NHS England Evidence Review:

MR-guided laser interstitial thermal therapy for children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection

NHS England URN: 2006a

NHS England Evidence Review:

MR-guided laser interstitial thermal therapy for children and adults with refractory focal epilepsy caused by hypothalamic hamartoma unsuitable for neurosurgical resection

Drafted: January 2021

Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of MR-guided laser interstitial thermal therapy (MRgLITT) compared to continued medical therapy alone for children and adults with refractory focal epilepsy caused by hypothalamic hamartoma (HH) unsuitable for neurosurgical resection. Drug-resistant or refractory epilepsy can cause significant impairment of quality of life. Patients are at risk of recurrent physical and cerebral injury from seizures, status epilepticus (prolonged seizures), sudden death in epilepsy, other causes of fatality and psychological, psychiatric, financial and social comorbidities. Patients with drug-resistant epilepsy (DRE) will have tried various anti-epileptic medications, often with adverse effects, and may have had frequent hospitalisations.

HH is a rare benign lesion in which an abnormal mass of tissue has grown adjacent to the hypothalamus at the central base of the brain. It is present from birth and does not grow, but may cause DRE, hormonal disturbance, cognitive decline and neurobehavioural problems. Seizures tend to start as involuntary laughing (sometimes termed gelastic seizures) that may then progress to focal seizures with loss of awareness and generalised seizures and which are almost invariably unresponsive to medical treatment. The location of HH also means that neurosurgery is difficult, although it remains a viable technique in children, but it is associated with a high risk of severe morbidity. The current standard treatment for the management of the group of patients with DRE in whom surgery is absolutely contraindicated is medical management alone.

MRgLITT is proposed as a treatment for DRE due to HH which carries less risk than open neurosurgery. It involves the identification of the HH lesion on MRI, and the insertion of a fine fibreoptic laser catheter into the target area through a burr hole in the skull. The procedure is carried out under continuous real-time MRI scanning to allow visualisation of the exact target area and the surrounding tissue, and to monitor the temperature in the brain during the procedure. Laser energy is applied with the aim of ablating the target tissue while causing minimal damage to the surrounding area.

In addition to considering the clinical effectiveness, safety and cost effectiveness of MRgLITT for DRE due to HH, the scope of this review also included the identification of possible subgroups of patients within the included studies who might benefit from treatment with MRgLITT more than others.

2. Executive summary of the review

Three non-comparator studies were included in the evidence review (Curry et al 2018, Wang et al 2020, Xu et al 2018). One was a systematic review and meta-analysis (SRMA) (Wang et al 2020) which included 83 adults and children with hypothalamic hamartoma (HH) from four case series. The other two were retrospective case series; Curry et al 2018 included 71 adults and children with gelastic seizures due to HH and Xu et al 2018 included 18 adults and children with both gelastic and non-gelastic seizures due to HH. No evidence was identified which compared MR-guided laser interstitial thermal therapy (MRgLITT) with medical therapy or other interventions. Studies reported outcomes at timepoints ranging from more than six months to a mean of more than 17.5 months after MRgLITT.

Research Question 1:

1. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the clinical effectiveness of MRgLITT compared with continued medical therapy?

Critical outcomes

The critical outcomes for decision making are seizure freedom, neuropsychological outcomes and quality of life.

The certainty of the evidence for all critical outcomes was very low when assessed using modified GRADE.

Seizure freedom

In total, three studies (one SRMA of four case series and two retrospective case series) provided evidence relating to seizure freedom for people with DRE due to HH who were treated with MRgLITT. Seizure freedom was measured at different time points up to a mean of >17.5 months and was defined using the Engel classification[1] (Wang et al 2020), the International League Against Epilepsy (ILAE)[2] classification (Xu et al 2018) or no definition (Curry et al 2018).

At more than 6 months follow-up the SRMA by Wang et al 2020 (n=83) reported a mean seizure free (Engel class I) rate of 99% (95% CI 92% to 100%).

Xu et al 2018 and Curry et al 2018 both reported outcomes for gelastic seizures separately. At mean 6.3 (+/- 4.8) months follow-up, Xu et al 2018 (n=15) reported a rate of good gelastic seizure control (ILAE class 1-3) of 73% (no CI reported). Curry et al 2018 (n in this outcome not stated, total n=71) reported a rate of freedom from gelastic seizures (not

[1] Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years; ID: Generalized convulsions with antiepileptic drug withdrawal only): *Class II: Rare disabling seizures* ("almost seizure-free") (IIA: Initially free of disabling seizures but has rare seizures now; IIB: Rare disabling seizures since surgery; IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years; IID: Nocturnal seizures only) *Class III: Worthwhile improvement* (IIIA: Worthwhile seizure reduction; IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years): *Class IV: No worthwhile improvement* (IVA: Significant seizure reduction; IVB: No appreciable change; IVC: Seizures worse

[2] ILAE: International League Against Epilepsy; Classification 1: Completely seizure free, no auras; 2: Only auras, no other seizures; 3: one to three seizure days per year: +/- auras; 4: Four seizure days per year to 50% reduction of baseline seizure days; ± auras; 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras; 6: More than 100% increase of baseline seizure days; ± auras

defined) of 78% (no CI reported) at less than one year's follow-up, and of 93% (no CI reported) at one year's follow-up. At mean >17.5 (+/- 7.5) months follow-up Xu et al 2018 (n=15) reported a rate of freedom from gelastic seizures (ILAE class 1) of 80% (no CI reported), and a rate of well-sustained gelastic seizure control (ILAE class 1-2) of 93% (no CI reported).

Xu et al 2018 also reported outcomes for non-gelastic seizures (n=9). At mean >17.5 (+/- 7.5) months follow-up they reported a rate of freedom from non-gelastic seizures (ILAE class 1) of 56% (no CI reported), and a rate of well-sustained non-gelastic seizure control (ILAE class 1-2) of 67% (no CI reported). They also reported that 11% of patients (no CI reported) had ILAE class 4 non-gelastic seizures (between four seizure days a year and a 50% reduction in seizure days) and 22% of patients (no CI reported) had ILAE class 5 non-gelastic seizures (between less than 50% reduction and 100% increase in seizure days).

Neuropsychological outcomes

No evidence was identified for this outcome.

Quality of life

No evidence was identified for this outcome.

