Health Policy Advisory Committee on Technology

Technology Brief Update

Magnetic resonance thermometry-guided laser interstitial thermal therapy for intracranial neoplasms

April 2016
2016 Summary of findings

Since the publication of the original technology brief there have been a number of new studies published on the use of magnetic resonance thermometry-guided laser interstitial thermal therapy (MRT-guided LITT) for intracranial neoplasms and epilepsy. All of the studies identified were level IV case series; therefore, the evidence base remains poor due the absence of a control group. In the absence of comparative data it is not possible to determine the efficacy of MRI-guided LITT compared with existing treatment techniques.

In patients with intracranial neoplasms, MRI-guided LITT offers a minimally invasive means of potentially extending survival to patients with limited therapeutic options. However, no comparative data was available to quantify this survival benefit. Overall the procedure appears to be well tolerated; however, complications have been observed that may impact negatively on quality of life, such as worsening (or new-onset) neurological deficit.

In patients with epilepsy, MRT-guided LITT has been the subject of small case series studies. One study found the majority of patients experienced a meaningful reduction in seizure frequency following ablation treatment. No evidence comparing the results of surgical resection and ablation of epilepsy-causing tissue were identified. Hence, the place of MRT-guided LITT in the therapeutic management of intractable epilepsy and its safety and comparative clinical effectiveness are unclear.

2016 HealthPACT Advice

Treatment with MRT-guided LITT may extend survival in patients with intracranial neoplasms who have limited treatment options and have failed first-line treatment. In addition, MRT-guided LITT is an emerging therapeutic option for, in particular, paediatric patients with refractory epilepsy. However, there is a paucity of data available describing the safety and effectiveness of this technology, or its impact on the quality of life of patients with either indication. Patients may seek treatment support through the Commonwealth’s Medical Treatment Overseas (MTO) programme, noting the strict criteria required for such support. However, few patients with refractory brain tumours or epilepsy choose this option.

HealthPACT does not support investment in this technology in clinical practice at this time. However, HealthPACT recommends that the evidence for MRT-guided LITT be reviewed in 24 months.
TECHNOLOGY BRIEF UPDATE 2016

Technology, Company and Licensing

Register ID  WP166

Technology name  Magnetic resonance thermometry-guided laser interstitial thermal therapy (MRT-guided LITT)

Patient indication  For use in patients with inoperable intracranial neoplasms and epilepsy

Reason for assessment

In 2013, a Technology Brief investigated the use of MRT-guided LITT for treating intracranial neoplasms that were not amenable to surgery. In light of the small body of evidence available in 2013, it was recommended that MRT-guided LITT be monitored for 24 months to coincide with the expected completion of larger case series studies. The purpose of the current Update is to consider the evidence that has emerged since 2013, and determine whether this new evidence may provide additional information to inform policy decisions.

Description of the technology

Laser interstitial thermal therapy (LITT) is a minimally invasive ablative treatment for intracranial neoplasms.\(^1\) In LITT, an applicator probe is placed within the tumour and deposits precise amounts of light energy. Light energy is converted to thermal energy within the tumour, resulting in a rise in local temperature. The heat generated damages intracellular proteins leading to coagulation and cell necrosis.\(^2\) LITT potentially enables tumour resection in patients who are unable to undergo open surgery. However, the inability to monitor tissue temperature and thermal energy deposition, and to view the resulting anatomical changes in real time, has hindered the application of LITT. Consequently, LITT has often resulted in suboptimal treatment, with patients receiving under or over ablation of their tumours.\(^3\)

Two systems, Visualase (Visualase Inc., Texas, USA) and the NeuroBlate® System (Monteris Medical Inc., Minnesota, USA), overcome these problems by combining LITT with magnetic resonance thermometry (MRT) imaging. MRT scans produce detailed images of internal organs and temperature patterns in real time. The Visualase and NeuroBlate software process the MRT scan data and generate real-time, colour-coded thermal and tissue images, allowing the surgeon to precisely monitor and guide tumour ablation. The software also includes safety limits. If the surgeon exceeds the required thermal dose or strays outside the tumour zone, the laser is automatically deactivated. The safety features and real-time feedback enable the surgeon to maximise tumour ablation while avoiding critical brain structures.
The Visualase and NeuroBlate Systems share many similar components, including an image-processing workstation, a laser applicator probe, a laser generator and a cooling catheter. However, the two systems differ in the efficiency of the laser. The Visualase laser functions at a wavelength of 980 nm, whereas the NeuroBlate laser operates at 1064 nm. The smaller wavelength of the Visualase laser enables it to rapidly heat tissue and produce sharper thermal gradients at lower power than the NeuroBlate laser. For example, ablation of a 2.5 cm metastatic tumour would take 6 minutes with the Visualase laser and 73 minutes with the NeuroBlate System. In addition, the NeuroBlate laser requires a larger cooling catheter than the Visualase laser. This feature is particularly relevant when trying to minimise damage to adjacent sensitive areas in the brain. A final point of contrast between the two LITT systems relates to the use of anaesthesia. Patients treated with the NeuroBlate System require general anaesthesia, whereas patients undergoing treatment with Visualase only require general anaesthesia if they are in the supine position. Consequently, the latter patient group may experience less postoperative morbidity and may be discharged earlier.

Since the original Technology Brief, there has been more evidence published using the technology in patients with medically refractory epilepsy. This indication was not included in the original Brief, but some available evidence has been included in this update as it appears to be an emerging indication for the technology.

2016 Stage of development in Australia

- [ ] Yet to emerge
- [ ] Experimental
- [ ] Investigational
- [ ] Nearly established
- [ ] Established
- [ ] Established but changed indication or modification of technique
- [ ] Should be taken out of use

2016 Licensing, reimbursement and other approval

Both Visualase and the NeuroBlate® System have received United States Food and Drug Administration (FDA) 510(k) clearance. NeuroBlate® has also been approved by Health Canada. The MRT-guided LITT system is approved for a range of indications, including the coagulation of soft tissue in cardiovascular thoracic surgery, dermatology, ear-nose-throat surgery, gastroenterology, general surgery, gynaecology, head and neck surgery, neurosurgery and plastic surgery.

At present, neither of these technologies has been listed on the Australian Register of Therapeutic Goods (ARTG) or has received a European CE mark.
2016 Australian Therapeutic Goods Administration approval

☐ Yes
☒ No
☐ Not applicable

2016 Diffusion of technology in Australia

The diffusion of MRT-guided LITT within Australia could not be determined through review of published literature. It appears that MRT-guided LITT has been largely studied and used in the United States of America.

