). Recently, promising results of long-term survival for nine patients with bevacizumab-naïve recurrent high-grade glioma undergoing LITT plus the PD-1 inhibitor pembrolizumab in a dose escalation phase I/II study (NCT02311582) was reported [62]. In this study, three pembrolizumab dose levels of 100 mg, 150 mg and 200 mg given shortly after LITT and every 3 weeks thereafter resulted in no reported intracranial dose limiting toxicity with all 3 dose levels. In long-term follow-up, 4 out of 9 patients achieved survival of at least 30 months, with 3 patients continuing to exhibit durable responses at the time of data presentation. The Phase II of this trial is currently ongoing and will seek to characterize the expression of PD-L1 in the tumor microenvironment as well as identification of tumor specific T cells in these patients for correlation with progression free and overall survival to further evaluate the in situ vaccination effect of LITT. At our institution, these early encouraging results provided the rationale for the design and initiation of a pilot study investigating LITT plus pembrolizumab in patients with intracranial metastases refractory to radiotherapy (NCT04187872).

Outside the context of clinical trials, the authors' institution has been using LITT in malignant glioma lesions amenable to thermal ablation in patients with newly diagnosed or recurrent high-grade gliomas who desire additional therapy besides standard approaches and who either are not eligible for or choose not to participate in clinical trials. For newly diagnosed GBM patients, the authors consider LITT when the proposed surgical intervention is biopsy only, with the size and location of the lesion being favorable for LITT. After thermal ablation, these patients with newly diagnosed GBM would receive adjuvant chemoradiation vs radiotherapy alone vs temozolomide alone, depending on their age and functional status. For recurrent tumors, LITT is considered when tumor size as well as

Table 1 Clinical trials investigating various combination therapies with LITT for malignant glioma

Principal investigator	Institution	NCT	Phase	Condition	Treatment modality
Hormigo	Mount Sinai Medical Center	03341806	I	Recurrent GBM	Adjuvant avelumab q2 weeks post-LITT
Sloan	Case Western Reserve University	03277638	I/II	GBM	Neoadjuvant pembrolizumab 7 days pre-LITT followed by 14 and 35 days post-LITT
O'Brien	M.D. Anderson Cancer Center	03022,78	II	Recurrent GBM Recurrent AA	Adjuvant lomustine q6 weeks for 6 cycles post-LITT
Campian	Washington University School of Medicine	02311582	II	GBM	Adjuvant pembrolizumab q3 weeks post-LITT

functional status make thermal ablation a more attractive and safer option than repeat resection. Following LITT, treatment options include an immune checkpoint inhibitor to take advantage of the potential in situ vaccination phenomenon caused by LITT and salvage chemotherapy including carboplatin, lomustine (CCNU) or temozolomide re-challenge based on the notion that the local BBB disruption may increase their peritumoral concentration and efficacy. Bevacizumab can also be used following LITT in the recurrent setting when post-ablative symptomatic edema is difficult to control with steroids alone and especially when immune checkpoint inhibitors are used. In the right clinical context, bevacizumab may be safely used within 4 weeks post LITT [63], in which case, the authors recommend delaying its use at least 4–6 weeks, if feasible, to minimize reversing the potentially beneficial peritumoral BBB disruption following LITT.

Conclusion

Despite recent dramatic successes, especially in the area of cancer immunotherapy for many extracranial malignancies [64–66], primary intracranial malignancies remain one of the dark spots in cancer therapeutics development. Long-term survivors in GBM are generally limited to case series with heterogeneous treatment plans. Despite an explosive growth in research and funding into this area, no large-scale definitive solutions have been found. Local hyperthermia as delivered by LITT provides a promising targeted method of therapeutic enhancement for both chemotherapy and immunotherapy. Increasingly, evidence points to LITT resulting in local and systemic immune effects akin to an in situ vaccination with a multifactorial mechanism including direct thermocoagulation of tumor tissue, generation of DAMPs that lead to immunogenic cell death, and sustained local disruption of the BBB that allows for bilateral trafficking of tumor antigens out of the tumor into secondary lymphoid organs and immune effector cells into the tumor microenvironment. These unique effects of LITT on malignant brain tumors have the potential to convert these cold tumors into inflamed tissues and provide a rationale for combining LITT with immune checkpoint blockade to create an efficacious therapeutic synergy. Nevertheless, much of the current data is limited to preclinical models and early phase human trials, and it remains to be seen whether these early successes can be translated into positive long-term clinical results.

