An Overview of MR-Guided Laser Interstitial Thermal Therapy (MRg-LITT) in Disrupting the Blood-Brain Barrier: Efficacy and Duration

Ahmed Abdulsalam Ali Bakrbaldawi¹,²,³, Zhoule Zhu¹,²,³, Zhe Zheng¹,²,³, Junming Zhu¹,²,³, Hongjie Jiang¹,²,³,*

¹Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, 310009 Hangzhou, Zhejiang, China
²Clinical Research Centre for Neurological Diseases of Zhejiang Province, 310009 Hangzhou, Zhejiang, China
³Epilepsy Centre, The Second Affiliated Hospital, School of Medicine, Zhejiang University, 310009 Hangzhou, Zhejiang, China
*Correspondence: insjhj@zju.edu.cn (Hongjie Jiang)

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Abstract

The blood-brain barrier (BBB) is a selectively semi-permeable layer, crucial in shielding the brain from external pathogens and toxic substances while maintaining ionic homeostasis and sufficient nutrient supply. However, it poses a significant challenge for drugs to penetrate the BBB in order to effectively target brain tumors. Magnetic resonance-guided laser interstitial thermal therapy (MRg-LITT) is a minimally invasive technique that employs thermal energy to cauterize intracranial lesions with the potential to temporarily disrupt the BBB. This further opens a possible therapeutic window to enhance patient outcomes. Here, we review the impact of MRg-LITT on BBB and blood tumor barrier (BTB) and the duration of the BBB disruption. Studies have shown that MRg-LITT is effective due to its minimally invasive nature, precise tumor targeting, and low complication rates. Although the disruption duration varies across studies, the average peak disruption is within the initial two weeks post-ablation period and subsequently exhibits a gradual decline. However, further research involving larger groups with extended follow-up periods is required to determine disruption duration more accurately. In addition, evaluating toxicity and glymphatic system disruption is crucial to circumvent potential risks associated with this procedure.

Keywords: blood-brain barrier; MR-guided laser interstitial thermal therapy; brain tumors; blood-tumor barrier; permeability; glymphatic system

1. Introduction

The blood-brain barrier (BBB) systematically regulates molecular traffic across the central nervous system (CNS). It selectively allows substances to pass through, while constantly protecting the brain from external hazardous substances; thus it regulates an optimal environment for glia-neuronal activities. This selective permeability is essential to maintain a healthy and functional brain [1]. However, the barrier undergoes substantial modifications in CNS disorders such as tumors and metastasis, to form the blood tumor barrier (BTB). The BTB is involved in the synthesis of new blood vessels to ensure a sufficient supply of oxygen and nutrients to the tumor. In addition, these newly formed vessels are often abnormal and exhibit a more convoluted, irregular, and twisted structure than normal vessels [2]. Interestingly, the permeability of the BTB evolves throughout tumorigenesis, proliferation, and infiltration, and also varies across different tumor microenvironment with the periphery exhibiting higher permeability than the core of the tumor [2]. Moreover, these barriers further restrict drug distribution across the brain, posing significant challenges in treating CNS diseases [3]. Consequently, the scientific community is actively exploring novel strategies to circumvent these barriers and improve treatment efficacy.

Treating brain tumors with drugs has been a challenging task due to the BBB restricting the entry of most drugs to deeper regions of the brain. To overcome this challenge, several methods have been experimented to facilitate drug delivery, which include intratumoral, intranasal, or intrathecal drug administration, chemical modification of molecules, BBB modulation, efflux transporter and tight junction inhibition, transcytosis enhancement, and structural or osmotic BBB disruption. Although these methods have only been tested in pre-clinical models or small phase 1–2 trials, their effectiveness and safety in extensive clinical trials are yet to be determined [1]. With technological advancements such as microwave and laser probes, the Laser Interstitial Thermal Therapy (LITT) has gained significant attention as an emerging approach for direct and precise targeting. LITT is used to treat glioma, adult and pediatric epilepsy [4], and its applications significantly extend beyond such as recurrent brain metastasis, radiation necrosis, spinal tumors, movement disorders, and intractable psychiatric diseases [5–8]. Furthermore, LITT has the potential to not only cauterize lesions but also to disrupt the BBB.
and BTB locally to potentially enhance intracranial access for systemically administered pharmacotherapies [9]. LITT technique involves the application of thermal energy, which can also activate immune responses within the affected area [9]. Moreover, an exponential permeability of the BBB has been observed for weeks post-LITT treatment which facilitates the entry of therapeutic agents throughout the brain [9]. Thus, LITT is a promising technique not only for cauterizing tumors but also enhancing pharmacotherapy [10]. In this review, we explore the characteristics of the BBB and BTB and therefore highlight magnetic resonance-guided laser interstitial thermal therapy (MRg-LITT) as an emerging technique for treatment. We further include the impact of LITT on the BBB and BTB, as well as the duration of BBB disruption.