2016 International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials underway or completed</td>
<td>Limited use</td>
</tr>
<tr>
<td>Canada</td>
<td>✔</td>
</tr>
<tr>
<td>France</td>
<td>✔</td>
</tr>
<tr>
<td>United States of America</td>
<td>✔</td>
</tr>
</tbody>
</table>

2016 Evidence and Policy

Safety and effectiveness

Since the Technology Brief in 2013 there have been a number of studies published on MRT-guided LITT for intracranial neoplasms and epilepsy. This update includes five case series studies: three on intracranial neoplasm, one on epilepsy and one that included both intracranial neoplasm and epilepsy (Table 1). A further three studies with less than 11 patients were not included in this update due to their small sample size.¹²-¹⁴

Table 1 Included study characteristics

<table>
<thead>
<tr>
<th>Study/design</th>
<th>Inclusion criteria (LITT system)</th>
<th>Exclusion criteria</th>
<th>Length of follow-up &amp; number of patients</th>
<th>Conflicts of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial neoplasm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohammadi et al 2014¹⁵</td>
<td>Patients with glioblastoma or anaplastic glioma (NeuroBlate®)</td>
<td>N=1 Patient with history of prior glioblastoma with multiple prior treatments including radiation. Pre-LITT biopsy showed necrosis without recurrent glioma</td>
<td>Median 7.2 months (range: 0.1-23) N=35 Losses to follow-up = NR</td>
<td>Five of the authors had financial or other ties with Monteris Medical, Inc.</td>
</tr>
</tbody>
</table>
### MR thermometry-guided laser interstitial thermal therapy for intracranial neoplasms

**Roa et al 2014**

- **Level IV evidence** (prospective)
- **Single centre**
- **USA**
- Patients with recurrent brain metastases and/or RN* (Visualase)
- Patients concurrently receiving other management for RN
- Median 24 weeks (range 4-84)
- N=17
- Losses to follow-up = 2
- None disclosed

**Missios et al 2013**

- **Level IV evidence** (retrospective)
- **Single centre**
- **USA**
- Patients with glioblastoma, initial (6) or recurrent (5) (NeuroBlate®)
- NR
- Median 8.3 months (range 2.7-26.2)
- N=11
- Losses to follow-up = NR
- One author is a consultant medical director of Monteris Medical, Inc.

**Epilepsy**

**Willie et al 2014**

- **Level IV evidence** (prospective)
- **Single centre**
- **USA**
- Adult patients with intractable mesial temporal lobe epilepsy, with and without mesial temporal sclerosis (Visualase)
- NR
- Median 14 months (range 5-26)
- N=13
- Losses to follow-up = NR
- Funding was provided to Emory University from Visualase, Inc. Two authors have financial ties to Visualase, Inc.

**Combined**

**Hawasli et al 2013**

- **Level IV evidence** (prospective)
- **Single centre**
- **USA**
- Patients with glioma (11), brain metastases (5) and epilepsy (1) (NeuroBlate®)
- NR
- N=17
- Losses to follow-up = NR
- One author has a consulting relationship with Monteris Medical, Inc.

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*Patients were also required to have Hamofsky performance status of >70, extracranial disease under reasonable control and life expectancy of at least three months. Patients with multiple metastases were allowed to participate as long as they had one or two dominant lesions that would be the target of laser ablation, no radiographic progression of disease elsewhere and a target lesion <5 cm in diameter.

LITT: laser interstitial thermal therapy; NR: not reported; RN: radiation-induced cerebral necrosis

**Studies using MRI-guided LITT to treat intracranial neoplasm**

**Mohammadi et al 2014**

Mohammadi et al reported on patients with high-grade glioma who were treated using the NeuroBlate® System. The study retrospectively reviewed patients who underwent MRI-guided LITT between May 2011 and December 2012 at three centres in the United States of America. Sixty patients underwent the procedure; however only patients with high-grade glioma (n=35) proven on pathology were eligible for inclusion in the study. The primary outcome measure was progression-free survival. Secondary endpoints included overall survival and rate of surgical complications. Median age at the time of the procedure was 56 years (range 19-79). Sixteen patients were treated for newly diagnosed high-grade glioma and 18 patients were treated for recurrent disease. Disease was located in the frontal lobe (15), thalamic region (7), parietal lobe (5), temporal lobe (5), insular cortex (2) and corpus callosum (2).
callosum (1). One patient with prior glioblastoma and multiple prior treatments (including radiation) was excluded from the study, therefore results were reported for 34 patients. In this excluded patient, pre-LITT biopsy showed necrosis without recurrent glioma. Perioperative steroid use was not reported.

**Effectiveness**

The estimated median progression-free survival for the 34 patients was 5.1 months; with 25 patients showing progression during follow-up. Two patients had died before the first follow-up MRI and were counted as progressions. Median overall survival had not been reached at the time of analysis as 66 per cent of patients were still being followed up; however, the authors estimated that one-year survival was 68 per cent (standard deviation [SD] 9%). Thirty-five per cent of patients (12/34) had died at the time of analysis and progression was the cause in two of these deaths. Survival-related outcomes are summarised in Table 2, and changes in tumour volume are summarised in Table 3.

**Table 2** Results of studies reporting on intracranial neoplasms or lesions

<table>
<thead>
<tr>
<th>Study</th>
<th>Indications</th>
<th>Median progression or recurrence free survival (range)</th>
<th>Overall survival</th>
<th>Local progression at last follow-up, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohammadi et al 2014</td>
<td>Glioblastoma or anaplastic glioma</td>
<td>5.1 months</td>
<td>Estimated 1-year survival: 68% (SD 9)</td>
<td>25/34 (74%)</td>
</tr>
<tr>
<td>N=34</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Roa et al 2014</td>
<td>Recurrent metastases or RN</td>
<td>37 weeks (range 4-92)</td>
<td>At 39 weeks: 57%</td>
<td>2/14 (14%)</td>
</tr>
<tr>
<td>N=14</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hawasali et al 2013</td>
<td>Glioma (11), brain metastases (5) and epilepsy (1)</td>
<td>7.6 months, brain tumour 8 months, glioma * 5.8 months, metastases</td>
<td>Median 10.7 months post procedure (5.8 for patients treated for metastases)</td>
<td>7/17† (41%)</td>
</tr>
<tr>
<td>N=17</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Missios et al 2014</td>
<td>Glioblastoma and recurrent glioblastoma</td>
<td>6.1 months (range 2-26)</td>
<td>Median 8.4 months (range 2-26)</td>
<td>8/11 (73%)</td>
</tr>
<tr>
<td>N=11</td>
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</table>

*For recurrent, deep-seated glioma it was 8.4 months and for de novo deep-seated glioma it was 2.9 months; †at or before 10 months; RN: radiation-induced cerebral necrosis; n/N: number with progression/sample size
Table 3  Changes in tumour volume following ablation

<table>
<thead>
<tr>
<th>Study</th>
<th>Indications</th>
<th>Original tumour volume</th>
<th>Final tumour volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohammadi et al 2014</td>
<td>Glioblastoma or anaplastic glioma</td>
<td>Median volume: 10.13 cm³ (range 0.7-49.9)</td>
<td>Median residual volume by blue TDT line: 0.66 cm³ (range 0-22.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median residual volume by yellow TDT line: 0.19 cm³ (range 0-15.5)</td>
</tr>
<tr>
<td>Roa et al 2014</td>
<td>Recurrent metastases or RN</td>
<td>Mean lesion size: 3.66 cm³ (range 0.46-25.45)</td>
<td>24 hour postoperative MRI showed a mean 278% increase in volumetric size (range 112-771) for 12/14 lesions. In 2 lesions a reduction to 74% and 91% of pre-treatment size was observed. Reduction to ≤10% of pre-treatment size was seen in seven patients after 24 hours (usually observed ≥ 16 weeks after)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Volume treated reported per patient.</td>
</tr>
<tr>
<td>Hawasali et al 2013</td>
<td>Glioma (11) brain metastases (5) and epilepsy (1)</td>
<td>Mean target volume: 11.6 cm³ (SD 9.6)</td>
<td>Volume treated reported per patient.</td>
</tr>
<tr>
<td>Missios et al 2014</td>
<td>Glioblastoma and recurrent glioblastoma</td>
<td>Median tumour volume: 12.40 cm³ (range 2.2-25.4)</td>
<td>Median residual volume by blue TDT line: 0.86 cm³ (range 0-9.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median residual volume by yellow TDT line: 0.09 cm³ (range 0-8.3)</td>
</tr>
</tbody>
</table>