Compliance with ethical standards

Conflicts of interest David H. Shin declares that he has no conflict of interest. Kaitlyn F. Melnick declares that she has no conflict of interest. David D. Tran is one of the primary investigators in the referenced trial at this institution (NCT02311582). David D. Tran also has received grant funding from Celldex, NWBiotech, Novocure, and Merck. David D. Tran has received personal fees from Novocure and prIME Oncology. Ashley P. Ghiaseddin has received personal fees from Monteris Medical. Ashley P. Ghiaseddin has also received research funding support from Orbus Therapeutics.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. Bettag M et al (1991) Stereotactic laser therapy in cerebral gliomas. Acta Neurochir Suppl (Wien) 52:81–83
2. Sugiyama K et al (1990) Stereotactic interstitial laser-hyperthermia using Nd-YAG laser. Stereotact Funct Neurosurg 54–55:501–505
3. Lee I, Kalkanis S, Hadjipanayis CG (2016) Stereotactic laser interstitial thermal therapy for recurrent high-grade gliomas. Neurosurgery 79(Suppl 1):S24–S34
4. Silva D et al (2017) Magnetic resonance thermometry and laser interstitial thermal therapy for brain tumors. Neurosurg Clin N Am 28(4):525–533
5. Beaumont TL et al (2018) Magnetic resonance imaging-guided laser interstitial thermal therapy for glioblastoma of the corpus callosum. Neurosurgery 83(3):556–565
6. Mohammadi AM et al (2014) The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. Cancer Med 3(4):971–979
7. Hawasli AH et al (2014) Stereotactic laser ablation of high-grade gliomas. Neurosurg Focus 37(6):E1
8. Ali FS et al (2019) Cerebral radiation necrosis: incidence, pathogenesis, diagnostic challenges, and future opportunities. Curr Oncol Rep 21(8):66
9. Rahmathulla G et al (2012) Laser interstitial thermal therapy for focal cerebral radiation necrosis: a case report and literature review. Stereotact Funct Neurosurg 90(3):192–200
10. Sharma M et al (2016) Laser interstitial thermal therapy in the management of brain metastasis and radiation necrosis after radiosurgery: An overview. Expert Rev Neurother 16(2):223–232
11. North RY, Raskin JS, Curry DJ (2017) MRI-guided laser interstitial thermal therapy for epilepsy. Neurosurg Clin N Am 28(4):545–557
12. Prince E et al (2017) Laser interstitial thermal therapy for epilepsy. Curr Neurol Neurosci Rep 17(9):63
13. Shukla ND et al (2017) Laser interstitial thermal therapy for the treatment of epilepsy: evidence to date. Neuropsychiatr Dis Treat 13:2469–2475
14. Wicks RT et al (2016) Laser interstitial thermal therapy for mesial temporal lobe epilepsy. Neurosurgery 79(Suppl 1):S83–S91
15. Pisipati S et al (2016) Intracerebral laser interstitial thermal therapy followed by tumor resection to minimize cerebral edema. Neurosurg Focus 41(4):E13
16. Wright J et al (2016) Laser interstitial thermal therapy followed by minimal-access transsulcal resection for the treatment of large and difficult to access brain tumors. Neurosurg Focus 41(4):E14