2. The Blood-Brain Barrier (BBB) and Blood Tumor Barrier (BTB)

The BBB is composed of endothelial cells which assemble to form a semi-permeable membrane, regulating selective flux of substances while protecting the brain. It is formed by a complex network of cells surrounding the cerebral vascular system comprising of endothelial cells, microglia, pericytes, astrocytes, and the vascular basement membrane [11]. This collective function of cells and membranes regulates a restrictive physical barrier that effectively separates the brain from systemic circulation [9]. Further, the neurovascular unit is comprised of a complex organization between endothelial cells, extracellular matrix, basal lamina, pericytes, astrocytes, and neurons [12]. Pericytes play a crucial role in forming the barrier characteristics such as tight junctions and the production of extracellular matrix proteins. They also regulate endothelial cell proliferation, migration, and differentiation [1]. In addition, pericytes modulate the BBB integrity, transcytosis rate, and efflux pump expression [1]. Furthermore, astrocytes are the most abundant cell types in the brain and provide a connection between neurons and blood vessels, encompassing more than 90% of capillaries [2]. Astrocytes contribute to various dynamic regulations in the nervous system and are involved in CNS inflammation as well as neurodegenerative diseases [11]. The Glymphatic System (GS) is a perivascular pathway between the vascular adventitia and astrocytic end-feet. GS is pivotal in eliminating neurotoxic waste products, distributing essential compounds, and maintaining brain homeostasis by facilitating the continuous exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) [13]. This exchange, driven by arterial pulsatility, breathing, and pressure gradients, is enabled by Aquaporin-4 (AQP4) water channels expressed in the polarized portion of astrocytic end-feet [13].

Moreover, the BBB comprises of occludins and claudins (mainly claudin-5) transmembrane proteins, junctional adhesion molecules and zonula occludens proteins [3]. Claudin-5 tight junction proteins establish a seal by linking actin cytoskeletons of adjacent endothelial cells to effectively limit the unrestricted diffusion of most solutes, polar molecules, and large molecules through the intercellular space of the BBB [9]. Thus, endothelial cells connected by adherens and tight junctions form the first barrier of the BBB. These cells work together as a robust barrier that regulates the paracellular, transcellular, and enzymatic flux of substances [2]. In addition, the physicochemical properties of molecules determine cell permeability and such lipophilic substances with molecular weight of less than 500 Da can diffuse freely across the barrier. In contrast, small polar molecules and larger solutes require active transcellular mechanisms [9]. Inner membrane transporters and drug efflux pumps also restrict the passage of lipophilic drugs, posing a significant challenge in delivering medications to the CNS [9]. Additionally, receptors and channels such as ATP-binding cassette (ABC) efflux transporters are located on the luminal and abluminal surfaces of the capillaries [11,14]. These transporters actively efflux substances out of the CNS, which provides the BBB with a selective nature, allowing cerebral blood vessels to regulate the transfer of ions and molecules from the bloodstream to the brain.

However, the BBB undergoes modifications in primary brain tumors, including glioblastomas and brain metastases, which is known as the BTB or also referred to as neo-barrier [2]. The compromised BBB comprises of significant loss or reduction of tight junction proteins, irregular distribution of mural cells, and astrocytic end-feet [2]. The permeability of the BTB varies across different regions of the tumor, with the highest permeability observed at the periphery compared to the core [2]. However, this inconsistency in permeability leads to an uneven distribution of therapeutic drugs within tumor lesions, subsequently affecting the effectiveness of the intended treatment [2]. In addition, this disparity primarily stems from the heterogeneous dysregulation of transporters (especially ABC transporters, mainly P-glycoprotein), receptors, angiogenesis pathways, and extracellular matrix components within the neurovascular unit [12,15,16]. Also, a dense extracellular matrix, edema, and increased interstitial pressures at the tumor site, often resulting from leaky and dysfunctional vessels further hinder the effectiveness of drug delivery [2,12,17]. Metabolic demands of primary and metastatic brain tumors trigger hypoxic regions, increase expression of vascular endothelial growth factor (VEGF) and angiogenesis, and subsequently the formation of abnormal vessels [1]. Therefore, this leads to a dysfunctional BTB [18], which poses a significant obstacle to effective brain tumor therapy.

3. MR-Guided Laser Interstitial Thermal Therapy (MRg-LITT)

The MRg-LITT is a minimally invasive technique that employs a thin fiber probe guided by real-time magnetic resonance imaging (MRI) towards the targeted tissue through a small burr hole using stereotactic methods...
The technology was first used in 1986 in the surgical treatment of brain metastases, and subsequent studies reported successful management of brain metastasis using LITT [20]. Once the laser fiber is inserted directly into the tumor, heating is initiated at a specific temperature, causing the tissue to undergo apoptosis and shrinkage [21]. The photons of laser are absorbed by surrounding tissue and thus heat redistribution occurs through convection and conduction via blood flow [22]. Thermal energy redistribution is not uniform and depends on the laser intensity and properties of the surrounding tissue [23]. The MRg-LITT offers multiple advantages compared to repeated surgical interventions, including decreased postoperative complications related to wound healing and CSF build-up. In addition, a shorter recovery period enables the safe treatment of deep-seated lesions that would otherwise be complicated for surgical resection [24]. The main goal of MRg-LITT is to accurately damage tumor tissue using thermal energy while ensuring a clear boundary between healthy and tumor tissues. This method can additionally disrupt the BBB and facilitate the effects of adjuvant drugs [25].