SD: standard deviation; TDT: thermal damage threshold; RN: radiation-induced cerebral necrosis

Safety

The authors noted the following postoperative complications: worsening of neurological deficit (7/34, 21%); new seizure (1/34, 3%); postoperative hyponatremia (abnormally low sodium level in the blood (1/34, 3%); bilateral deep vein thrombosis (1/34, 3%) and infection (2/34, 6%). Moderate to large intra-cerebral haemorrhage was observed in three cases (9%).

Roa et al 2014

Roa et al assessed the Visualase system for treating patients with recurrent brain metastases and/or radiation necrosis. All patients had received prior stereotactic radiosurgery for their metastases. Patients were recruited at a single centre between November 2010 and March 2013. In total 15 procedures were performed on 14 patients. Two patients were lost to follow-up due to compliance issues; hence only data from 12 patients were available for analysis. The primary endpoint was local control of the tumour and/or radiation necrosis. Secondary endpoints included changes in tumour volume after MRT-guided LITT, steroid use, symptomatic relief, progression-free survival and overall survival. The age range of included patients was between 46 and 82 years, and the lesions were located in the frontal lobe (6), cerebellum (6), cerebellar peduncle (1), temporal lobe...
(1) and parietal lobe (1). The majority of patients received a 1-2 week post-operative steroid taper and four out of 15 patients required steroids prior to the procedure.

**Effectiveness**

Overall there were 14 lesions evaluated with MRI at more than four weeks after treatment. Median radiological follow-up was 24 weeks (range 4-84), and in patients who remained alive at the point of analysis the median follow-up time was 52 weeks (range 10-84). There were two recurrences observed within the thermal ablation zone and both were treated successfully with craniotomy and resection. In terms of steroid use, three patients continued steroids for more than three months for persisting preoperative symptoms; 11 patients did not require long-term steroids. Of the seven symptomatic patients, five had resolution or decreased incidence of symptoms, one had progression of symptoms and another had improved walking ability but worsened facial weakness. The median progression-free survival for the cohort was 37 weeks (range 4-92); six of the 14 patients had died at the time of manuscript preparation. Overall survival at 39 weeks was 57 per cent, and causes of death were neurological progression elsewhere in the brain (n=1) and extracranial disease progression (n=5). Survival-related outcomes are summarised in Table 2, and changes in tumour volume are summarised in Table 3.

**Safety**

The authors reported no misplaced laser catheters and no incidence of stroke, infection or haemorrhage requiring operation. Two postoperative complications occurred: one patient suffered a non-operative peri-procedural haemorrhage and another had new-onset left-sided weakness.

Hawasli et al 2013

Hawasali et al reported on 17 patients treated with the Neuroblate® System at a single centre between September 2010 and November 2012. Patients were treated for deep-seated glial neoplasms or recurrent gliomas (11), recurrent brain metastases after radiosurgery (5) and deep-seated epilepsy focus (1). The mean age of the patients was 59 years (range 38-78), and the lesions were in the frontal/parietal lobe (8), thalamus (4), insula (3), basal ganglia (1) and corpus callosum (1). Six patients had MRT-guided LITT as their first treatment, whilst 11 had undergone prior therapy. A range of outcome data was reported. Follow-up data were collected from hospital and clinical charts, with MRI results analysed at five and ten months. Steroid therapy was offered to patients who experienced perioperative aphasia or hemiparesis.

**Efficacy**

The single patient treated for epilepsy was reported seizure-free 8 months after treatment. In MRI scans up to 10 months post-procedure, seven patients had evidence of progression. Two patients had rapid distant disease progression, one had local progression of disease at
six months and four had distant progression at eight to nine months. Local disease control was achieved for most patients for more than six months. One patient had a repeat LITT procedure. Survival-related outcomes are summarised in Table 2, and changes in tumour volume are summarised in Table 3.

Safety

Seven patients experienced complications including transient aphasia (language impairment; 3/17), transient hemiparesis (one-sided body weakness; 3/17), transient hyponatremia (2/17), deep vein thrombosis (1/17) and fatal meningitis (1/17). Patients with aphasia or hemiparesis improved with steroid therapy, and the hyponatremia resolved spontaneously. The authors reported that the meningitis resulted from contaminated operating room infrastructure. Patients spent an average of 1.8 days (SD 1.7) in the intensive care unit, and an average of 3.2 days (SD 1.7) or 9.4 days (SD 11) in hospital for superficial targets or thalamic/basal targets, respectively.

Missios et al 2013

Missios et al retrospectively reviewed 11 patients with glioblastoma multiforme who were treated at a single centre with the NeuroBlate® System. The included patients had a median age of 53.3 years (range 34-79). The procedure was performed as a first treatment in six patients and as a salvage therapy in five patients with recurrent disease. For patients receiving LITT as an initial treatment a diagnostic biopsy was obtained. Tumours were located in the frontal lobe (6), the thalamic region (2) and in the temporal lobe (3). Six patients had mild pre-operative neurological impairment. The median maximum tumour diameter was 3.2 cm (range 1.6-4.5), with a median volume of 12.4 cm$^3$ (range 2.2-25.4). Patients had MRI scans every three months, and the median follow-up was 8.3 months (range 2.7-26.2). Perioperative steroid use was not reported.

Efficacy

The authors reported that at the last follow-up six of the 11 patients had died (55%) and that disease progression was the cause of death in five cases. A total of eight patients progressed during follow-up, with six cases of recurrence. Recurrence was seen inside the surgical field in three patients and along the treatment periphery in the other three. Overall survival following the procedure was 8.4 months (range 2-26) and median progression-free survival was 6.1 months (range 2-26). The authors also investigated prognostic factors for overall survival using a Cox proportional hazards analysis. Post-operative adjuvant treatment with radiation and/or chemotherapy was the only factor that reached statistical significance, with a positive effect on overall survival (hazard ratio 11.03, 95% confidence interval [CI] 8.60 to 13.50; $p=0.05$). Survival-related outcomes are summarised in Table 2, and changes in tumour volume are summarised in Table 3.
Safety
The authors reported that two patients experienced worsening of neurological deficit after the procedure, one patient had new onset seizure and another patient developed a *Staphylococcus aureus* infection and ventriculitis (inflammation of the brain ventricles). One patient experienced a haematoma at the surgical site, but no surgical intervention was required.