17. Salem U et al (2019) Neurosurgical applications of MRI guided laser interstitial thermal therapy (LITT). Cancer Imaging 19(1):65
18. Leuthardt EC et al (2016) Hyperthermic laser ablation of recurrent glioblastoma leads to temporary disruption of the peritumoral blood brain barrier. PLoS ONE 11(2):e0148613
19. Mansor NI et al (2019) Crossing the blood-brain barrier: a review on drug delivery strategies for treatment of the central nervous system diseases. Curr Drug Deliv 16:698–711
20. Hersh DS et al (2016) Evolving drug delivery strategies to overcome the blood brain barrier. Curr Pharm Des 22(9):1177–1193
21. Weiss N et al (2009) The blood-brain barrier in brain homeostasis and neurological diseases. Biochim Biophys Acta 1788(4):842–857
22. Wang Z, Sun H, Yakisich JS (2014) Overcoming the blood-brain barrier for chemotherapy: limitations, challenges and rising problems. Anticancer Agents Med Chem 14(8):1085–1093
23. Zhan C, Lu W (2012) The blood-brain/tumor barriers: challenges and chances for malignant gliomas targeted drug delivery. Curr Pharm Biotechnol 13(12):2380–2387
24. Ostermann S et al (2004) Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. Clin Cancer Res 10(11):3728–3736
25. Pombo Antunes AR et al (2020) Understanding the glioblastoma immune microenvironment as basis for the development of new immunotherapeutic strategies. eLife. 9:e52176
26. Aldape K et al (2019) Challenges to curing primary brain tumours. Nat Rev Clin Oncol 16(8):509–520
27. Tomaszewski W et al (2019) Brain tumor microenvironment and host state: implications for immunotherapy. Clin Cancer Res 25(14):4202–4210
28. Tabatabai G et al (2006) Irradiation and hypoxia promote homing of haematopoietic progenitor cells towards gliomas by TGF-β-dependent HIF-1α-mediated induction of CXCL12. Brain 129(9):2426–2435
29. Tseng D, Vasquez-Medrano DA, Brown JM (2011) Targeting SDF-1/CXCR4 to inhibit tumour vasculature for treatment of glioblastomas. Br J Cancer 104(12):1805–1809
30. Vogelbaum MA et al (2018) First-in-human evaluation of the Cleveland Multiport Catheter for convection-enhanced delivery of topotecan in recurrent high-grade glioma: results of pilot trial 1. J Neurosurg 130:476–485
31. Brown CE et al (2016) Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med 375(26):2561–2569
32. Eichberg DG et al. (2019) multiple iterations of magnetic resonance-guided laser interstitial thermal ablation of brain metastases: single surgeon's experience and review of the literature. Oper Neurosurg (Hagerstown)
33. Goldberg SN, Gazelle GS, Mueller PR (2000) Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques, and diagnostic imaging guidance. AJR Am J Roentgenol 174(2):323–331
34. Mirza FN, Khatri KA (2017) The use of lasers in the treatment of skin cancer: a review. J Cosmet Laser Ther 19(8):451–458
35. Weston AP, Sharma P (2002) Neodymium:yttrium-aluminum garnet contact laser ablation of Barrett's high grade dysplasia and early adenocarcinoma. Am J Gastroenterol 97(12):2998–3006
36. Ellis MJ et al (2018) Management of an adolescent athlete with sports-related concussion and intraparenchymal hemorrhage. Curr Sports Med Rep 17(1):7–9
37. Vacchelli E et al (2014) Trial watch: chemotherapy with immunogenic cell death inducers. Oncoimmunology 3(1):e27878
38. Ma Y et al (2019) Near-infrared II phototherapy induces deep tissue immunogenic cell death and potentiates cancer immunotherapy. ACS Nano 13(10):11967–11980
39. Kiyatkin EA, Sharma HS (2009) Permeability of the blood-brain barrier depends on brain temperature. Neuroscience 161(3):926–939
40. Wang H et al (2014) Brain temperature and its fundamental properties: a review for clinical neuroscientists. Front Neurosci 8:307
41. Yamaguchi T et al (2019) Effect of heat stress on blood-brain barrier integrity in iPS cell-derived microvascular endothelial cell models. PLoS ONE 14(9):e0222113
