The efficacy of laser interstitial thermal therapy for brain metastases with in-field recurrence following SRS: systemic review and meta-analysis

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ABSTRACT

Objective: To study the efficacy of LITT for BM patients experiencing in-field recurrence following SRS.

Methods: A literature search was conducted to identify studies investigating local control (LC) rate and overall survival (OS) of LITT for BMs with IFR following SRS.

Results: Analysis included 14 studies (470 patients with 542 lesions). The 6-month (LC-6) and 12-month (LC-12) local control rates were 78.5% (95% CI: 70.6–84.8%) and 69.0% (95% CI: 60.0–76.7%) separately. Pooled median OS was 17.15 months (95% CI: 13.27–24.8). The overall OS-6 and OS-12 rates were 76.0% (95% CI: 71.4–80.0%) and 63.4% (95% CI: 52.9–72.7%) separately. LITT provided more favorable local control efficacy in RN than BM recurrence (LC-6: 87.4% vs. 67.9%, \( p = 0.009 \); LC-12: 76.3% vs. 59.9%, \( p = 0.041 \)).

Conclusions: LITT is an effective treatment for BM patients experiencing IFR following SRS. For different pathological entities, LITT showed more satisfactory local control efficacy on RN than BM recurrence.

Introduction

An estimated 20% of cancer patients will develop brain metastases (BM) with the majority occurring in those with lung, breast cancers and melanoma [1]. Stereotactic radiosurgery (SRS) alone or postoperatively to surgical cavity is now well-established as a standard first-line treatment for patients with a limited number of BMs [2,3]. However, recurrence within the previously irradiated field (also known as in-field recurrence, IFR) could be as high as 40% for radiation resistant cancers in radiological follow up [4,5], which may represent true tumor recurrence or radiation necrosis (RN) or a combination of both. Both BM recurrence and RN could be irreversibly progressive, leading to neurological deterioration and shortened lifespan [6].

Currently no consensus on the treatment modality for IFR has been established. Surgical resection may be considered as the preferred salvage option [7–9], but some patients are not amenable for resection due to deep-seated lesions or cannot tolerate the modality due to poor clinical performance status. Effective medical therapy in this setting remains elusive as significant heterogeneity exists with regard to pathology and drug related variables.

MRI-guided laser interstitial thermal therapy (LITT, also known as laser thermal ablation, SLA) is an emerging option which offers a minimally invasive approach for IFR following prior SRS [10–34]. Although an increasing usage of LITT has been reported in the setting of IFR over the past decade [10–34], they are limited by small sample sizes generally and lack of differentiation between BM recurrence and RN in some studies, which possibly resulted in wide variation on efficacy among different studies.

Here, we performed a systemic review and meta-analysis of the literature to determine the overall efficacy of LITT for IFR and to elucidate underlying causes of the variation.

Materials and methods

Data source

The literature search was conducted in PubMed, EMBASE and Cochrane Library (until October, 2020). Our search strategy included the terms ‘LITT’, ‘laser interstitial’, ‘thermal therapy’, ‘stereotactic laser ablation’ AND ‘brain’, ‘cerebral’, ‘intracranial’ AND ‘metastases’, ‘metastasis’, ‘metastatic’ and was restricted to human studies published in English. The following search strategy was used to search PubMed: (((LITT) OR (laser interstitial) OR (thermal therapy) OR (stereotactic laser ablation)) AND (brain)) AND (tumor) OR (neoplasms) OR (metastasis) OR (radiation necrosis)) AND
Articles were screened by title and abstract, and those passed screening were read in full. Additionally, we manually searched the reference lists of all accepted articles to screen for articles missed in the initial search.