*Studies using MRI-guided LITT to treat epilepsy*
Willie et al 2014

In Willie et al, 17 patients with intractable mesial temporal lobe epilepsy were offered standard open temporal lobe surgery or MRT-guided LITT of the amygdala and hippocampus with the Visualase system. Of 17 consecutive, prospectively enrolled patients, 13 chose LITT. Two surgeons performed the procedure on patients between July 2011 and June 2013. Patients were evaluated at two, six, 12 and 24 months after treatment. Data collection included seizure frequency, complications, medication status and quality-of-life measures. The median patient age was 24 years (range 16-64). Two patients had undergone prior placement of a vagal nerve stimulator and two had undergone previous open temporal lobe surgery. Patients typically received 24 hours of dexamethasone post-procedure and were discharged with a 1 week oral steroid taper.

Efficacy
The authors reported that the laser assembly was correctly placed in 12 of 13 patients; in one patient incorrect placement meant that the amygdalohippocampal complex was not ablated. Two patients underwent repeat ablation procedures to correct insufficient initial ablation (as deemed by a lack of seizure control). The median follow-up in patients was 14 months (range 5-26). Ten patients (77%) had a meaningful reduction in seizures, with all failures to achieve seizure freedom occurring within an interval of no more than six months. Some patients underwent multiple procedures, with one patient having two ablations followed by an open anterior temporal lobectomy with amygdalohippocampectomy. These outcomes have been summarised in Table 4.

Safety
There were five complications (in five patients) within 30 days of the first or second procedure; these included visual field loss on the same side in both eyes (1/13), emergency hospital visits for seizures (2/13), multiple emergency visits and readmissions for psychogenic non-epileptic seizure (1/13) and acute subdural hematoma (collection of blood outside the brain; 1/13). The patient who experienced visual field loss had a persistent deficit at last follow-up that was attributed to the procedure. The subdural haematoma was seen on MRI during the ablation and was evacuated via craniotomy; the patient recovered without any ill effects. The average hospital stay for the cohort was 1.6 days (range 1-3).
Table 4  Outcomes following MRT-guided LITT for epilepsy in Willie et al

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for repeat or revision</td>
<td></td>
</tr>
<tr>
<td>Number of repeat LITT procedures</td>
<td>2/13</td>
</tr>
<tr>
<td>Number of subsequent surgeries</td>
<td>2/13*</td>
</tr>
<tr>
<td>Engel Class (I to IV) at last follow-up</td>
<td></td>
</tr>
<tr>
<td>Free of disabling seizures (I)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>Worthwhile improvement (III)</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>No worthwhile improvement (IV)</td>
<td>3/13 (23%)</td>
</tr>
</tbody>
</table>

LITT: laser interstitial thermal therapy;
*One patient had a repeat LITT followed by an open procedure 14 months after the second LITT.

2016 Economic evaluation

No economic literature was identified.

2016 Ongoing research

Eight ongoing or as yet unpublished clinical trials were identified through searches of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Registry (Table 5). All are being undertaken in the United States of America. The majority of trials identified are case series studies with only two (NCT02451215 and NCT02311582) having a comparative design. However, correspondence with an author of Missios et al indicated that a retrospective multicentre review of LITT for newly diagnosed glioblastoma multiforme, with a control group of biopsy patients, should be published in the next few months. No clinical trial identifier is associated with this study. The majority of ongoing trials concern patients with brain neoplasms, although one trial concerning epilepsy patients was identified (NCT01703143).

Table 5  Ongoing clinical trials of MRT-guided LITT

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Study Design</th>
<th>Number of patients Indication</th>
<th>Intervention</th>
<th>Primary outcomes</th>
<th>Trial status (Estimated completion date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>RCT Single centre</td>
<td>45 patients with recurrent glioblastoma multiforme</td>
<td>NeuroBlate® plus doxorubicin hydrochloride (chemotherapy drug)</td>
<td>Vascular transfer constant from DSC-MRI, peritumoral permeability scores, 6-month PFS, overall survival, quality of life</td>
<td>Recruiting (December 2017)</td>
</tr>
<tr>
<td>USA</td>
<td>RCT Single centre</td>
<td>52 patients with recurrent malignant glioma</td>
<td>NeuroBlate® plus MK-3475 immunotherapy drug</td>
<td>Maximal tolerated dose of MK-3475 with MLA, progression-free survival</td>
<td>Recruiting (December 2019)</td>
</tr>
</tbody>
</table>
### Study Location

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Number of patients</th>
<th>Intervention</th>
<th>Primary outcomes</th>
<th>Trial status (Estimated completion date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Case series</td>
<td>18 patients with paediatric brain tumours</td>
<td>MRI-guided LITT Visualase or NeuroBlate®</td>
<td>Recruiting (April 2025)</td>
</tr>
<tr>
<td>USA</td>
<td>Comparative study with historical controls</td>
<td>Single centre</td>
<td>Morbidity, rate of recurrence or progression, tumour control, MRI changes following ablation</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>Retrospective registry</td>
<td>300 patients previously treated for primary brain tumours</td>
<td>NeuroBlate®</td>
<td>Recruiting (December 2015)</td>
</tr>
<tr>
<td>USA</td>
<td>Case series</td>
<td>20 patients with metastatic brain tumours</td>
<td>Visualase</td>
<td>Unknown (last verified in December 2009)</td>
</tr>
<tr>
<td>USA</td>
<td>Case series</td>
<td>40 (patients with recurrence following stereotactic radiosurgery)</td>
<td>NeuroBlate®</td>
<td>Recruiting (December 2015)</td>
</tr>
<tr>
<td>USA</td>
<td>Case series</td>
<td>14 patients with medically refractory partial epilepsy</td>
<td>Visualase</td>
<td>Completed (January 2015)</td>
</tr>
<tr>
<td>USA</td>
<td>Case series</td>
<td>22 patients with metastatic brain tumours</td>
<td>Visualase</td>
<td>Completed (March 2014)</td>
</tr>
</tbody>
</table>

*listed in the original technology brief; NA: not available; MRI: magnetic resonance imaging; RCT: randomised controlled trial; DCS-MRI: dynamic susceptibility contrast-magnetic resonance imaging; PFS: progression free survival; MLA: MRI-guided laser ablation.

### 2016 Other issues

The intracranial neoplasm studies pooled results from patients with progressive or recurrent lesions in whom maximal or subtotal resection was not feasible. These patients have different prognoses, making it difficult to interpret survival and progression or recurrence outcomes when the results are pooled for the entire cohort. Furthermore, some patients received MRT-guided LITT as their first treatment, whilst for others it was a salvage therapy. This is likely owing to the limited therapeutic options facing patients with intracranial neoplasms; however, it does introduce complexity in terms of interpreting and quantifying the potential benefit of MRI-guided LITT.

It is not clear whether it would be appropriate to use MRT-guided LITT in patients who are eligible for surgical interventions such as second craniotomy. No comparative evidence was
available to enable analysis of the relative efficacy and safety of MRT-guided LITT as an alternative to established therapeutic options. However, authors appear to agree that it can offer increased survival for patients who are ineligible for surgery and would otherwise receive supportive or palliative care, although no quantitative comparative data are provided to support this claim.