42. Ji C et al (2016) Hyperthermia exacerbates the effects of cathepsin L on claudin-1 in a blood-brain barrier model in vitro. Brain Res 1631:72–79
43. Chen YZ et al (2003) Effect of hyperthermia on tight junctions between endothelial cells of the blood-brain barrier model in vitro. Di Yi Jun Yi Da Xue Xue Bao 23(1):21–24
44. Sabel M et al (2003) Locoregional opening of the rodent blood-brain barrier for paclitaxel using Nd:YAG laser-induced thermo therapy: a new concept of adjuvant glioma therapy? Lasers Surg Med 33(2):75–80
45. Appelboom G et al (2016) Stereotactic modulation of blood-brain barrier permeability to enhance drug delivery. Neuro Oncol 18(12):1601–1609
46. Rossmann C et al (2017) Temperature sensitive liposomes combined with thermal ablation: effects of duration and timing of heating in mathematical models and in vivo. PLoS ONE 12(6):e0179131
47. Mehta A, Oklu R, Sheth RA (2016) Thermal ablative therapies and immune checkpoint modulation: can locoregional approaches effect a systemic response? Gastroenterol Res Pract 2016:9251375
48. Kakinuma K et al (1996) Drug delivery to the brain using thermosensitive liposome and local hyperthermia. Int J Hyperthermia 12(1):157–165
49. Kakinuma K et al (1996) Targeting chemotherapy for malignant brain tumor using thermosensitive liposome and localized hyperthermia. J Neurosurg 84(2):180–184
50. Bredlau AL et al (2018) Localized delivery of therapeutic doxorubicin dose across the canine blood-brain barrier with hyperthermia and temperature sensitive liposomes. Drug Deliv 25(1):973–984
51. Kwiatkowski S et al (2018) Photodynamic therapy-mechanisms, photosensitizers and combinations. Biomed Pharmacother 106:1098–1107
52. Lim CK et al (2013) Nanophotosensitizers toward advanced photodynamic therapy of Cancer. Cancer Lett 334(2):176–187
53. Agostinis P et al (2011) Photodynamic therapy of cancer: an update. CA Cancer J Clin 61(4):250–281
54. Dolmans DE, Fukumura D, Jain RK (2003) Photodynamic therapy for cancer. Nat Rev Cancer 3(5):380–387
55. Eljamel S (2010) Photodynamic applications in brain tumors: a comprehensive review of the literature. Photodiagnosis Photodyn Ther 7(2):76–85
56. Cramer SW, Chen CC (2019) Photodynamic therapy for the treatment of glioblastoma. Front Surg 6:81
57. Zhou F et al (2015) InCVAX–a novel strategy for treatment of late-stage, metastatic cancers through photoimmunotherapy induced tumor-specific immunity. Cancer Lett 359(2):169–177
58. Qi X et al (2016) Development of inCVAX, In situ Cancer Vaccine, and Its Immune Response in Mice with Hepatocellular Cancer. J Clin Cell Immunol. https://doi.org/10.4172/2155-9899.1000438
59. Naylor MF et al (2017) Treatment of advanced melanoma with laser immunotherapy and ipilimumab. J Biophoton 10(5):618–622
60. Laman JD, Weller RO (2013) Drainage of cells and soluble antigen from the CNS to regional lymph nodes. J Neuroimmune Pharmacol 8(4):840–856

61. Tran D et al (2019) SCIDOT-43. Final data analysis of a pilot study testing the efficacy of using laser interstitial thermal therapy (LITT) to induce temporary disruption of the peritumoral blood brain barrier (BBB) to improve effectiveness of BBB-impermeant chemotherapy in recurrent glioblastoma. Neuro Oncol 21(6):6280–6281
62. Campian J et al (2019) ATIM-45. long term follow-up of a phase I/II study testing the toxicities and efficacy of pembrolizumab in combination with MRI-guided laser interstitial thermal therapy (LITT) in recurrent malignant gliomas. Neuro Oncol 21(6):611
63. Ali SC et al (2018) The safety of bevacizumab administered shortly after laser interstitial thermal therapy in glioblastoma: a case series. World Neurosurg 117:e588–e594
64. Verdegaal EM (2016) Adoptive cell therapy: a highly successful individualized therapy for melanoma with great potential for other malignancies. Curr Opin Immunol 39:90–95
65. De Santis CE et al. (2019) Breast cancer statistics 2019. CA Cancer J Clin.
66. DeSantis CE et al (2014) Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 64(4):252–271