### 3.1 The Laser Probe

A disposable laser for soft-tissue ablation is used, which includes three main components: a laser generator, a disposable laser applicator probe, and a computer workstation. The probe comprises of a cooling catheter enclosing a diffusor-tipped optic fiber (Fig. 1) and the computer workstation is connected to a standard MRI to monitor real-time temperature maps and estimates of tissue coagulation during the ablation process. Subsequent developments in probe design introduced the optical fiber to be enclosed in a protective sheath that diffuses light, reducing power density across the tip and allow the distribution of a higher laser power [26,27]. One of the most essential improvements in LITT probe designs was the addition of a cooling mechanism. This system cools the optical fiber with a constant stream of fluid (normal saline) or cooled gas (liquid CO₂) and therefore effectively dissipates heat from the interface between the probe and tissue. This process further prevents substances from vaporizing or carbonizing, while increasing the performance at higher temperatures for extended periods without damaging the diffusing tip or causing tissue charring upon contact with the tumor [23]. Advances in probe design led to the development of side-firing laser probes which facilitates asymmetrical tissue penetration [23].

### 3.2 Types of Lasers Used in MRg-LITT

Currently, the Visualase™ and NeuroBlate® MRI-guided laser systems are commercially available and differ slightly in wavelength and design [23]. However, both utilize optical fibers sheathed in a catheter to deliver targeted light energy from the tip to surrounding tissues [9]. The size of tissue necrosis achieved through MRg-LITT depends on several factors such as the laser source’s specific wavelength, type of fiber, and light absorption and perfusion characteristics of the tumor tissue [28–31]. The two main types of MRg-LITT lasers are continuous-wave neodymium-doped yttrium aluminum garnet (Nd: YAG) lasers and diode lasers. The Nd: YAG has a wavelength of 1064 nm and tissue penetration ranging from 2 to 10 mm [32]. The diode lasers have wavelengths between 800 and 980 nm and operate at a wider power range [23]. These lasers are used for soft tissues with high blood perfusion such as highly vascularized and perfused brain tissues. Also, diode lasers have a higher water absorption coefficient than Nd: YAG lasers, facilitating thermal damage in a shorter time [26].

### 3.3 MR-Thermometry

Magnetic Resonance (MR) thermometry is a valuable non-invasive modality for monitoring temperature changes during LITT [23]. The proton-resonance frequency shift thermometry is a commonly used method that allows real-time, rapid volumetric temperature monitoring in multiple slices with high in-plane resolution and slice thickness every second [23,33]. Another MR thermometry technique is the spin-lattice or longitudinal relaxation time T1 method which measures temperature changes by acquiring amplitude and phase shift images. The imaging protocol defines thermal damage thresholds as reference points for estimating the treatment effect [34], and thus allows accurate monitoring of the LITT procedure and heat distribution. This imaging modality has demonstrated promising results due to its soft-tissue contrast, sensitivity to temperature, and ability to visualize thermal lesions [23]. In addition, the primary objective of thermal therapy is to selectively expose tumor tissue to an adequate temperature over a specific time to induce necrosis while preserving surrounding healthy tissue [35]. One of the limitations is for patients contraindicated for MRI such as those with metallic implants and body habitus [10].

### 4. Impact of LITT on Tumor Tissues

During laser ablation process of a typical tumor tissue, the central region of the tumor experiences elevated temperatures exceeding 46 °C, which therefore causes rapid and irreversible cellular damage and subsequent necrosis [9]. Consequently, intracellular components including DNA, RNA and heat shock proteins (HSPs) are released into the tumor microenvironment as a result of necrotic tumor cells. These intracellular components further act as inflammatory signals, initiating the recruitment and activation of natural killer (NK) cells within the tumor vicinity [9,36]. Furthermore, laser ablation stimulates the maturation and migration of dendritic cells toward the tumor, releases inflammatory cytokines and chemokines often observed alongside antigen-presenting cells (APCs), and collectively amplifies responses in the local inflammatory environment [9]. In
the tumor microenvironment, necrotic tumor cells release intracellular components like DNA, RNA, and HSPs post-ablation. These act as inflammatory signals triggering NK cells, dendritic cells and APCs to release inflammatory cytokines and chemokines. In addition, antigens released by tumor cells are phagocytosed by APCs and then transported to cervical lymph nodes. APCs presentation of tumor antigens to T cells activate tumor-specific T cells and thus lead to antigen-specific anti-tumor responses [9,37] (Fig. 2).

Typical tissue damaged by thermal energy is divided into three zonal areas: central, intermediate, and periphery. The central zone is characterized by high temperatures exceeding 46 °C, resulting in coagulative necrosis. The intermediate zone is outside the coagulation zone with temperatures ranging between 41 and 45 °C. Although the temperature is lower than the central zone, it still induces irreversible cellular damage. The primary cause of cell death within the intermediate zone is protein denaturation and cellular function loss [38]. Lastly, the periphery zone experiences temperatures between 38 and 41 °C, and tissue damage is reversible in comparison to other zones (Fig. 1). An inflammatory response in this area indicates the release of cytokines and other signaling molecules [39,40].