It is also important to note the procedure carries some risks, including new-onset or worsening neurological deficit, new-onset seizures and deep vein thrombosis. Intracranial haemorrhage was occasionally observed to be greater than expected, and can result in the need for surgical intervention.

For patients with intractable epilepsy the Visualase system has been used to ablate epileptogenic tissue. The one study included for this indication offered patients the option of an open surgical procedure or the minimally invasive procedure. The authors reported the procedure to be a success; however, it is not clear how this compares to surgical resection of epileptogenic tissue in terms of seizure freedom or complications. One patient experienced persisting visual field loss as a result of the procedure and another experienced subdural haematoma.

An additional study using the Visualase system to remove epileptogenic tissue in patients with medically refractory epilepsy, in the form of a conference abstract, was identified but not included in this update as it did not report quantitative results. This study included ten patients with MRI-visualised lesional epilepsy. Procedural length was approximately two hours and all ten patients had successful ablation of the target tissue. The authors stated that no major complications occurred and that the procedure was highly effective and well tolerated. As both the safety and efficacy outcomes related to this intervention for epilepsy are unclear, further information on the appropriate patient group is required. Its current use should be considered experimental and only provided in cases where existing treatments have been exhausted.

According to one study, having intraoperative MRI capability can allow the procedure to take place in a single room. At sites without intraoperative MRI, the surgical portion is performed in a conventional operating room and the patient must be transported to a diagnostic MRI suite. Apparently this may limit the number of penetrations of the laser into the tumour and may potentially reduce the success of treatment.

Four of the included studies were associated with the manufacturers of either the Visualase or NeuroBlate® system. Since completion of the original Technology brief, Visualase Inc., has been purchased by Medtronic Inc., (Minnesota, USA).

This update also identified a recent systematic review of the literature on LITT, with or without MRT guidance, for brain neoplasms. Voight and Torchia undertook a systematic review that included 22 studies with a total of 169 patients. Many of these studies were
published more than 15 years ago, prior to FDA approval of the NeuroBlate® (2013 and 2009 for precursor device) and Visualase (2007) system. However, this study has been summarised here to provide an overview of the type of evidence published on LITT for intracranial neoplasm. Only one comparative trial was available in which LITT was used as an adjunct to brachytherapy, and ten of the included studies had less than 10 patients in total. The treated tumours were glioblastomas, astrocytomas and metastatic tumours. All tumours treated had a diameter of less than 5 cm. The authors concluded that LITT, with or without MRT guidance, can lengthen survival, with complications similar to open resection in patients with brain cancer, although quantitative data regarding this comparison was not provided. They noted that LITT is a viable therapeutic option in patients with glioblastoma, or recurrent glioblastoma, who are not indicated for surgery or are refractory to other treatments. The lack of comparative evidence made it difficult to draw conclusions about survival effects and complication rates as compared to other therapies such as craniotomy. Both authors had financial ties to Monteris Medical, Inc.

2016 Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies 5
Total number of Level IV studies 5

Search criteria to be used (MeSH terms)

Magnetic Resonance Imaging
Laser Therapy
Brain Neoplasm

Date searched

26/10/2015

2016 References


Technology Brief 2013

Technology, Company and Licensing

Register ID  WP166

Technology name  Magnetic resonance thermometry-guided laser interstitial thermal therapy for intracranial neoplasms

Patient indication  For use in patients with inoperable intracranial neoplasms

Description of the technology

Laser interstitial thermal therapy (LITT) is a minimally invasive ablative treatment for intracranial neoplasms.\(^1\) In LITT, an applicator probe is placed within the tumour and deposits precise amounts of light energy. Light energy is converted to thermal energy within the tumour, resulting in a rise in local temperature. The heat generated damages intracellular proteins leading to coagulation and cell necrosis.\(^2\) LITT potentially enables tumour resection in patients who are unable to undergo open surgery. However, the inability to monitor tissue temperature and thermal energy deposition, and to view the resulting anatomical changes in real time, has hindered the application of LITT. Consequently, LITT has often resulted in suboptimal treatment, with patients receiving under or over ablation of their tumours.\(^3\)

Two systems, Visualase and the NeuroBlate® System, overcome these problems by combining LITT with magnetic resonance thermometry (MRT) imaging. MRT scans produce detailed images of internal organs and temperature patterns in real time. The Visualase and NeuroBlate® software process the MRT scan data and generate real-time, colour-coded thermal and tissue images, allowing the surgeon to precisely monitor and guide tumour ablation. The software also includes safety limits. If the surgeon exceeds the required thermal dose or strays outside the tumour zone, the laser is automatically deactivated. The safety features and real-time feedback enable the surgeon to maximise tumour ablation while avoiding critical brain areas.

The Visualase and NeuroBlate® System share many similar components, including an image-processing workstation, a laser applicator probe, a laser generator and a cooling catheter. However, the two systems differ in the efficiency of the laser. The Visualase laser functions at a wavelength of 980 nm, whereas the NeuroBlate® laser operates at 1064 nm. The smaller wavelength of the Visualase laser enables it to rapidly heat tissue and produce sharper thermal gradients at lower power than the NeuroBlate® laser.\(^4\) For example, ablation of a 2.5 cm metastatic tumour would take 6 minutes with the Visualase laser and 73 minutes with the NeuroBlate® System.\(^5\) In addition, the NeuroBlate® laser requires a larger cooling catheter than the Visualase laser. This feature is particularly relevant when trying to minimise damage to adjacent sensitive areas in the brain. A final point of contrast...
between the two LITT systems relates to the use of anaesthesia. Patients treated with the NeuroBlate® System require general anaesthesia, whereas patients undergoing treatment with Visualase only require general anaesthesia if they are in the supine position. Consequently, the latter patient group may experience less postoperative morbidity and may be discharged earlier.

Company or developer

Visualase is produced by Visualase, Inc. (Texas, United States of America (USA)). The NeuroBlate® System is manufactured by Monteris Medical, Inc. (Minnesota, USA).

Reason for assessment

MRT-guided LITT provides a novel treatment option that enables tumour resection in patients who are unable to undergo open craniotomy.

Stage of development in Australia

- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

Licensing, reimbursement and other approval

Both Visualase⁶ and the NeuroBlate® System⁷ have received United States Food and Drug Administration (FDA) 510(k) clearance.⁸⁻⁹ NeuroBlate® has also been approved by Health Canada.¹⁰

At present, neither of these technologies has been listed on the Australian Register of Therapeutic Goods (ARTG), or received a European CE mark.
Intracranial neoplasms, or brain tumours, are abnormal, uncontrolled proliferations of cells within the brain. Brain tumours are defined by their cell type, pattern of growth and origin. Primary tumours originate in the brain, whereas secondary tumours have metastasised to the brain from another location. Tumour growth is broadly divided into benign or malignant. Benign tumours are slow growing, are composed of non-cancerous cells, and do not metastasise from their original location. Conversely, malignant tumours are composed of cancerous cells that grow rapidly and infiltrate healthy tissue. Metastatic tumours are the most common intracranial neoplasm in adults, followed by primary malignant and benign tumours. Common examples of brain tumours are as follows:

- primary benign
  - meningioma
  - vestibular schwannoma
  - pituitary adenoma
- primary malignant
  - glioblastoma multiforme
  - astrocytoma
  - oligodendroglioma
- secondary
  - metastatic cancer.