Important outcomes

The important outcomes for decision making are need for medical therapy, hospitalisations and cognitive development in children.

The certainty of the evidence for all important outcomes was very low when assessed using modified GRADE.

Need for medical therapy

One case series provided evidence in relation to the need for medical therapy for people with DRE due to HH after treatment with MRgLITT. Curry et al 2018 (n=71) reported that 12% of patients (no CI reported) were free from seizures and free of antiepileptic medicines at an unspecified follow-up period.

Hospitalisations

No evidence was identified for this outcome.

Cognitive development in children

No evidence was identified for this outcome.

Research Question 2

2. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the safety of MRgLITT compared with continued medical therapy?

The safety outcome for decision making is complications from the procedure. The certainty of the evidence for safety outcomes was very low when assessed using modified GRADE.

Complications from the procedure

Two case series (Curry et al 2018, Xu et al 2018) provided evidence in relation to complications from the MRgLITT procedure in people with DRE due to HH.

Xu et al 2018 (n=18) reported that in the immediate post-operative period there were neurological deficits in seven (39%) subjects (no CI reported), consisting of strength deficit in five, unilateral Horner's syndrome in one, and both strength deficit and unilateral Horner's syndrome in one.

At mean 6.3 (+/- 4.8) months follow-up, Xu et al 2018 (n=18) reported neurological deficits in five (28%) subjects, two of which were new deficits; short-term memory deficits in five (28%) subjects, three of which were new; newly diagnosed hypothyroidism in two (11%) subjects, and weight gain from increased appetite in four (22%) subjects (no CI reported).

At mean >17.5 (+/- 7.5) months follow-up, Xu et al 2018 (n=18) reported persistent neurological deficits in four (22%) subjects, hypothyroidism in two (11%) subjects, short-term memory issues in four (22%) subjects, and persistent weight gain in four (22%) subjects (no CI reported).

At an unspecified follow-up period, Curry et al 2018 (n=71) reported two episodes of persistent complications (one worsening diabetes insipidus, and one severe deficit in short-term memory which did not resolve) and 16 episodes of complications which resolved (four delayed wound healing, three single episodes of hyponatremia, and nine temporary increases in non-gelastic seizures that resolved at four months post-surgery).

Research Question 3

3. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the cost-effectiveness of MRgLITT compared with continued medical therapy?

No evidence was identified on the cost-effectiveness of MRgLITT compared with continued medical therapy.

Research Question 4

4. From the evidence selected, are there any subgroups of patients that may benefit from MRgLITT more than the wider population of interest?

No evidence was identified on any subgroups of patients that may benefit from MRgLITT more than the wider population of interest.

Limitations

There were no comparative studies which considered the clinical effectiveness or safety of MRgLITT compared to continued medical therapy for adults and children with drug-resistant focal epilepsy who have HH. All the evidence identified (including the studies included in a SRMA) was from retrospective case series. Factors relating to the design and conduct of

the studies meant that all were at high risk of bias, and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

Limited demographic and clinical information was provided about study subjects. Studies reported outcomes at timepoints ranging from more than six months to a mean of at least 17.5 months but there was lack of clarity in all three studies on the actual duration of follow-up for some outcomes and/or the number of subjects included in follow-up. All studies included both adults and children but none analysed different age groups separately. Each study used a different (or no) classification of seizure outcomes meaning that outcomes were not directly comparable across studies.

Conclusion

The SRMA and two case series included in this review all reported improvements in seizure outcomes after MRgLITT compared to baseline. Between 56% and 99% of subjects with drug-resistant epilepsy who had HH were reported to be free of various types of seizures at follow-up periods of more than 6 months to a mean of more than 17.5 months. The lack of studies comparing MRgLITT with continued medical therapy means that none of these outcomes can be compared with the MCID threshold defined in the PICO. Two studies also reported a range of complications following the procedure, which included some which resolved in the short to medium term, and some neurological, short-term memory and endocrine problems which persisted at 17.5 months follow-up. One case series reported that 12% of patients were free from seizures and free of antiepileptic medicines at an unspecified follow-up period. No evidence was identified in relation to neuropsychological outcomes, quality of life, hospitalisations or cognitive development in children.

The evidence from these studies must be regarded as very low certainty due to their observational design, conduct and reporting. No comparative studies were identified so it is not possible to reach any conclusions about the outcomes of MRgLITT in these patients compared with continued medical therapy or any other intervention. There was also no evidence on cost effectiveness or on any subgroups who may benefit from MRgLITT more than the general population of interest.

The studies identified for this review therefore provide very low certainty evidence that MRgLITT for adults and children with drug-resistant focal epilepsy who have HH improves seizure outcomes.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the clinical effectiveness of MRgLITT compared with continued medical therapy?

2. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the safety of MRgLITT compared with continued medical therapy?

3. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the cost-effectiveness of MRgLITT compared with continued medical therapy?

4. From the evidence selected, are there any subgroups of patients that may benefit from MRgLITT more than the wider population of interest?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 17th November 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review. Studies were excluded if they had been included in one of the SRMAs and if their key outcomes were already included in the reported meta-analysis.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three papers were identified for inclusion (Curry et al 2018, Wang et al 2020, Xu et al 2018). One was a systematic review and meta-analysis (SRMA) (Wang et al, 2020) which included 83 patients with hypothalamic hamartoma from four case series. The other two were retrospective case series; Curry et al 2018 included 71 patients and Xu et al 2018 included 18 patients. No evidence was identified which compared MRgLITT with medical therapy or other interventions. Table 1 provides a summary of these included studies and full details are given in Appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Curry et al, 2018 Retrospective case series Texas, USA	n=71 Gelastic epilepsy related to HH. Age range 5 months to 20 years.	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** Freedom from gelastic seizures (not defined) at less than 1 year and at 1 year f/u **Important outcomes** Freedom from seizures and freedom from antiepileptic medications at latest f/u (duration not stated) **Safety** Complications (f/u duration not stated)
Wang et al, 2020 SRMA Beijing, China All included studies carried out in the USA	n=83 in 4 studies HH with DRE. Age range of all subjects was 0.4 years to 58 years (the age range of the HH patients included was not clear).	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** Seizure freedom (Engel class I) (f/u period not stated, all >6 months) **Important outcomes** None reported
Xu et al, 2018 Retrospective case series Arizona, USA	n=18 HH. Nine (50%) had gelastic seizures only, three (17%) had non-gelastic seizures only, six (33%) experienced both. Age range 3.3 years to 68.9 years.	**Intervention** MRgLITT **Comparison** No comparator	**Critical Outcomes** Seizure freedom (ILAE classification), gelastic and non-gelastic seizures, at mean 6.3 months and mean >17.5 months f/u **Important outcomes** None reported **Safety** Immediate, intermediate (mean 6.3 months) and longer-term (mean 17.5 months) complications