**Selection criteria and process**

Studies that met the following criteria were chosen for the analysis: (i) clinical studies designed to evaluate the efficacy of LITT for IFR; (ii) using laser ablation, not cryotherapy or radiofrequency ablation; (iii) including intracranial BM recurrence or RN after SRS, not spinal lesions; (iv) more than five patients enrolled; (v) data for local control rate or overall survival (OS) was available. All the potentially relevant papers were reviewed independently by two investigators (CC and GYB) and disagreements were resolved by discussion and consensus. Details on study design, patient characteristics, local control rates and follow-up of survival were extracted by the two investigators. When data were solely provided in graphical form, figures were digitized to extract the numerical value using Engauge Digitizer version 11.1 (http://digitizer.sourceforge.net/).

**Statistical analysis**

The pooled median OS and corresponding 95% CI were pooled by R software 4.0.1 with ‘metamedian’ package [35]. The pooled LC-6, LC-12, OS-6 and OS-12 rates were estimated with Comprehensive Meta-Analysis program version 3 (Biostat, Englewood, NJ, USA). For each meta-analysis, the Cochrane’s Q and I² statistic were estimated to assess the heterogeneity of the included studies. For I² > 50%, the assumption of homogeneity was deemed invalid, and the random-effects model was used. The fixed-effects model was chosen when I² ≤ 50%. A two-tailed p value of < 0.05 was deemed statistically significant.

**Results**

**Identification of relevant studies**

The flow diagram of the selection process for relevant studies was shown in Figure 1. Our search yielded a total of 576 articles. 539 articles were excluded for not being related to the topic after reviewing the titles and abstracts, and the remaining 37 articles were reviewed further [10,11,13–34,36–48]. Twenty one studies were considered to be ineligible for inclusion for the following reasons: (i) five studies enrolled no more than five patients [36–40]; (ii) nine studies did not describe the clinical endpoints of interest [11,14,16,18,20,26,28,33,41]; (iii) one study enrolled patients who were included in another larger study [13]; (iv) one study mixed brain metastases with primary brain tumor [22]; (v) seven articles were reviews [42–48]. Finally, 14 studies were included in the meta-analysis [10,15,17,19,21,23–25,27,29–32,34]. It should be noted that patients enrolled in the study conducted by Hernandez et al. [24] were included in the study conducted by Kaye et al. [29], but the former provided local control rate which was not provided by the latter study, so the study conducted by Hernandez et al. was only included for local control analysis. Although enrolling both brain metastases and primary brain tumors, the study conducted by Smith et al. was included because the clinical endpoints of BMs could be calculated from raw data [17].

![Figure 1. Studies identified and screened for eligibility.](http://digitizer.sourceforge.net/).
**Characteristics of included studies and patients**

Clinical and treatment related characteristics for all included studies were summarized in Tables 1 and 2. The 14 studies were comprised of nine retrospective case series, two retrospective case-control studies, one phase I clinical trial, one phase II clinical trial and one prospective registry study. The two case-control studies compared LITT with surgical resection [25] and bevacizumab [34] on RN separately.

A total of 470 patients with 542 lesions were included in the final analysis. Median age was 59.6 years (range 23–90). A female predominance (female: 281/429, 65.5% vs. male: 148/429, 34.5%) was noted. Median Karnofsky Performance Status (KPS) was 85 (range 50–100). The most common primary tumor type was lung cancer (127/299, 42.5%), following by breast cancer (65/299, 21.7%) and melanoma (44/299, 14.7%). Median pre-operative lesion volume was 4.6 cm³ (range 0.2–38.9).

**Local control**

Local control rate was available for analysis from a total of 342 lesions enrolled in ten studies. The 6-month local control rate (LC-6) ranged between 66.7% and 96.0% and the pooled effect was 78.5% (95% CI: 70.6–84.8%) as determined by the random-effects model (heterogeneity analysis: $I^2 = 50.350\%$, $p = 0.034$) (Figure 2(a)). The 12-month local control rate (LC-12) ranged between 56.0% and 84.7% and the pooled effect was 69.0% (95% CI: 60.0–76.7%) as determined by the random-effects model (heterogeneity analysis: $I^2 = 50.584\%$, $p = 0.048$) (Figure 2(b)).