5. Impact of LITT on BBB/BTB

Several methods are available to detect changes in BBB permeability but none can fully characterize the alterations due to the complexity of the BBB. Exogenous labeled molecules and tight junction detection methods are mainly used in animal experiments [41,42]. Imaging is the primary method, due to its non-invasive nature, to detect BBB alteration in patients. However, there are limitations such as lack of sensitivity and accuracy, reliance on the physician experience to interpret images, and high-cost [43,44]. A summary of the marker and methods is in Table 1 (Ref. [41,45–65]).

The impact of LITT on the BBB/BTB disruption has not been fully assessed in most studies. For instance, Luther et al. [66], focused more on the clinical applications of LITT for cerebral metastases without directly addressing whether it has any effect on the BBB. However, recent studies have shown that thermal damage can increase permeability, facilitating plasma protein leakage [12]. In addition, LITT can generate mechanical stress on blood vessels through rapid temperature fluctuations, leading to transient openings in the BBB/BTB [1]. Furthermore, inflammatory responses induced by LITT in brain tissue and tumors elicit alterations in transporters, receptors expression and mechanisms responsible for regulating the BBB/BTB [15]. Clinical trials presented compelling evidence regard-
ing MRg-LITT’s capacity to induce transient and localized disruption of the BBB [10]. In addition, Patel et al. [3] provided an overview of thermal therapy’s ability to disrupt the BBB/BBT, where hyperthermia of 42.5 °C increased permeability to Trypan blue. A study by Chandar et al. [67] reported that a patient with no evidence of tumor recurrence for over three years post-LITT. The patient was administered adjuvant Temozolomide and 60 Gy fractionated radiotherapy and is still alive nine years after diagnosis [67]. Chandar et al. [67] also observed increased cluster of differentiation 8 (CD8), activated macrophage infiltration and programmed death ligand-1 (PD-L1) expression. This study also points to LITT as a treatment approach with the potential for long-term delay of tumor recurrence and improving immunotherapy responses [67]. Despite these findings, the precise mechanisms underlying MRg-LITT-mediated disruption of the BBB/BBT remain unclear [1]. However, the potential mechanisms such as thermal damage inflicted upon the endothelial cells and tight junctions of the BBB/BBT, as well as the presence of CD8, are illustrated in (Fig. 2).

Numerous techniques have been suggested to improve drug delivery for the treatment of brain tumors. These include drug administration directly into the tumor, using intranasal or intrathecal drug administration, modification of molecules chemically, modulating the BBB, inhibiting efflux transporters and tight junctions, enhancing transcytosis, and physically or osmotically disrupting the BBB [1]. However, the efficacy of these methods has only been tested in pre-clinical models or small phase 1–2 trials [1]. A summary of LITT advantages over these methods in Table 2 (Ref. [1,2,12,68–74]).

6. BBB Disruption Duration Post-LITT

Several studies have evaluated the BBB disruption duration after thermal ablation in both humans and animals. For instance, Sakai et al. [75] used a neurosurgical laserthermia system to target deeper brain region tumors in animals and found that the BBB remains open for 6 days following the procedure. In a review, Patel et al. [3] expressed that laser ablation transiently increased the BBB/BBT permeability, with peak disruption duration after one week and thus persisting for up to 30 days post-ablation. In addition, they found that molecules as large as human Immunoglobulin G (IgG, approximately 150 kDa) could penetrate the CNS following LITT procedure [3]. Other studies used imaging and serum to precisely assess the BBB opening and closing windows. As such, Leuthardt et al. [10] reported elevated serum levels of Neuron-specific enolase (NSE) a neuronal marker typically confined to the CNS, following laser ablation in patients with recurrent glioblastoma. Furthermore, this increased permeability in the peritumoral region was attributable by LITT, with peak disruption duration around 1–2 weeks post-ablation and therefore returning to the base-line by weeks 4–6. This disruption period enables a window to potentially distribute intra-arterial drugs to deeper brain regions. Moreover, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) revealed Ktrans elevation perioperation and gradually decreased over four weeks [10]. A longer duration of BBB opening was reported by Morris et al. [76], where the BBB dysfunction persisted for up to eight months post-thermal therapy in epilepsy patients. NSE peaked 1–3 weeks post-ablation and subsequently returned to the baseline by the sixth week post therapy [76]. In addition, Bartlett et al. [77] observed a transient increase in the BBB permeability, indicated by elevated serum enolase levels in 24 hours post-ablation, peaking during the first two weeks post-LITT and thus returned to baseline by the eighth week postoperative. The Ktrans images for four patients revealed increased BBB dysfunction in 24 hours perioperative which persisted for two weeks [77].