High rates of morbidity and mortality are associated with intracranial neoplasms owing to the functional importance of the brain. For example, glioblastoma multiforme has one of the lowest 1- and 5-year survival rates for all cancers. Tumour growth within the brain often results in damage to sensitive brain regions, and symptoms of a tumour often reflect its location within the brain. General symptoms of a brain tumour can include severe recurring headaches, nausea and vomiting. More specific symptoms can include difficulty speaking and remembering; seizures; weakness or paralysis; loss of balance; change in personality; and disturbed vision, taste, hearing or smell.
At present, it is difficult to determine who will develop intracranial neoplasms. However, age, race, genetics, sex and previous cranial irradiation or neoplasm are all potential risk factors.\textsuperscript{16}

**Number of patients**

Between 1991 and 2012, the incidence of brain cancer in Australia has remained stable at an age-standardised rate of 7 per 100,000 people. Compared with other cancers—for example, prostate (age-standardised rate of 163 per 100,000)—the incidence of brain cancer is relatively low. However, the mortality associated with brain cancer is among the highest for all cancer types, with an age-standardised rate of 6 deaths per 100,000 people. The 5-year survival rate for patients diagnosed with a brain tumour is only 22 per cent.\textsuperscript{17}

Brain cancer occurs more frequently in men and the elderly. In 2009, 928 men and 667 women were diagnosed with brain cancer. In addition, men have a lower 5-year survival rate than women, as well as an increased risk of being diagnosed with brain cancer before 75 years of age and of dying before the age of 85 years.\textsuperscript{17}

The Australian Institute of Health and Welfare estimates that by 2020, approximately 2,095 new cases (1,230 men and 865 women) of brain cancer will be diagnosed per year, with the highest prevalence occurring among men aged between 80 and 84 years.\textsuperscript{18}

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Neurosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology setting</td>
<td>Specialist and General Hospitals</td>
</tr>
</tbody>
</table>

**Impact**

**Alternative and/or complementary technology**

MRT-guided LITT is an option for patients who have recurrent tumour growth despite undergoing maximal resection in conjunction with optimal chemotherapy and radiotherapy treatment. The procedure is considered an alternative for patients who are unable to receive standard surgical resection because of the location or type of their tumour.

**Current technology**

Surgery, radiotherapy and chemotherapy are the standard of care in patients diagnosed with intracranial neoplasms.\textsuperscript{19} Maximal surgical resection is the preferred treatment and is associated with an increased long-term survival compared with no treatment.\textsuperscript{20, 21} However, surgical resection is often not possible in patients who are high-risk surgical candidates or who have a tumour that is difficult to access. Radiotherapy and chemotherapy both increase survival in patients with intracranial neoplasms, but they have limited applicability.\textsuperscript{22} For example, many chemotherapeutic agents are unable to cross the blood-brain barrier,
reducing their effectiveness, and radiotherapy is most effective for the treatment of small tumours less than 3 cm.

Patients with recurrent or progressive intracranial neoplasms have few therapeutic options. Consequently, approximately one-third of these patients participate in clinical trials. New therapies currently under investigation include dendritic cell vaccination, oncolytic viral infection, radiolabeled antibody conjugates and signal pathway inhibitors.

**Diffusion of technology in Australia**

The diffusion of MRT-guided LITT within Australia could not be determined through review of published literature.

**International utilisation**

The Visualase and NeuroBlate® System are the subjects of completed and ongoing clinical trials in the United States. Visualase has also undergone clinical trials in France.

In April 2013, Visualase, Inc. reported that more than 250 patients with brain tumours had been successfully treated using Visualase across 20 centres in the United States.

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td></td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>United States of America</td>
<td></td>
<td></td>
<td>✅</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td>✅</td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

Infrastructure costs associated with MRT-guided LITT include the purchase of the laser system (Visualase or NeuroBlate® System) and a compatible 1.5 T magnetic resonance imaging (MRI) scanner. Currently, MRI scanners are mainly installed in large referral hospitals. If the hospital has an existing MRI machine, an increase in demand would be expected.

Increased costs associated with the procedure include the need for specialist and support staff, staff training, consumables such as the single-use laser probes, and access to MRI.

**Ethical, cultural or religious considerations**

No ethical, cultural or religious considerations were identified in the published literature.
Evidence and Policy

Safety and effectiveness

Two case series (level IV intervention evidence) evaluating MRT-guided LITT for intracranial neoplasms were included in this Technology Brief. Jethwa et al. (2012) evaluated the use of Visualase in patients with benign, malignant and metastatic intracranial neoplasms. Sloan et al. (2013) evaluated the NeuroBlate® System in patients with recurrent or progressive glioblastoma multiforme in whom radiotherapy (with or without chemotherapy) had failed. Collectively, the safety and effectiveness of MRT-guided LITT was evaluated in 30 patients. A summary of the details of the included studies is outlined in Table 1.

Table 6 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Jethwa et al. 2012</th>
<th>Sloan et al. 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td>IV (retrospective)</td>
<td>IV (prospective)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Patient diagnosis</td>
<td>Benign or malignant intracranial neoplasms</td>
<td>Recurrent or progressive glioblastoma multiforme despite previous radiotherapy therapy</td>
</tr>
<tr>
<td>Intervention</td>
<td>Visualase</td>
<td>NeuroBlate® System</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Not stated</td>
<td>At least 14 days; median 8 months</td>
</tr>
<tr>
<td>Conflict of interest</td>
<td>Drs Godwa and Sheety, the third and fourth authors respectively, are employees of Visualase, Inc.</td>
<td>Drs Sloan, Ahluwalia, Torchia and Barnett, the first, second, fifth and last authors respectively are paid consultants for Monteris Medical, Inc.</td>
</tr>
</tbody>
</table>

Jethwa et al. 2012

A case series (level IV intervention evidence) was conducted at a single centre in the USA by Jethwa et al (2012). Twenty consecutive patients with an intracranial neoplasm underwent MRT-guided LITT using Visualase. The decision to perform LITT was made on an individual basis according to four main factors: personal preference, disease recurrence despite previous surgical resection and maximal adjuvant therapy, the presence of surgically inaccessible tumours, and classification as high-risk surgical candidates. The tumour types were diverse and included glioblastoma multiforme (n=6), metastatic cancer (n=4), ependymoma (n=3), hemangioblastoma (n=2), meningioma (n=2), supratentorial primitive neuroectodermal tumour (n=1), chordoma (n=1) and anaplastic astrocytoma (n=1). The average age of the patients was 60.5 years (range 9-85 years). The patient selection criteria were not reported, nor were the pre-intervention tumour volume and length of follow-up.

Safety

No deaths associated with the procedure were reported. However, major complications were reported in 20 per cent of patients: an insertion-related haemorrhage (n=1), an oedema (n=1), a pituitary injury manifesting as diabetes insipidus and metabolic
derangement (n=1), and a missed lesion due to an inaccurate registration (n=1). All major complications were successfully treated. No minor complications were reported. Post-ablation oedema occurred in the majority of patients and was effectively managed using steroids. It was not considered a procedural complication.