Abbreviations: DRE: Drug-resistant epilepsy; f/u: follow-up; HH: Hypothalamic hamartoma; ILAE: International League Against Epilepsy; MRgLITT: MR-guided laser interstitial thermal therapy; SRMA: systematic review and meta-analysis;

5. Results

In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the clinical effectiveness of MR-guided LITT compared with continued medical therapy?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Seizure freedom **Certainty of evidence**: Very low	Seizure freedom is key to patients and their carers because it can result in reduced hospital admissions and outpatient attendance, reduced reliance on medication as well as improved health over time and improved quality of life. In total three studies (one SRMA of four case series and two retrospective case series) provided evidence relating to seizure freedom for people with hypothalamic hamartoma treated with MRgLITT. Seizure freedom was measured at different time points up to a mean of >17.5 months and was defined using the Engel classification[1] (Wang et al 2020), the International League Against Epilepsy (ILAE)[2] classification (Xu et al 2018) or no definition (Curry et al 2018). At more than six months follow-up: • one meta-analysis of four case series (Wang et al 2020) (n=83) reported a mean seizure free (Engel class I) rate of 99% (95% CI 92% to 100%). (**VERY LOW**) At mean 6.3 months (+/- 4.8 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of good gelastic seizure control (ILAE class 1-3) of 73% (no CI reported). (**VERY LOW**) At less than one year's follow-up: • one case series (Curry et al 2018) (n in this outcome not stated, total n=71) reported a rate of freedom from gelastic seizures (not defined) of 78% (no CI reported). (**VERY LOW**) At one year's follow-up • one case series (Curry et al 2018) (n in this outcome not stated, total n=71) reported a rate of freedom from gelastic seizures not defined) of 93% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of freedom from gelastic seizures (ILAE class 1) of 80% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=15) reported a rate of well-sustained gelastic seizure control (ILAE class 1-2) of 93% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of freedom from non-gelastic seizures (ILAE class 1) of 56% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up:

	• one case series (Xu et al 2018) (n=9) reported a rate of well-sustained non-gelastic seizure control (ILAE class 1-2) of 67% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of ILAE class 4 non-gelastic seizures of 11% (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • one case series (Xu et al 2018) (n=9) reported a rate of ILAE class 5 non-gelastic seizures of 22% (no CI reported). (**VERY LOW**) **These studies provided very low certainty evidence from non-comparative case series that between 92-100% of patients with drug-resistant focal epilepsy who had hypothalamic hamartoma were not having disabling seizures (Engel class I) more than 6 months after MRgLITT.** **Of patients who had suffered from gelastic seizures, at mean 6.3 months follow-up after MRgLITT, 73% were reported to have good seizure control (ILAE class 1-3) and at between less than one year to mean >17.5 months follow-up, between 78% and 93% were reported to be free of gelastic seizures (ILAE class 1 or no definition).** **Of patients who had suffered from non-gelastic seizures, at mean >17.5 months follow-up after MRgLITT, 56% were reported to be free of non-gelastic seizures and 67% were reported to have well-sustained seizure control (ILAE class 1-2). 11% were reported to have ILAE class 4 seizures (between four seizure days a year and a 50% reduction in seizure days) and 22% to have ILAE class 5 seizures (between less than 50% reduction and 100% increase in seizure days).**
Neuropsychological outcomes **Certainty of evidence**: Not applicable	This outcome is key to patients and their carers because it can help to identify areas of difficulty and improvement in cognitive function and also the relationship between epilepsy and a patient's emotional function. **No evidence was identified for this outcome**.
Quality of Life **Certainty of evidence**: Not applicable	Quality of life is important to patients because its holistic evaluation incorporating contributing factors (such as emotional well-being, social and physical functioning, medication effects and role limitations) reflects impact upon the patient's life and its improvement is a marker of successful treatment. **No evidence was identified for this outcome**.
Important outcomes	
Need for medical therapy **Certainty of evidence**: Very low	Assessing reduction or discontinuation in medical therapy following MRgLITT is important to patients because it is a marker of the effectiveness of the intervention, especially considering that many patients will have previously been taking multiple medications with sub-optimal control of their epilepsy and potentially with side effects. At an unspecified follow-up period: • one case series (Curry et al 2018) (n=71) reported that 12% of patients were free from seizures and free of antiepileptic medicines (no CI reported). (**VERY LOW**) **This study provided very low certainty evidence that 12% of patients with drug-resistant focal epilepsy who had hypothalamic hamartoma were free from seizures and free of antiepileptic medicines at an unspecified follow-up period after MRgLITT**.