Using glioma implantation murine models, Salehi et al. [19] investigated the BBB disruption duration and tracked post-LITT BBB permeability using a BBB-impermeable tracer. They observed increased tracer presence in the tumor-bearing hemisphere following treatment, indicating increased BBB permeability up to 30 days post-treatment. Histopathological analyses revealed a significant increase of endothelial transcytosis and disrupted gap junctions between BBB endothelial cells as potential mechanisms underlying transient BBB disruption [19]. These Studies provide compelling evidence that LITT effectively disrupts the BBB, allowing typically brain-impermeable substances to penetrate the CNS as shown in Table 3 (Ref. [10,19,75–77]). The most pronounced disruption reported was within one week post-ablation, which persisted for up to 30 days or even up to eight months in cases such as epilepsy [76]. However, further investigations are required to understand the mechanisms underlying this disruption such as increased endothelial transcytosis and disrupted gap junctions between the BBB endothelial cells. Although BBB disruption duration varies across studies, it is observed to peak within the initial two weeks post-ablation and subsequently exhibits a gradual decline. It is essential to note that these studies included both human and animal subjects, both applied to tumors and non-tumors regions with a limited number of participants [3,10,19,75–77]. Further studies with larger groups of participants and extended follow-up periods are required for accurate assessment of the BBB disruption duration. Therefore, identifying precise opening of the BBB/BBT post-LITT can increase the potential efficacy of administering adjuvant pharmacological agents.