Effectiveness

Overall, MRT-guided LITT was successfully performed in 95 per cent (n=19) of patients. One patient was converted to standard surgical resection after inaccurate pre-operative registration caused the laser to miss the target tumour. Suboptimal placement of the laser probe (>5 mm from or outside of the target) occurred five times due to inaccurate patient registration.

Most patients required a single treatment of MRT-guided LITT, although three patients returned for a second laser ablation. Two of these patients repeated MRT-guided LITT two months after the initial procedure as part of a staged ablation. The third patient repeated MRT-guided LITT 17 months after the initial procedure owing to tumour recurrence. Patients were hospitalised for an average of 2.3 days following the procedure.

The volume of tumour treated using Visualase ranged from 0.4 cm$^3$ to 68.9 cm$^3$, with an average treated volume of 7 ± 9 cm$^3$. However, the percentage of tumour ablated was not reported. The area of thermal damage ranged from 0.95 cm$^2$ to 9.63 cm$^2$. The average maximal postoperative lesion diameter and area were 2.4 ± 0.85 cm and 3.99 ± 2.60 cm$^2$ respectively.

Sloan et al. 2013

A case series study (level IV intervention evidence) was conducted across two centres in the USA by Sloan et al. (2013). Ten patients were enrolled into the study following diagnosis of progressive or recurrent glioblastoma multiforme that had recurred despite radiotherapy with or without chemotherapy. One patient who was initially registered for the trial was subsequently excluded as the tumour was too deep for the laser probe. Additional exclusion criteria included: previous treatment with stereotactic radiosurgery, brachytherapy or carmustine-impregnated wafers; symptoms due to the mass effect of the tumour; uncontrolled hypertension; angina pectoris; cardiac dysrhythmia; recent intracranial haemorrhage; serious infection; immunosuppression; pregnancy; abnormal neutrophil count or coagulopathy; inadequate bone marrow; impaired liver or renal function; contraindications to MRI; medical or other conditions that may reduce the patient’s safety; an inability or unwillingness to provide consent; posterior fossa neoplasms; neoplasms with treatment boundaries that were within 5 mm of critical brain regions; and multiple tumours. The included patients had a mean age of 55 years and 20 per cent were female. The size of the tumours ranged from 22 x 15 mm to 36 x 34 mm, with an average size of 27.5 x 22.5 mm. The average tumour volume was 6.8 cm$^3$, ranging from 2.6 cm$^3$ to 19 cm$^3$. Although the
location of each tumour varied, the majority were on the left side of the brain. Further investigation revealed that two tumours were near the non-eloquent cortex, five were near the eloquent cortex and three were within the eloquent cortex. The median pre-operative Karnofsky performance status (KPS) score, which measures patients’ general well-being and activities of daily living (range 0 [death]–100 [perfect health]), was 80 (range 70–90).

At the time of the procedure, an average of 614 days (standard deviation (SD) 482.0) had passed since the initial diagnosis of glioblastoma multiforme and an average of 539 days (SD 496.8) had elapsed since initial radiotherapy. On average, each patient had undergone two (SD 0.9) rounds of chemotherapy 210 days (SD 249.0) before the current treatment. Recurrence was first recorded, on average, 58 days (SD 61.2) prior to MRT-guided LITT.

Prior to the procedure, patients were assigned to one of three treatment groups corresponding to a low (n=3), medium (n=2) or high (n=5) thermal dose. Patients were followed for a minimum of six months or until death, with the first follow-up scheduled for 14 days after the procedure.

Two patients died before the six month follow-up due to the progression of the underlying disease.

**Safety**

No deaths associated with the NeuroBlate® System occurred. All patients were alert and responsive one to two hours post-operatively. Nine patients were ambulatory 12 hours post-operatively. An MRI scan conducted 48 hours after the procedure indicated the presence of treatment-related oedema in nearly all patients. The oedemas were effectively managed using steroids.

Temporary neurological deficits (impaired ability to communicate together with mild upper limb weakness and mild weakness with visual field loss) occurred in two patients several days after the procedure. In both cases, deficits presented contralateral to the ablated area and were successfully treated. Fourteen severe adverse events were observed, including neutropenia (n=1), a cerebral cyst (n=1), brain abscess (n=1), dysphasia (n=1), partial seizure (n=1), post-operative wound infection (n=1), hemiparesis (n=1), haematoma (n=2), glioma (n=1), vascular pseudoaneurysm rupture (n=1), pulmonary embolism (n=1) and deep vein thrombosis (n=2). Less serious adverse events included a mild balance disorder (n=1), dizziness (n=1), partial seizure (n=2), speech disorders (n=1), hemiparesis (n=1), blurred vision (n=2), confused state (n=1), partial seizures (n=2) and headaches (n=5).

Long-term severe complications included a white matter tract injury, an intracerebral haemorrhage six weeks after treatment and an epicranial gliosarcoma at the probe entry site nine months post-treatment. All severe complications were successfully managed.
Effectiveness

MRT-guided LITT was successfully performed in all patients. MRI scans taken 24 and 48 hours after the NeuroBlate® procedure demonstrated necrosis at the tumour site in all patients. The NeuroBlate® System M•Vision™ software accurately predicted the region of cell death at medium and high thermal doses. The volume of tumour ablated ranged from 1.98 cm$^3$ to 11.03 cm$^3$, with an average ablated volume of 5 cm$^3$ (SD 3.2). Thus, on average, 78 per cent (range 57–90%) of the total tumour volume was treated.

At the 14-day follow-up, one patient who received a medium thermal dose and two patients receiving high thermal doses had increased KPS scores. One patient who received the highest thermal dose reported a decreased KPS score. The remaining patients did not report any change.

The median survival of patients after MRT-guided LITT was 316 days (range 62–767 days). Thirty per cent of patients had a median progression-free survival time of six months.

Economic evaluation

No cost effectiveness studies of MRT-guided LITT were identified in the literature.

Ongoing research

Two trials were identified from ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Register (Table 7).

Table 7 Summary of current clinical trials

<table>
<thead>
<tr>
<th>Trial Identifier/Location</th>
<th>Trial Status</th>
<th>Intervention</th>
<th>N</th>
<th>Study Design</th>
<th>Interventions</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01651078 USA</td>
<td>Recruiting</td>
<td>MRT-guided LITT with NeuroBlate® System</td>
<td>40</td>
<td>Case-series</td>
<td>MRT-guided LITT for metastatic brain tumours</td>
<td>December 2013</td>
</tr>
<tr>
<td>NCT01736722 USA</td>
<td>Recruiting</td>
<td>MRT-guided LITT with Visualase</td>
<td>22</td>
<td>Case-series</td>
<td>MRT-guided LITT for 1-3 metastatic brain tumours</td>
<td>January 2015</td>
</tr>
</tbody>
</table>

NCT01651078 - Laser Ablation After Stereotactic Radiosurgery for Patients With Metastatic Brain Tumors (LAASR)

The study aims to recruit participants across multiple sites within the USA. The primary endpoints are the patient’s quality of life before and after the NeuroBlate® procedure, and the progression of the tumour or radionecrosis as measured using MRI. Secondary outcomes include adverse events and utilisation of healthcare resources.