Hospitalisations **Certainty of evidence**: Not applicable	Patients may require hospitalisation for treatment of seizures and their aftermath to prevent consequences such as physical injury, cognitive damage and psychiatric complications. However, a reduction in number and length of hospitalisations is important to patients and their carers as it indicates that their treatment has been successful in reducing severe seizure activity. **No evidence was identified for this outcome**.
Cognitive development in children **Certainty of evidence**: Not applicable	This outcome is key to patients and their carers because an improvement in cognitive learning can increase independence, ability to learn and problem-solve and enhance confidence during formative years. **No evidence was identified for this outcome**.
Safety	
Complications from procedure **Certainty of evidence**: Very low	Procedural complications are important to patients because they may be irreversible, can be serious and need be considered to inform treatment choices. In the immediate post-operative period: • One case series (Xu et al 2018) (n=18) reported neurological deficits in seven (39%) subjects (no CI reported), consisting of strength deficit in five; unilateral Horner's syndrome in one; and both strength deficit and unilateral Horner's syndrome in one. (**VERY LOW**) At mean 6.3 (+/- 4.8 months) follow-up: • One case series (Xu et al 2018) (n=18) reported neurological deficits in five (28%) subjects, two of which were new deficits; short-term memory deficits in five (28%) subjects, three of which were new; newly diagnosed hypothyroidism in two (11%) subjects, and weight gain from increased appetite in four (22%) subjects (no CI reported). (**VERY LOW**) At mean >17.5 months (+/- 7.5 months) follow-up: • One case series (Xu et al 2018) (n=18) reported persistent neurological deficits in four (22%) subjects, hypothyroidism in two (11%) subjects, short-term memory issues in four (22%) subjects, and persistent weight gain in four (22%) subjects (no CI reported). (**VERY LOW**) At an unspecified follow-up period: • One case series (Curry et al 2018) (n=71) reported two episodes of persistent complications (one worsening diabetes insipidus, and one severe deficit in short-term memory which did not resolve) and 16 episodes of complications which resolved (four delayed wound healing, three single episodes of hyponatremia, and nine temporary increases in non-gelastic seizures that resolved at four months post-surgery). (**VERY LOW**) **These studies provided very low certainty evidence that both short-term and persistent complications were experienced by patients following MRgLITT. These included persistent neurological deficits, short-term memory deficits and endocrine problems. However the proportion of patients not affected by complications in the studies was not clear and the type and frequency of complications reported varied between studies**.

Seizure classifications (Wieser et al 2001)

[1] Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years; ID: Generalized convulsions with antiepileptic drug withdrawal only): *Class II: Rare disabling seizures* ("almost seizure-free") (IIA:

Initially free of disabling seizures but has rare seizures now; IIB: Rare disabling seizures since surgery; IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years; IID: Nocturnal seizures only) *Class III: Worthwhile improvement* (IIIA: Worthwhile seizure reduction; IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years): *Class IV: No worthwhile improvement* (IVA: Significant seizure reduction; IVB: No appreciable change; IVC: Seizures worse [2] ILAE: International League Against Epilepsy; Classification 1: Completely seizure free, no auras; 2: Only auras, no other seizures; 3: one to three seizure days per year: +/- auras; 4: Four seizure days per year to 50% reduction of baseline seizure days; ± auras; 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras; 6: More than 100% increase of baseline seizure days; ± auras
Abbreviations: CI: Confidence Intervals; ILAE: International League Against Epilepsy; MRgLITT: MR-guided laser interstitial thermal therapy; SRMA: systematic review and meta-analysis;

In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the cost effectiveness and safety of MR-guided LITT compared with continued medical therapy?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of people that may benefit from MR-guided LITT more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with MR-guided LITT.

6. Discussion

This review considered the evidence for the clinical effectiveness and safety of MR-guided Laser Interstitial Thermal Therapy (MRgLITT) compared to continued medical therapy for children and adults with refractory focal epilepsy caused by hypothalamic hamartoma (HH) unsuitable for neurosurgical resection. The critical outcomes of interest were seizure freedom, neuropsychological outcomes and quality of life. The important outcomes were need for medical therapy, hospitalisations and cognitive development in children. Evidence was also sought on safety and cost effectiveness.

No comparative studies were identified. Evidence was available from one SRMA of 83 subjects from four case series (Wang et al 2020), and two case series with 71 and 18 subjects respectively (Curry et al 2018, Xu et al 2018). All three studies were at high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

All the interventions included in all three studies were carried out in the USA. All three studies included both adults and children; in Curry et al 2018 the age range was five months to 20 years, in Xu et al 2018 it was 3.3 years to 68.9 years, and the studies included in the Wang et al SRMA included subjects with a range of aetiologies aged from 0.4 years to 58 years (although the age range of the HH patients included was not clear).

All three studies reported seizure outcomes, but each used a different (or no) classification. Wang et al 2020 reported the rate of Engel Class 1 seizures (Wieser et al 2001), Xu et al 2018 used the International League Against Epilepsy (ILAE) classification and Curry et al 2018 did not define seizure freedom. Xu et al 2018 and Curry et al 2018 also reported outcomes separately for gelastic and non-gelastic seizures.

All studies reported improved seizure control after MRgLITT at follow-up periods which ranged from an unspecified period of more than six months (Wang et al 2020) to one year (Curry et al 2018) and a mean of more than 17.5 months (Xu et al 2018). Wang et al 2020 reported confidence intervals around their estimate of seizure freedom but Curry et al 2018 and Xu et al 2018 did not report any statistical measures. Because there were no studies comparing MRgLITT with continued medical therapy, none of the reported outcomes could be compared with the minimum clinically important difference (MCID) threshold defined in the PICO.

Curry et al 2018 reported that 12% of patients were free of seizures and free of antiepileptic medications at an unspecified time period after MRgLITT. Xu et al 2018 and Curry et al 2018 reported a range of complications following the procedure, some of which resolved, and some of which, including neurological, short-term memory and endocrine problems, were persistent at a mean of 17.5 months follow-up.

In addition to the non-comparative nature of the evidence in the included studies a number of other factors which may have affected the outcomes have increased the uncertainty of the results. These include:

- All studies included both adults and children, with an age range across all studies from 0.4 years to 68.9 years. No studies analysed different age groups separately.
- All studies included very limited demographic or clinical information about the subjects.
- There was lack of clarity in all three studies on the duration of follow-up and/or number of subjects included in follow-up.

- Differences in definitions of seizure outcomes mean that reported rates of seizure control cannot be directly compared across the three studies.
- All studies were retrospective (including those included in the SRMA by Wang et al 2020), adding additional potential biases due to risk of selection bias and incomplete reporting of the original cohort which may be harder to identify retrospectively.
- There is some duplication of findings as the case series by Curry et al 2018 was included in the SRMA by Wang et al 2020, to which it contributed the majority of subjects included in the HH meta-analysis. It was included in this review because it reported additional outcomes of interest which were not reported by Wang et al 2020.

7. Conclusion

This review included one SRMA including patients from four case series, and two retrospective case series, which provide very low certainty evidence on critical and important outcomes following MRgLITT for adults and children with drug-resistant focal epilepsy who have HH. Compared to baseline, all studies reported improvements in seizure outcomes which were reported at follow-up periods of more than 6 months to a mean of more than 17.5 months, with between 56% and 99% of subjects reported to be free of various types of seizures. However the lack of studies comparing MRgLITT with continued medical therapy means that none of these outcomes can be compared with the MCID threshold defined in the PICO. Two studies also reported a range of complications following the procedure, which included some which resolved in the short to medium term, and some neurological, short-term memory and endocrine problems which persisted at 17.5 months follow-up.