7. Toxicity and Glymphatic System

The disruption of the BBB/BBT by LITT can lead to serious conditions where there is no filtration of components from the bloodstream to the brain parenchyma. As such, harmful effects could result from neurotoxic compo-
Fig. 2. Overview of neurovascular unit in healthy BBB and post-LITT BTB. (a) The diagram shows normal state of BBB on the bottom side, with an intact neurovascular unit, and disrupted BBB/BTB on the top. (b) Illustrates the BBB/BTB disruption by LITT. Tumor cells undergo necrosis, T cells move to the ablation site, and Antigen-presenting cells (APCs) phagocytose tumor antigens. The image also depicts a cervical lymph node, where antigen presentation to T cells and expansion of CD8 T cells occurs. (c) Represents the complex network of interactions within the BBB; signaling pathways connect to endothelial cells, pericytes, and astrocytes. These pathways influence transcellular and paracellular transport by modulating transporter expression and disrupting protein complexes involved in cell-to-cell junctions. This also highlights the intricate balance within the BBB ensuring its proper functioning. BBB, blood-brain barrier; BTB, blood tumor barrier; PDGFRβ, platelet-derived growth factor receptor beta; SLIT2, slit homologue 2 protein; VEGF, vascular endothelial growth factor; SEMA2A, semaphorin 2A; WNT, wingless-related integration; LRP1, lipoprotein receptor-related protein 1; TGFβ, transforming growth factor beta; Angl/Angll, angiotensin I/angiotensin II; SHH, sonic hedgehog; ApoE, apolipoprotein E; HSPGs, heparan sulfate proteoglycans; PDGF, platelet-derived growth factor; CAMs, cell adhesion molecules; PTC1, protein patched homologue 1; AT1, angiotensin II receptor type 1; TIE2, tyrosine kinase with Ig and epidermal growth factor (EGF) homology domains 2; TGFβR2, transforming growth factor-beta receptor 2; NRP1, neuropilin receptor 1; Gpr124, protein-coupled receptor 124; VEGFR2, vascular endothelial growth factor receptor 2; Plexin 1A, transmembrane protein; S1P/S1RP, sphingosine-1-phosphate; LRP5/6, low-density lipoprotein receptor-related protein 5/6; HSPs, heat shock proteins.
<table>
<thead>
<tr>
<th>Markers/methods</th>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
<th>Molecular Weight; size</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100β</td>
<td>Astrocyte-specific protein synthesized by glial cells and upregulated in neurological disorders. Increases in serum levels in CNS disorders.</td>
<td>Early detection of BBB dysfunction especially in young individuals and pregnant women.</td>
<td>Low sensitivity in detecting mild BBB and disruption site of BBB remains unidentified.</td>
<td>21 kDa; NR</td>
<td>[41,45,46]</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G permeation into CNS parenchyma is considered as pathological marker of BBB disruption.</td>
<td>Low cost and high availability. Nontoxic.</td>
<td>IgG not only comes from disrupted vessels but also from other areas.</td>
<td>150 kDa; 5.3 nm</td>
<td>[41,47,48]</td>
</tr>
<tr>
<td>Albumin</td>
<td>Albumin ratio in CSF/serum shows BBB disruption, indicating albumin leakage from blood into CSF.</td>
<td>Low cost and high availability. No tracer is required. Variety of methods for detecting.</td>
<td>Low sensitivity in detection of mild BBB disruption due to albumin large size.</td>
<td>69 kDa; 3.5 nm</td>
<td>[41,49]</td>
</tr>
<tr>
<td>Dextran</td>
<td>Polysaccharides of branched glucose molecules used to determine BBB permeability.</td>
<td>Can be administered at any time. Multiple molecular weights.</td>
<td>High cost. False positive due to low molecular weight. Can pass intact BBB. Renal clearance only for small molecular size.</td>
<td>286 Da–2000 kDa; 0.8–38.2 nm</td>
<td>[41,50]</td>
</tr>
<tr>
<td>Evans blue</td>
<td>High molecular weight marker to assess capillary and cellular membrane permeability.</td>
<td>Visible on examination. Low cost.</td>
<td>Low specificity binding to albumin and tissues. Low renal clearance; toxic.</td>
<td>961 Da; NR</td>
<td>[41]</td>
</tr>
<tr>
<td>Horseradish peroxidase</td>
<td>Interacts with 3′,3′-diaminobenzidine to generate a brown product to characterize BBB breakdown.</td>
<td>Low cost and stable. Available for light and electron microscopy.</td>
<td>No renal clearance; toxic. Vascular permeability varies in different strains of rat models.</td>
<td>44 kDa; 3 nm</td>
<td>[41,51]</td>
</tr>
<tr>
<td>Radiolabeled sources</td>
<td>Markers with different sizes labeled with radioactive isotopes. Enable evaluation of BBB permeability.</td>
<td>No interaction with proteins. Metabolically stable for quantitative determination of BBB.</td>
<td>High cost. Cannot be visualized. No morphological determination.</td>
<td>342 kDa; 0.51 nm</td>
<td>[41,52,53]</td>
</tr>
<tr>
<td>Sodium fluorescein</td>
<td>A fluorescent tracer utilized to detect BBB disruptions. Infiltrates the brain upon BBB compromise.</td>
<td>Low cost and easily available. Can be visually assessed. Small weight molecules detected with low concentration.</td>
<td>Interaction with BBB transporters. Weakly bind to plasma proteins.</td>
<td>376 kDa; NR</td>
<td>[54,55]</td>
</tr>
<tr>
<td>Components of BBB</td>
<td>Alterations observed in expression of tight junctions. Micro-perspectives in BBB disruption. Include, not limited to occludin, claudin-5, claudin-12, ZO-1, ZO-2, JAM-A, JAM-B, and β-catenin.</td>
<td>Direct detection of BBB breakdown.</td>
<td>Altered expression of tight junctions does not represent changes in BBB. Site of disruption is unknown.</td>
<td>/</td>
<td>[46,56]</td>
</tr>
<tr>
<td>Multi-photon microscopy</td>
<td>Detects solutes like IgG, dextrans, and sodium fluorescein to evaluate BBB permeability.</td>
<td>Fast detection imaging, real-time measurement with minimum invasion.</td>
<td>Observation is limited to cerebral microvessels beneath the pia mater.</td>