To explore the heterogeneity of the included studies, different pathological entities were further analyzed. In RN subgroup, 149 lesions enrolled in seven studies were available for LC-6 analysis and 75 lesions enrolled in four studies for LC-12 analysis. The pooled effects were 87.4% (95% CI: 75.6–93.9%) for LC-6 (Figure 3(a)) and 76.3% (95% CI: 65.0–84.8%) for LC-12 (Figure 3(b)) separately. In BM recurrence subgroup, 176 lesions enrolled in six studies were available for LC-6 analysis and 153 lesions enrolled in five studies for LC-12 analysis. The pooled effects were 67.9% (95% CI: 59.0–75.6%) for LC-6 (Figure 3(a)) and 59.9% (95% CI: 47.9–70.9%) for LC-12 (Figure 3(b)) separately. LITT provided more favorable local control efficacy in RN than BM recurrence (LC-6: 87.4% vs. 67.9%, $p = 0.009$; LC-12: 76.3% vs. 59.9%, $p = 0.041$) (Figure 3).

With the median pre-operative lesion volume 4.6 cm³ as the cutoff point, a subgroup analysis regarding pre-operative lesion volume was carried out from 321 lesions enrolled in eight studies. And a trend was noted favoring studies with lower median pre-operative lesion volume on LC-6 without reaching statistical significance (81.8% vs 78.3%, $p = 0.709$) (Supplementary Figure S1).

**Overall survival**

Overall survival (OS) was available for analysis from a total of 410 patients enrolled in 11 studies. The pooled median OS
was 17.15 months (95% CI: 13.27–24.8). The 6-month overall survival rate (OS-6) ranged between 52.3% and 96.0% and the pooled effect was 76.0% (95% CI: 71.4–80.0%) as determined by the fixed-effects model (heterogeneity analysis: $I^2 = 46.10\%$, $p = 0.059$) (Figure 4(a)). The 12-month overall survival rate (OS-12) ranged between 26.1% and 84% and the pooled effect was 63.4% (95% CI: 52.9–72.7%) as determined by the random-effects model (heterogeneity analysis: $I^2 = 68.20\%$, $p = 0.001$) (Figure 4(b)).

Different pathological entities were further analyzed. In RN subgroup, 141 patients enrolled in seven studies were available for OS-6 analysis and 122 patients enrolled in six studies for OS-12 analysis. The pooled effects were 83.1% (95% CI: 68.4–91.8%) for OS-6 (Figure 5(a)) and 66.8% (95% CI: 52.9–72.7%) for OS-12 (Figure 5(b)).

### Table 2. Summary of local control efficacy, overall survival benefit and predictive factors of included studies.

| Author, Year | Follow-up (months) | Local control rate (%) | Median/ Mean OS (months) | Overall survival rate (%) | Factors related to local control efficacy or OS |
|--------------|--------------------|------------------------|--------------------------|---------------------------|-----------------------------------------------|
|              |                    | 6-month | 12-month |                        | 6-month | 12-month |
| Carpentier, 2011 | 13.3               | 66.9    | 58.3     | 17.4 ± 3.5              | 83.3    | 66.6     | Extend of Ablation |
| Ali, 2016      | 4.7 (range: 2.1-26.5) | 72.6    | 56       | NA                      | NA      | NA       | Extend of Ablation |
| Smith, 2016    | NA                 | 56.5    | 40.8     | NA                      | 66.7    | 66.7     | Pathology (RN vs. BM recurrence) |
| Ahluwalia, 2018| NA                 | NA      | NA       | NA                      | 72.2    | NA       | Pathology (RN vs. BM recurrence) |
| RN             | NA                 | 100     | NA       | NA                      | 82.1    | NA       | Extend of Ablation |
| BM recurrence  | NA                 | 54      | NA       | NA                      | 64.5    | NA       | Pathology (RN vs. BM recurrence) |
| Chaunzwa, 2018 | 5.9 (range: 1-31)  | 92.90%  | NA       | 13.27 (9.83-23.20)      | 76.3    | 59.4     | Pre-operative KPS score |
| Salehi, 2018   | 32.26 (range: 7.2-46.73) | NA     | NA       | 79.4                    | 69.0    | NA       | Extend of Ablation and pre-operative lesion volume |
| Hong, 2019     | NA                 | 75.6    | 72.2     | NA                      | 79.4    | 69.0     | Extend of Ablation |
| RN             | NA                 | 87.8    | 87.8     | NA                      | 94.4    | 73.8     | Pathology (RN vs. BM recurrence) |
| BM recurrence  | NA                 | 62.5    | 54.7     | NA                      | 62.5    | 62.5     | Pathology (RN vs. BM recurrence) |
| Bastos, 2020   | 7 (IQR:4-21.5)     | 69.6    | 59.4     | 29 (12.7-45.2)          | 80.6    | 65.8     | Extend of Ablation, receiving systemic therapy before and after LITT |