The evidence from these studies must be regarded as very low certainty due to their observational design, conduct and reporting. There is a significant risk of bias associated with the retrospective case series design of the studies included in the Wang et al 2020 SRMA and the studies reported by Curry et al 2018 and Xu et al 2018. There was lack of clarity about the study subjects included and about follow-up, and the only measure of statistical significance reported was in Wang et al 2020.

No comparative studies were identified so it is not possible to reach any conclusions about the outcomes of MRgLITT in these patients compared with continued medical therapy or any other intervention. There was also no evidence on cost effectiveness or on any subgroups who may benefit from MRgLITT more than the general population of interest.

The studies identified for this review therefore provide very low certainty evidence that MRgLITT for adults and children with drug-resistant focal epilepsy who have HH improves seizure outcomes. It is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of MRgLITT compared with continued medical therapy.

Appendix A PICO Document

The review questions for this evidence review are:

1. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the clinical effectiveness of MR-guided LITT compared with continued medical therapy?

2. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the safety of MR-guided LITT compared with continued medical therapy?

3. In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the cost-effectiveness of MR-guided LITT compared with continued medical therapy?

4. From the evidence selected, are there any subgroups of patients that may benefit from MR-guided LITT more than the wider population of interest?

P –Population and Indication	Adults and children with drug-resistant focal epilepsy[3] caused by hypothalamic hamartoma for whom open neurosurgical resection is not a viable treatment option. Sub-groups of interest • Adults • Children above the age of 1 year • Lesion/zone type
I – Intervention	• Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) [Systems for delivery of MRgLITT include Visualase and Neuroblate] *[Please note that MRI-guided laser interstitial thermal therapy (MRgLITT) may also be referred to as 'laser interstitial thermal therapy (LITT) in the literature. This is a minimally invasive treatment which can be used to treat focal refractory epilepsy. Continuous real-time MRI scanning is done to allow visualisation of the exact target area and a fine fibreoptic laser catheter is inserted into the target area under stereotactic guidance. Under computer guidance, laser energy is applied to the target area.]*
C – Comparator(s)	The alternative treatment to compare with MRgLITT is: • Continued medical therapy alone [*The current standard treatment is medical management alone.]*
O – Outcomes	**Clinical Effectiveness** Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. *Critical to decision-making:* • Seizure freedom *The minimum clinically important difference for this outcome can be considered as seizure freedom one-year post MRgLITT to be 20% better than continued medical therapy. This can include the patient still experiencing auras, but with no seizures. The ILAE epilepsy surgery outcome scale can be used to quantify seizures post intervention. The Engel Epilepsy Surgery Outcome Scale is also used.*

[3] Drug-resistant or refractory epilepsy is defined as failure to achieve adequate seizure control with adequate trials of two or more AEDs, taken individually or in combination.

	Seizure freedom is key to patients and their carers because it can result in reduced hospital admissions and outpatient attendance, reduced reliance on medication as well as improved health overtime and improved quality of life. • Neuropsychological outcomes *These include the effect on language, memory and executive function. This can be evaluated through several tools as reported in studies, including but not limited to the following:* ○ *Language can be evaluated using the Mckenna graded naming test, semantic fluency test and phonemic fluency test. Patients can have their visual and verbal memory tested through immediate and delayed recall of a complex figure and a short story.* ○ *The Wechsler Adult Intelligence Scale (WAIS) is an IQ test designed to measure intelligence and cognitive ability in adults and older adolescents. It has four components; verbal comprehension index, perceptual reasoning index, working memory index and processing speed index.* *This outcome is key to patients and their carers because it can help to identify areas of difficulty and improvement in cognitive function and also the relationship between epilepsy and a patient's emotional function.* • Quality of life *To evaluate quality of life, the Quality of Life Epilepsy Inventory (QOLIE-89) contains comprehensive measures to evaluate overall quality of life, emotional well-being, social support, energy and fatigue, anxiety related to health, medication effects, health discouragement, work/driving/social function, attention/concentration, language, memory, physical function, pain, role limitations due to physical problems, and health perceptions. The shorter QOLIE-31 can also be used.* *Quality of life is important to patients because its holistic evaluation incorporating contributing factors (such as emotional well-being, social and physical functioning, medication effects and role limitations) reflects impact upon the patient's life and its improvement is a marker of successful treatment.* *Important to decision-making:* • Need for medical therapy *Assessing reduction or discontinuation in medical therapy following MRgLITT is important to patients because it is a marker of the effectiveness of the intervention, especially considering that many patients will have previously been taking multiple medications with sub-optimal control of their epilepsy and potentially with side effects.* *[Medication use should be assessed up to 1-year post-intervention.]* • Hospitalisations *Patients may require hospitalisation for treatment of seizures and their aftermath to prevent consequences such as physical injury, cognitive damage and psychiatric complications. However, a reduction in number and length of hospitalisations is important to patients and their carers as it indicates that their treatment has been successful in reducing severe seizure activity.* • Cognitive development in children *This will be assessed through a number of assessments and tools as documented in the literature.* *This outcome is key to patients and their carers because an improvement in cognitive learning can increase independence, ability to learn and problem-solve and enhance confidence during formative years.* **Safety and adverse events** • Complications from procedure

	Complications may include a persistent physical deficit including loss of limb power, loss of part of a field of vision, impairment of language or memory and endocrine complications. *Procedural complications are important to patients because they are irreversible, can be serious and need be considered to inform treatment choices.* **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2010 to 17th November 2020