<td>/</td>
<td>[57,58]</td>
</tr>
<tr>
<td>DCE-NIRS</td>
<td>Dynamic contrast-enhanced near-infrared spectroscopy is mainly used to detect cerebral blood flow and quantify BBB permeability.</td>
<td>Quantitative evaluation; easily transportable to patient bedside.</td>
<td>Limited availability; affected by numerous factors (rate of dye delivery and cerebral hemodynamics). Low resolution quality.</td>
<td>/</td>
<td>[59,60]</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Detects BBB leakage and quantify differences between intravascular and extravascular contrast agents.</td>
<td>Quick data acquisition; quantification of BBB permeability. High resolution.</td>
<td>Patients contraindicated to MRI. (e.g., pacemaker device implanted). Irregularities associated with measurement of minor BBB leakage.</td>
<td>/</td>
<td>[61,62]</td>
</tr>
<tr>
<td>DCE-CT</td>
<td>Functional test that involves a dynamic series of images before and after administration of intravenous iodinated contrast agents.</td>
<td>Simple image acquisition and processing. High-resolution. Widely available at low cost.</td>
<td>Ionizing radiation is required. Limited to anatomical coverage of the cranial-caudal region.</td>
<td>/</td>
<td>[63–65]</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Routes</th>
<th>Mechanism of action</th>
<th>Molecules used</th>
<th>Disadvantages over LITT</th>
<th>REF</th>
</tr>
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<tbody>
<tr>
<td>Direct injection of drugs</td>
<td>Bypass BBB</td>
<td>Intrathecal, intratumoral, Intraventricular and intranasal delivery.</td>
<td>Carmustine, cyclophosphamide gold-iron oxide nanoparticles (plus systemic temozolomide). Trastuzumab ± cytarabine or methotrexate lysosomal cytarabine. lyposomal cytarabine. Trastuzumab ± cytarabine or methotrexate lysosomal cytarabine.</td>
<td>Limited to selectively target brain regions. Limited by the dosage volume. Risk of infection and hemorrhage. CSF leakage. repetitive administration.</td>
<td>[2,12,68]</td>
</tr>
<tr>
<td>Osmotic and chemical</td>
<td>Paracellular</td>
<td>Expression of caveolin-1 and downregulation of tight junction (TJ) proteins; stimulation of the endocytic process; activation of cyclic monophosphate cGMP; and activation of bradykinin B2 receptors to increase BBB permeability.</td>
<td>Minoxidil sulfate, NS1619, vardenafil, Cerport (RMP-7), and mannitol.</td>
<td>Extensive BBB disruption; unwanted side effects; and high possibility of neurotoxicity.</td>
<td>[1,68]</td>
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<td>modification of BBB</td>
<td></td>
<td></td>
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<td>Chemical modification of</td>
<td>Paracellular</td>
<td>Drug coupling to a receptor-targeted delivery reduce interaction with the multidrug resistance and increase the drug’s lipophilicity and plasma half-life making it capable of crossing the BBB.</td>
<td>Tx67 (paclitaxel with a succinate group in C10 position), chlorambucil-tertiary butyl ester, etirinotecan pegol, and liposomal irinotecan.</td>
<td>Obstacles include first-pass clearance; immune response; off-target effects; and low levels of drug extravasation.</td>
<td>[69–72]</td>
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<tr>
<td>drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanoparticle-based delivery</td>
<td>Paracellular and</td>
<td>Nanoparticles with ligands interact with receptors on endothelial cell surface to form vesicles that release nanoparticles into the parenchymal side. Coating nanoparticles with albumin or chitosan increases BBB permeability via adsorptive transcytosis.</td>
<td>Insulin, transferrin, lactoferrin, or antibodies against some endothelial receptors, and polysorbate 80.</td>
<td>Limited therapeutic efficacy due to efflux pump.</td>
<td>[2,12,73]</td>
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<td></td>
<td>Transcellular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-intensity focused</td>
<td>Paracellular and</td>
<td>Stress on endothelial cells (EC); stretching of cerebral blood vessels; and elevation of EC temperature lead to altered membrane proteins and increase trans-endothelial fenestrations. Changes in TJ-integrated adhesion molecules and caveolae formation. Combined with microbubbles.</td>
<td>Low energy pulse waves. Exogenous administration of microbubbles (lipid, albumin or polymer-shelled gas pockets).</td>
<td>Potential neuronal damage. Toxicity (due to excess drug delivery). Excessive immune response and hemorrhage.</td>
<td>[2]</td>
</tr>
<tr>
<td>ultrasound (LIFU) assisted</td>
<td>Transcellular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell-based approach</td>
<td>Transcellular</td>
<td>Genetic modification of carrier cells for anticancer properties.</td>
<td>Anticancer proteins, antiangiogenic factors, or immunosupportive factors like IL-12.</td>
<td>Toxicity of cell carriers. Low therapeutic loading of carrier cells.</td>
<td>[2,12,74]</td>
</tr>
<tr>
<td>Physical disruption of BBB</td>
<td>Paracellular and</td>
<td>Radiofrequency electromagnetic radiation, microbeam radiation therapy (MRT), implantable devices, and convection-enhanced delivery (CED).</td>
<td>Combination with chemotherapeutic drugs such as paclitaxel, doxorubicin, temozolomide, and carboplatin.</td>
<td>Risks include infection and hemorrhage. Low infusion rates and volumes. Rapid efflux of drugs from injection sites.</td>
<td>[1,2]</td>
</tr>
<tr>
<td></td>
<td>Transcellular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LITT, laser interstitial thermal therapy; cGMP, cyclic guanosine monophosphate; NS1619, Naphthalenesulfonamide 1619; IL-12, Interleukin-12; RMP, Cereport.
port mechanisms, therefore exacerbating GS dysfunction. A disruption in the BBB can alter cell polarity and trans-structure and functionality of the BBB.