NCT01736722 - MRT-Guided LITT for Treatment Metastatic Brain Tumors
The study’s primary outcome is to determine the safety and feasibility of the Visualase system by examining morbidity and mortality at 30, 90, and 180 days post-operatively, as well as the rate of technical success or failure. Secondary outcomes include the survival of patients, concordance between Visualase software predicted and postoperative MRI lesions, duration of the procedure, required facilities, personnel and costs for the procedure, and the local control of the lesion at 30, 90 and 180 days postoperative.

Other issues

Study Issues

- At least three patients enrolled in Sloan et al. (2013) entered subsequent clinical trials. It is unclear whether this influenced mean survival time.³
- Jethwa et al. (2012) noted that the response to Visualase thermal ablation was different among each tumour type and showed variability within the same tumour category. It is, therefore, unclear which tumour type responds best to thermal ablation, and whether it is appropriate for all tumour types.⁵
- Sloan et al. noted that those who had poor health pre-operatively were more likely to develop complications.³
- Sloan et al. noted that the favourable survival results may be due to the selection bias in the enrolled patients. Patients were required to have single tumours no bigger than 4 cm in diameter.³

MRT-guided LITT issues

- A significant problem of MRT-guided LITT is the survival of neoplastic cells at the margin of the lesion leading to secondary tumour growth.
- At present, the laser probe is of limited length, which potentially limits its application in patients with deep intracranial neoplasms.
- Unexpected patterns of thermal energy deposition were observed in both studies. This led to severe complications such as a white matter tract injury.

Additional studies

Two studies were conducted at the same institution in Germany by Schwarzmaier et al.²⁴, ²⁵ However, these studies used Dornier Medizintechnik 4060N 1064(nm) lasers.

In Schwarzmaier et al. (2005), two patients with recurrent glioblastoma multiforme received partial ablation treatment due to the irregular shape of their tumours.²⁴ The patients died 13 and 15 months after the procedure corresponding to 16 and 20 months survival since their initial diagnosis respectively.

In Schwarzmaier et al. (2006)²⁵, 16 patients with recurrent glioblastoma multiforme were treated with MRT-guided LITT and chemotherapy. The mean follow-up period was 9.1 months (SD 6.3). Twenty-six MRT-guided LITT procedures were performed in 16 patients.
There were no deaths or serious adverse events associated with the procedure. However, there were six minor complications: temporary weakness of the right arm (n=1), neutropenia (n=3), thrombocytopenia (n=1) and increased transaminases (n=1). At the 30-day follow up, one patient had died, and at the end of the study, 12 of the 16 patients had died. The median overall survival time after LITT was 6.9 months (1.7 SD). However, the authors note a substantial learning curve. The first ten and the last six cases exhibited a survival of 5.2 (SD 0.6) and 11.2 (SD 2.0) months following LITT respectively ($p=0.0267$).

Three smaller case series from a single centre in France have reported the use of Visualase in patients with intracranial neoplasms.

In Carpentier et al. (2008)$^{26}$, four patients with treatment-resistant metastatic brain tumours were treated. The procedure was successfully performed in all patients with no major or minor complications. At the 3-month follow up, peripheral tumour recurrence was slightly visible in three patients who only received partial tumour ablation.

In Carpentier et al. (2011)$^{27}$, seven patients with treatment-resistant metastatic brain tumours were treated. Patients were followed up to 30 months post-treatment. Fifteen MRT-guided LITT procedures were performed in the seven patients. Total tumour ablation was possible in 57 per cent of patients, with partial ablation occurring in the remaining 43 per cent. No salvage surgical interventions were required. Although no patients died as a result of the procedure, four complications occurred: blood suffusion without increased mass effect, a probe misplacement, a transient increase in cerebellar syndrome, and transient aphasia. Mean overall survival since diagnosis was 17.4 (SD 3.54) months. The average progression-free survival time following MRT-guided LITT was 3.8 (SD 1) months. Total tumour ablation was associated with a higher mean survival compared with partial tumour ablation (9.2 [SD 3.5] and 3.3 [SD 1.3] months respectively). However, the statistical significance of this result was not reported.

In Carpentier et al. (2012)$^{28}$, four patients with recurrent glioblastoma multiforme underwent MRT-guided LITT. Overall, the procedure was successfully performed in all patients. No significant adverse events were recorded. However, minor complications such as a transient neurological deficit, convulsive seizure, mild dysphasia and cerebrospinal leak occurred in three patients. All minor complications were successfully treated. Patients experienced a mean progression-free survival of 30 days, with an overall survival time after the procedure of 10.5 months.

Visualase has also been used to successfully ablate epileptogenic foci in children and brain lesions which have regrown after radiosurgery.$^{29, 30}$

**Summary of findings**

The treatment of recurrent or inoperable intracranial neoplasms remains a significant problem with limited successful therapeutic options. The current Technology Brief utilised
two case series to assess whether MRT-guided LITT could treat intracranial neoplasms. However, there were some limitations to the current studies. For example, the average tumour volume pre-intervention and the mean percentage of the tumour ablated were not reported by Jethwa et al. (2012). In addition, the heterogeneous population of neoplasms used in this study makes determining the efficacy of MRT-guided LITT difficult to determine. Finally, patient-related outcomes were not reported across both studies; therefore, it is unclear whether MRT-guided LITT is associated with an improved quality of life.

Collectively, the literature suggests MRT-guided LITT is fairly well tolerated among patients and that unless immediate complications occur, patients can be safely discharged within 24 to 48 hours. However, 18 severe adverse events were observed across both case series, of which all were successfully managed. There were no deaths attributable to the procedure. The mean volume of tumour treated using NeuroBlate® ranged from 5 cm to 7 cm, corresponding to 78 per cent tumour ablation. While this did not meet the goal of maximal surgical resection (≥ 98%), the median survival of the patients (316 days) was longer than the 90 to 150 days observed for recurrent glioblastoma.25

Future studies should focus on patient-relevant outcomes, such as improvement in quality of life, and should define the patient and tumour type most appropriate for MRT-guided LITT, determine who is at risk for unexpected thermal energy deposition or serious adverse events, optimise the treatment dose, and compare to an appropriate comparator treatment.

**HealthPACT assessment**

MRT-guided LITT is an emerging therapeutic technique for patients in cases where surgical resection of an intracranial neoplasm is not possible. At present, the effectiveness of MRT-guided LITT is unknown. Consequently, the small body of evidence cannot be used to make an informed decision regarding the use of MRT-guided LITT. Therefore, it is recommended that MRT-guided LITT be monitored for 24 months, at which time the results of three larger case series will be available.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

| Total number of studies | 2 |
| Total number of Level IV studies | 2 |
References


**Search criteria to be used (MeSH terms)**

Mesh terms: Brain Neoplasm, Laser Therapy, Magnetic Resonance Imaging

Text: Visualase, NeuroBlate, AutoLITT, laser interstitial thermal therapy, laser, magnetic resonance thermometry