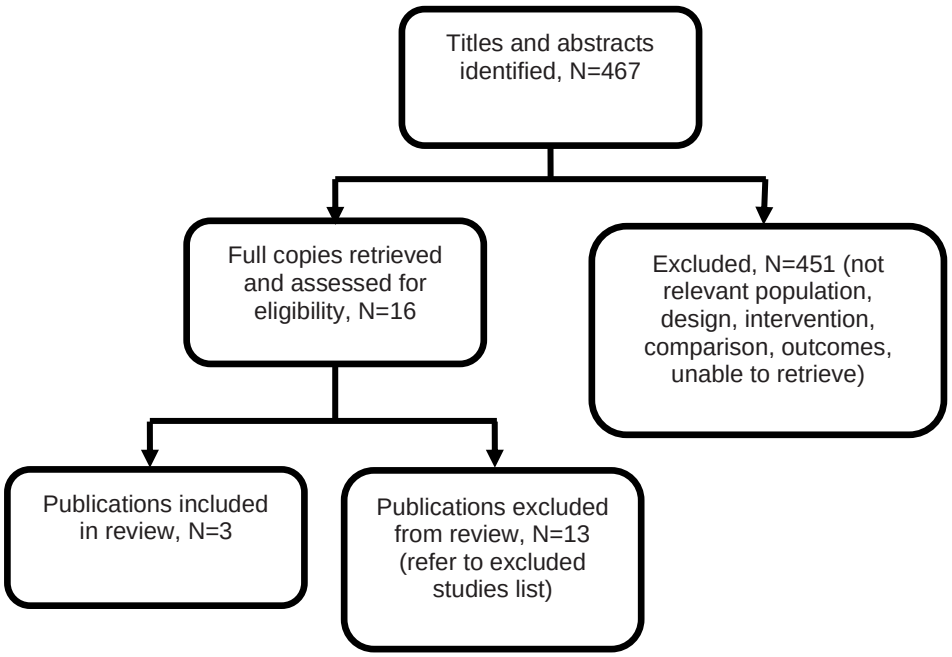
Medline search

# ▲	Searches
1	exp epilepsy/
2	epilep*.mp.
3	seizure*.mp.
4	1 or 2 or 3
5	laser.mp.
6	mrgLITT.mp.
7	LITT.mp.
8	exp laser therapy/
9	visualase.mp.
10	neuroblate.mp.
11	5 or 6 or 7 or 8 or 9 or 10
12	hamartoma/
13	hamartoma.mp.
14	12 or 13
15	4 and 11 and 14
16	limit 15 to (english language and yr="2010-Current")

Appendix C Evidence selection

The literature searches identified 467 references. These were screened using their titles and abstracts and 16 references were obtained in full text and assessed for relevance. Of these, three references are included in the evidence summary. The remaining 13 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Rolston, J. and Chang, E., 2016. Stereotactic Laser Ablation for Hypothalamic Hamartoma. *Neurosurgery Clinics of North America*, 27(1), pp.59-67.	Excluded. Narrative review and two case reports which are not reported in enough detail to be able to extract useful results for specified outcomes.
Du, V., Gandhi, S., Rekate, H. and Mehta, A., 2017. Laser interstitial thermal therapy: A first line treatment for seizures due to hypothalamic hamartoma? *Epilepsia*, 58, pp.77-84.	Excluded. Eight patients with hypothalamic hamartoma, included in Wang et al SRMA.
Xu, D., Chen, T., Hlubek, R., Bristol, R., Smith, K., Ponce, F., Kerrigan, J. and Nakaji, P., 2018. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for the Treatment of Hypothalamic Hamartomas: A Retrospective Review. *Neurosurgery*, 83(6), pp.1183-1192.	Included.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Buckley RT, Wang AC, Miller JW, Novotny EJ, Ojemann JG. Stereotactic laser ablation for hypothalamic and deep intraventricular lesions. Neurosurg Focus. 2016;41(4):E10. 10.3171/2016.7.FOCUS16236	6 patients with hypothalamic hamartoma, no additional useful outcomes to those reported in SRMA and larger studies.
Du VX, Gandhi SV, Rekate HL, Mehta AD. Laser interstitial thermal therapy: A first line treatment for seizures due to hypothalamic hamartoma? Epilepsia. 2017;58 Suppl 2:77-84. 10.1111/epi.13751	8 patients with hypothalamic hamartoma, included in Wang et al SRMA.
Fayed I, Sacino MF, Gaillard WD, Keating RF, Oluigbo CO. MR-Guided Laser Interstitial Thermal Therapy for Medically Refractory Lesional Epilepsy in Pediatric Patients: Experience and Outcomes. Pediatr Neurosurg. 2018;53(5):322-9. 10.1159/000491823	Four patients had hypothalamic hamartoma. Included in Wang et al SRMA.
Gupta K, Cabaniss B, Kheder A, Gedela S, Koch P, Hewitt KC, et al. Stereotactic MRI-guided laser interstitial thermal therapy for extratemporal lobe epilepsy. Epilepsia. 2020;61(8):1723-34. 10.1111/epi.16614	One patient had hypothalamic hamartoma. Case reports are excluded.
Landazuri P, Shih J, Leuthardt E, Ben-Haim S, Neimat J, Tovar-Spinoza Z, et al. A prospective multicenter study of laser ablation for drug resistant epilepsy - One year outcomes. Epilepsy Res. 2020;167:106473. 10.1016/j.eplepsyres.2020.106473	Two patients had hypothalamic hamartoma, outcomes are not reported separately for this group.
Lewis EC, Weil AG, Duchowny M, Bhatia S, Ragheb J, Miller I. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. Epilepsia. 2015;56(10):1590-8. 10.1111/epi.13106	One patient had hypothalamic hamartoma. Case reports are excluded.
Pruitt R, Gamble A, Black K, Schulder M, Mehta AD. Complication avoidance in laser interstitial thermal therapy: lessons learned. J Neurosurg. 2017;126(4):1238-45. 10.3171/2016.3.JNS152147	Includes n=6 with hypothalamic hamartoma, as well as patients with other pathologies. Outcomes not reported separately for hypothalamic hamartoma.
Rolston, J. and Chang, E., 2016. Stereotactic Laser Ablation for Hypothalamic Hamartoma. Neurosurgery Clinics of North America, 27(1), pp.59-67.	Narrative review and two case reports which are not reported in enough detail to be able to extract useful results for specified outcomes.
Southwell DG, Birk HS, Larson PS, Starr PA, Sugrue LP, Auguste KI. Laser ablative therapy of sessile hypothalamic hamartomas in children using interventional MRI: report of 5 cases. J Neurosurg Pediatr. 2018;21(5):460-5. 10.3171/2017.10.PEDS17292	5 case reports, no pooled results. No additional useful outcomes to those reported in SRMA and larger studies.
Wilfong AA, Curry DJ. Hypothalamic hamartomas: optimal approach to clinical evaluation and diagnosis. Epilepsia. 2013;54 Suppl 9:109-14. 10.1111/epi.12454	Overlapping population with Curry 2018 and no additional useful information.
Wilfong AA, Quach MM, Shetty A, Curry DJ. MR guided stereotactic laser ablation of hypothalamic hamartoma (HH). Epilepsy Currents. 2013;13:283-4. http://www.aesnet.org/file/13-1-s-2012-meeting-abstract-supplement	Abstract.
Wilfong AA, Shetty A, Curry DJ. Stereotactic MRI-Guided Laser Ablation of Epileptogenic Foci in Children. Epilepsia. 2013;54:280-. http://dx.doi.org/10.1111/epi.12229	Abstract.
Youngerman BE, Save AV, McKhann GM. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for Epilepsy: Systematic Review of Technique, Indications, and Outcomes. Neurosurgery. 2020;86(4):E366-E82. 10.1093/neuros/nyz556	Narrative review, no pooled results.