The BBB and the GS are integral to the clearance of metabolic waste products and maintenance of homeostasis in the brain. Metabolic wastes are therefore eliminated through the blood by efflux transporters located at the BBB or by the GS into the ISF through perivascular spaces (PVS) towards cervical lymph nodes. The BBB and the GS collectively maintain cerebral homeostasis. However, a disruption in the BBB can alter cell polarity and transport mechanisms, therefore exacerbating GS dysfunction. Similarly, disruptions of the GS can result in the obstruction of drainage space, metabolite imbalance, and accumulation of toxic substances, further affecting the structure and functionality of the BBB. A recent study involving 109 participants with cerebral small vessel disease (cSVD), revealed the association of GS dysfunction with BBB integrity. They further found a correlation between high-grade enlarged perivascular spaces (EPVS) and GS dysfunction with a higher BBB leakage rate. Therefore, GS dysfunction is implicated in the pathophysiology of compromised BBB integrity. However, further studies are required to support the causal relationship between the increased BBB permeability and GS dysfunction.

Numerous factors can disrupt the BBB and lead to neurotoxicity. As such, chemotherapy increases BBB permeability to allow chemotherapeutic agents into the CNS and further promote inflammation. Studies have shown that exposure to certain neurotoxic substances such as organophosphorus esters, tributyltin oxide, and trimethyltin can lead to neurotoxic effects with alterations in neurotransmitters, ATPase suppression, and subsequently neurodegeneration. The relationship between neurotoxicity and LITT is complex and multifaceted due to the lack of large scale studies involving large groups of participants. In addition, BBB disruption methods have been reported to be safe and tolerable in early-phase clinical trials. Meanwhile, long-term analyses and the effects of other concomitant medications when exposed to a more permeable BBB have yet to be detailed in studies. Therefore, a comprehensive evaluation of the safety profile of drugs currently in use for other disorders is required before clinical implementation towards BBB disruption. While LITT presents promising benefits, its application requires careful regulation to prevent potential toxic effects and preserve brain health. Maintaining the integrity of the BBB is paramount in this regard by maintaining a balanced microenvironment. However, further research is urged to investigate the correlation between LITT and neurotoxicity.

8. Discussion and Future Direction

In this review, we highlighted the role of the BBB and its components in protecting the brain by forming a selective membrane for the flux of specific molecules. In addition, the BBB prevents even adjuvant drugs from being distributed throughout the brain parenchyma. Over the years, numerous methods have been reported to disrupt the BBB for pharmacotherapy of deep-seated lesions and other neurovascular, neurodegenerative, and neuroinflammatory diseases, brain injury, and tumors. However, GS functionality is enhanced during sleep and general anesthesia but impaired in diseases and conditions such as aging, traumatic brain injury, Alzheimer’s disease, stroke, and diabetes.

Table 3. Summary of studies evaluated BBB disruption duration.

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Year</th>
<th>Sample size</th>
<th>Subject</th>
<th>Disruption duration</th>
<th>Method for assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Sakai et al. [75]</td>
<td>1992</td>
<td>5</td>
<td>Wistar rats</td>
<td>6 days</td>
<td>Macroscopic (Trypan blue)</td>
</tr>
<tr>
<td>Study 2</td>
<td>Leuthardt et al. [10]</td>
<td>2016</td>
<td>14</td>
<td>human</td>
<td>1–6 weeks</td>
<td>DCE-MRI ($K_{trans}$); neuron-specific enolase (NSE)</td>
</tr>
<tr>
<td>Study 3</td>
<td>Morris et al. [76]</td>
<td>2017</td>
<td>12</td>
<td>human</td>
<td>5–8 months</td>
<td>Volumetric contrasted (Gadolinium) T1 weighted MRI; BSE</td>
</tr>
<tr>
<td>Study 4</td>
<td>Salehi et al. [19]</td>
<td>2020</td>
<td>N/A</td>
<td>mice</td>
<td>1 month</td>
<td>Fluorimetry, microscopy, and immunofluorescence</td>
</tr>
<tr>
<td>Study 5</td>
<td>Bartlett et al. [77]</td>
<td>2023</td>
<td>4</td>
<td>human</td>
<td>1–8 weeks</td>
<td>DCE-MRI ($K_{trans}$); neuron-specific enolase (NSE)</td>
</tr>
</tbody>
</table>

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; BSE, brain-specific enolase; N/A, Not Available.
disorders. However, these methods have pros and cons that could elevate associated risks and affect patients’ effective treatment. Therefore, we reiterate that crossing the BBB/BBT is an essential step toward adjuvant drugs to achieve better outcomes especially for intracranial disorders.

LITT is an emerging technique effective in disrupting the BBB/BBT and mainly to cauterize brain lesions and treatment for epilepsy. Although the average disruption duration peaked in the initial two weeks, further studies are required especially post-LITT and administration of adjuvant drugs. In vitro and animal models experimentations would be beneficial to assess specific drugs with low toxicity and side effects for deep-rooted brain disorders. Future research involving larger groups of participants is needed to explore the correlation between thermal dosage, wavelength impact, and the spatiotemporal relationship of molecule diffusion across the BBB/BBT. Advancements in this field could further improve the sensitivity and specificity of LITT on targeted tissues, thereby optimizing efficacy and reducing complications.

The LITT technique is a challenging procedure with limitations and as such it may result in complications such as edema, hematoma, hyperthermic injury, worsening of the patient’s health and eventually death. This technique is simpler than craniotomy but requires proper training and availability of the LITT equipment. However, LITT is mainly available at specialized hospitals in urban areas due to the requirement for MRI during surgery and the lack of technical support, trained physicians and appropriate equipment which are not available in other medical centers. These also contribute to health inequality for rural or underserved communities. Until now, studies have yet to assess the potential neurotoxicity and dysfunctional lymphatic system post-LITT. The clearance of toxic substances from the CNS and maintenance of homeostasis are crucial for proper brain functioning. In addition, once the BBB/BBT is disrupted by LITT, external factors such as health-risk behaviors and exposure to pathogens can lead to further complications and death.

9. Conclusion

MRg-LITT capability extends beyond merely cauterizing deep intracranial lesions which are typically non-resectable with traditional surgery. We reviewed the advantages, disadvantages and limitations of using LITT. However, LITT can also be used to open the BBB/BBT with low complications for adjuvant drugs administration which further promote its importance. In short, further studies are required to evaluate the post-procedural toxicity that could escalate the risk associated with this procedure.

Author Contributions

AAAB and HJ designed the research study. ZZheng and ZZhu collected the references, JZ provided help and advice on the table and figures. AAAB wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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