#### Figure 2.
Local control efficacy of LITT for BMs with IFR following SRS, including 6-month local control rate (a) and 12-month local control rate (b).
CI: 49.1–80.8%) for OS-12 (Figure 5(b)) separately. In BM recurrence subgroup, 85 patients enrolled in four studies were available for OS-6 analysis and 65 patients enrolled in three studies for OS-12 analysis. The pooled effects were 69.2% (95% CI: 58.5–78.2%) for OS-6 (Figure 5(a)) and 66.5% (95% CI: 54.3–76.9%) for OS-12 (Figure 5(b)) separately. No significant difference between RN and BM recurrence (66.8% vs. 66.5%, \( p = 0.978 \)) was detected in OS-12 (Figure 5(b)); however, a trend favoring RN subgroup was noted in OS-6 (83.1% vs. 69.2%, \( p = 0.104 \)) (Figure 5(a)).

**Discussion**

Due to advances in systemic treatments which allow better control of extracerebral disease and prolong patients overall survival, practitioners are encountering a growing number of patients with BMs failed first-line treatment, particularly those relapse after surgical resection and SRS [45]. Limited salvage local control options are available, especially when lesions are not amenable for resection or patients cannot tolerate surgery. LITT is an emerging minimally invasive procedure that consists of a laser probe inserted under stereotactic guidance and destroys tissue through generation of heat. Real-time intraoperative magnetic resonance thermal imaging (MRTI) qualitatively allows the technique to create thermal ablation safely in deep-seated and high eloquent regions [49].

In this study, we showed that LITT is a viable salvage option for IFR of brain metastases following SRS with 12-month local control rate ranging from 62% to 93% and median OS of 8.7 months after surgery [7–9]. LITT shows comparable local control rate but more satisfactory overall survival benefit.

In field recurrence following SRS can be attributable to BM recurrence or RN or a combination of both. Our study showed that LITT provided more satisfactory local control efficacy on RN than BM recurrence with higher LC-6 (87.4% vs. 67.9%, \( p = 0.009 \)) and LC-12 (76.3% vs. 59.9%, \( p = 0.041 \)). Tumor recurrence is greatly contributed to tumor stem cell, which is resistant to thermal damage and overexpression of heat shock protein family might involve in the mechanism of...
thermoresistance [50, 51]. RN has been described as a radiation dose-dependent central area necrosis surrounded by vascular hyalinization [52]. As heat diffuses rapidly in necrotic tissue with higher water content, higher temperature is achieved inside the RN lesion and in the perilesional area [53], which may contribute to higher local control efficacy in RN.