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. Epilepsy Res. 2018;142: 131-134. **Study location** Texas, USA **Study type** Retrospective case series. **Study aim** To present findings on the impact of MR-guided stereotactic laser ablation in the treatment of epilepsy related to Hypothalamic Hamartoma. **Study dates** 2011-2018	**Study inclusion criteria** Gelastic epilepsy related to HH. Treated at one institution. **Study exclusion criteria** None stated. **Total sample size** n=71 **Baseline characteristics** Male: 46 (65%) Age range 5 months to 20 years. Had a gelastic seizure frequency of a seizure every two weeks to over 75 seizures a day. Sixteen had failed other surgical or radiosurgical interventions.	**Intervention details** MR-guided stereotactic laser ablation. The majority used Visualase. 14 (20%) required two ablations. 2 required three ablations. **Comparator details** No comparator	**Critical outcomes** *Freedom from gelastic seizures* At one year f/u (n not stated): 93% (no CI reported) At less than one year f/u (n not stated): 78% (no CI reported) **Important outcomes** *Need for medical therapy* Free from seizures and free of antiepileptic medicines on last f/u (n not stated, f/u duration not stated): 12% (no CI reported) **Safety** *Complications* (n not stated, f/u duration not stated) Worsening diabetes insipidus: 1 Severe deficit in short-term memory postoperatively which did not resolve: 1 Delayed wound healing: 4 Single episode of hyponatremia requiring readmission for sodium supplementation: 3 Temporary increase in non-gelastic seizures that resolved at 4 months post surgery: 9	This study was appraised using the JBI critical appraisal checklist for case series. 1. No 2. Unclear 3. Yes 4. Unclear 5. Unclear 6. No 7. No 8. No 9. No 10. No **Other comments:** This is a retrospective case series which reports outcomes from a single institution; it is not clear how generalisable these would be to other settings. The paper included limited details on the patients' demographic or clinical background. It was not clear how the condition was diagnosed or whether consecutive patients were included and whether any were lost to f/u. There was no definition of seizure freedom. It was not stated how many subjects were included in each outcome measure reported, and there were no measures of statistical significance. Outcomes were collected by phone for three patients; it was not stated whether this had

				equal validity to collecting outcomes in person. **Source of funding:** No comment on source of funding
Full citation Wang Y, Xu J, Liu T, Chen F, Chen S, Xie Z, et al. Magnetic resonance-guided laser interstitial thermal therapy versus stereoelectroencephalography-guided radiofrequency thermocoagulation for drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsy Res. 2020;166 (no pagination). http://dx.doi.org/10.1016/j.eplepsyres.2020.106397 **Study location** Beijing, China All included studies carried out in the USA **Study type** SRMA **Study aim** To undertake a meta-analysis to assess the effectiveness and safety of MRgLITT and/or SEEG-	**Study inclusion criteria** Prospective or retrospective, reporting the efficacy of SEEG-RFTC and/or MRgLITT in patients with DRE. Sample size ≥5. Reports the specific number of seizure-free patients and complications. Published in English. **Study exclusion criteria** Case reports or reviews. Conference abstracts without full text. MRgLITT and/or SEEG-RFTC used as a secondary procedure after failure of a prior operation. Overlapping populations across publications. Use of an optimized or self-modified (surgical) technology. **Total sample size**	**Intervention details** MRgLITT **Comparator details** No comparator in studies including patients with HH. The review also reported separately outcomes for subjects undergoing SEEG-RFTC in 10 studies.	**Critical outcomes** n=83 patients with HH in 4 studies. f/u period not stated, all >6months *Seizure freedom (Engel class I)*[4] Mean seizure free rate: 99% (95% CI 92% to 100%) Low study heterogeneity (I^2 = 0.00, (p=0.56)) **Important outcomes** None reported	This study was appraised using the JBI critical appraisal checklist for systematic reviews and research synthesis. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. No 8. Yes 9. Yes 10. NA 11. NA **Other comments:** This SRMA included observational studies only. Two studies included only patients with HH, and two included patients with HH along with other aetiologies. Decisions about study inclusion were made by two independent reviewers, but it was not stated whether data extraction was done by one or two reviewers. There was very limited information about patient clinical or demographic background. Duration of f/u for the

[4] Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years; ID: Generalized convulsions with antiepileptic drug withdrawal only): *Class II: Rare disabling seizures* ("almost seizure-free") (IIA: Initially free of disabling seizures but has rare seizures now; IIB: Rare disabling seizures since surgery; IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years; IID: Nocturnal seizures only) *Class III: Worthwhile improvement* (IIIA: Worthwhile seizure reduction; IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years): *Class IV: No worthwhile improvement* (IVA: Significant seizure reduction; IVB: No appreciable change; IVC: Seizures worse; From: Surgical Treatment of Epilepsies, 2nd Edition. Engel J., Editor. Raven Press, 1993. Page 615.