It is quite challenging to distinguish BM recurrence from RN. No standard has been established on radiographic modalities for differentiation and histopathology study is still considered as the gold standard. But pre-ablation biopsy during LITT was not performed routinely in some studies, which took MRI as the differentiation modality or didn’t distinguish the two pathological entities. Some researchers argued that sampling bias in needle biopsy specimen may result in an inaccurate diagnosis while possible bleeding or air entry during biopsy could impair the visualization of ablation extension during MRTI [45]. Since effectiveness of LITT on RN was proven to be better than BM recurrence in several studies [19, 25, 27] and biopsy result is paramount for guiding post-treatment decision-making, it is recommended to preform pre-ablation biopsy routinely [32].

Although LITT showed more satisfactory local control efficacy on RN than BM recurrence, the overall survival benefits of the two pathological entities did not present the same pattern. The higher overall survival rate on RN compared with BM recurrence at 6 months follow up (83.1% vs. 69.2%, p = 0.104) did not extend to 12 months follow up (66.8% vs. 66.5%, p = 0.978). Although LITT provided good local control of intracranial diseases, control of extracerebral disease was the main determinator of BM patients overall survival time.

Besides pathological type, pre-operative lesion volume was reported as predictive factor correlated with local control efficiency in two studies [23, 27] and extent of ablation was reported as predictive factor in six studies [10, 15, 23, 27, 31, 32]. In our study, sub-group analysis showed higher 6-month local control rate in studies with mean pre-operative lesion volume $< 4.6 \text{ cm}^3$ for LC-6 (81.8% vs 74.3%). Beechar et al. showed that pre-operative lesion volume played a significant role in determining response to LITT with smaller lesions responding better to LITT than lesions with larger volumes [20]. Although extent of ablation was not analyzed due to wide variability of data, several studies showed that higher extent of ablation was associated with improved local control and OS [10, 15, 23, 27, 31, 32]. The correlation between lesion volume and local control/survival was partially caused by higher extent of ablation in small lesions [27]. Because a single laser trajectory has a maximal diameter of 4 cm, smaller lesions have more favorable thermal damage threshold coverage compared with their larger counterparts [33]. Currently, the ideal lesion to be treated with LITT is a circumscribed lesion with a diameter less than 3 cm [32, 45]. For larger lesions, multiple fibers could be used to cover the entire target, but this must be balanced against the increased risk for malignant cerebral edema and neurological deficits, particularly for lesions located near critical structure [45].

![Figure 4](image-url) Overall survival benefit of LITT for BMs with IFR following SRS, including 6-month overall survival rate (a) and 12-month overall survival rate (b).
For larger lesions or lesions with complex geometry that may not be ablated completely, there may be a role for adjuvant SRS for the residual and for systemic therapy in the post-LITT period. Ali et al. [15] showed that BM recurrence with extent of ablation <80% had higher risk of recurrence, but adjuvant hypofractionated SRS 1 months later could enhance the efficacy of LITT. Bastos et al. [27] showed that patients receiving systemic therapy within 3 months after LITT had a longer freedom of local recurrence. Radiological study with dynamic contrast-enhancement MRI showed that hyperthermia caused by LITT might be able to induce disruption of the BBB and the peak of permeability occurred in one to two weeks and resolved in four to six weeks after LITT [54]. Validation of the synergistic effect between LITT and adjuvant therapy in future studies is warranted.

This study must be interpreted in the context of certain limitations. Firstly, most of the included studies are retrospective and enrolled small case series. Secondly, significant heterogeneity exists in the studies enrolled. Substantial efforts were made to explore the possible causes for heterogeneity and found that different pathological entities (RN vs. BM recurrence) could explain the heterogeneity adequately. Random-effects model was used when heterogeneity exists within a group to minimize the bias. Thirdly, a lack of standardized definition on local control across different series represents a potential source of bias and should be addressed by consensual use of objective criteria such as the RANO-BM in future studies.

**Conclusion**
For brain metastasis patients experiencing IFR following SRS, LITT is an effective salvage treatment option with 6-month local control rate of 78.5% and 12-month local control rate of 69.0%. For different pathological entities, LITT showed more satisfactory local control efficacy on RN than BM recurrence.

**Disclosure statement**
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