RFTC in treating drug-resistant epilepsy. **Study dates** Search to November 2019. Included studies were published in 2017-2018.	n=83 with hypothalamic hamartoma (HH) in four MRgLITT studies. **Baseline** Two studies included patients with HH only, with age rages 0.4-20 years and 3-40 years. Two studies included patients with HH and other aetiologies, with age ranges 2-22 years and 21-58 years. The ages of the HH patients in these studies was not reported. No further details provided.			patients included in the analysis was not stated. Seizure freedom was defined using the Engel scale. Risk of bias in the included studies was assessed using a standardised approach (MINORS, the methodological index for nonrandomized studies). The authors considered the quality of evidence from the included studies to be low due to the retrospective design, lack of blinding and lack of comparator. Risk of publication bias was assessed and considered to be low. The subgroup analysis by aetiology for the HH group was not planned but carried out because of significant study heterogeneity across all the studies. The HH studies had low heterogeneity. **Source of funding:** The study was supported by the National Natural Science Foundation of China and Beijing Municipal Natural Science Foundation.
Full citation Xu DS, Chen T, Hlubek RJ, Bristol RE, Smith KA, Ponce FA, et al. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for the Treatment of Hypothalamic Hamartomas: A Retrospective Review. Neurosurgery.	**Study inclusion criteria** HH - discrete lesion of ≥1cm and <2cm in diameter that could be accessed through a safe stereotactic tract. ≥1 year f/u **Study exclusion criteria** None stated.	**Intervention details** MRgLITT Fifteen patients underwent one ablation treatment, and three patients underwent two. **Comparator details** No comparator	**Critical outcomes** *Seizure control: gelastic seizures* (n=15*) At mean 6.3 months (SD +/- 4.8 months): 11 (73%) had good seizure control (ILAE[5] class 1-3) (no CI reported). At latest f/u (duration not stated but mean >17.5 months (SD +/- 7.5 months))	This study was appraised using the JBI critical appraisal checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. No

[5] ILAE: International League Against Epilepsy; Classification 1: Completely seizure free, no auras; 2: Only auras, no other seizures; 3: one to three seizure days per year: +/- auras; 4: Four seizure days per year to 50% reduction of baseline seizure days; ± auras; 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras; 6: More than 100% increase of baseline seizure days; ± auras

2018;83(6):1183-92. 10.1093/neuros/nyx604 **Study location** Arizona, USA **Study type** Retrospective case series **Study aim** To evaluate a single centre's outcomes for the LITT treatment of Hypothalamic Hamartoma **Study dates** 2012-2015	**Total sample size** n=18 **Baseline characteristics** Mean age, 21.1 years; median age, 11 years; range 3.3-68.9 years. Nine aged ≥18 years. Male: 14 (78%) Nine (50%) patients had impaired cognitive development, as determined by neurocognitive assessments. Nine (50%) patients had gelastic seizures only, three (17%) had non-gelastic seizures only, six (33%) experienced both. Five had had previous surgery, three had had previous radiotherapy.		(including after second LITT for 3 non-responders): 14/15 (93%) had well-sustained seizure control (ILAE class 1-2), of whom: 12/15 (80%) were seizure free (ILAE class 1) (no CI reported). *Seizure control: non-gelastic seizures* (n=9*) At latest f/u (duration not stated but mean >17.5 months (SD +/- 7.5 months)) (including after second LITT for 1 non-responder): 6/9 (67%) had well-sustained seizure control (ILAE class 1-2), of whom: 5/9 (56%) were seizure free (ILAE class 1). 1/9 (11%) were ILAE class 4 2/9 (22%) were ILAE class 5 (no CI reported). The authors reported that 2 patients had initially good response but later deteriorated, and 2 had initially poor response but had improved at latest f/u (one of whom had a second LITT). *Note: 6 patients who experienced both gelastic and non-gelastic seizures are included in both groups. **Important outcomes** None reported **Safety** *Immediate post-operative complications* New neurological deficit: 7 (39%). Strength deficit: 6 (one requiring hospitalisation and rehabilitation). Unilateral Horner's syndrome: 2 (11%). (no CI reported).	8. No 9. No 10. No **Other comments:** This is a small retrospective case series which reports outcomes from a single institution; it is not clear how generalisable these would be to other settings. The paper included limited details on the patients' demographic or clinical background. Duration of f/u was not clearly reported for some outcomes. There were no statistical analyses. Seizure outcomes were determined in person, or through a mailed survey and telephone interview for some patients; it was not stated whether all methods had equal validity. Seizure outcomes were defined using the International League Against Epilepsy (ILAE) treatment scale. **Source of funding:** No comment on source of funding.

			Intermediate complications At mean 6.3 months (SD +/- 4.8 months): Neurological deficits: 5 (28%), two of which were new deficits. Short-term memory deficits: 5 (25%), three of which were new. Newly diagnosed hypothyroidism: 2 (11%). Weight gain from increased appetite: 4 (22%). (no CI reported). *Longer-term complications* At mean 17.5 months (SD +/- 7.5 months): Persistent neurological deficit: 4 (22%) (functional impact in one patient only). Hypothyroidism: 2 (11%). Short-term memory issues: 4 (22%). Persistent weight gain: 4 (22%). (no CI reported).	
Abbreviations CI: Confidence interval; f/u: follow-up; HH: Hypothalamic hamartoma; ILAE: International League Against Epilepsy; MINORS: methodological index for nonrandomized studies; MRgLITT: MR-guided Laser Interstitial Thermal Therapy; NA: not applicable; SD: standard deviation; SEEG-RFTC: stereoelectroencephalography-guided radiofrequency thermocoagulation; SRMA: systematic review and meta-analysis;				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were there methods to minimize errors in data extraction?
8. Were the methods used to combine studies appropriate?
9. Was the likelihood of publication bias assessed?
10. Were recommendations for policy and/or practice supported by the reported data?
11. Were the specific directives for new research appropriate?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 1: Question: In adults and children with drug-resistant focal epilepsy who have hypothalamic hamartoma, what is the clinical effectiveness and safety of MR-guided LITT compared with continued medical therapy?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	MRgLITT	Comparator	Result (95% CI)		
Seizure freedom. For seizure freedom and freedom from antiepileptic medicines, higher rates are better.									
Seizure free rate (Engel class I) [A] (>6 months f/u)									
1 SRMA Wang et al 2020	Serious limitations [1]	Serious indirectness [2]	No serious inconsistency	No serious imprecision	83	No comparator	Mean seizure free rate at >6months f/u: 99% (95% CI 92% to 100%)	Critical	Very low
Rate of good seizure control (gelastic seizures) (ILAE class 1-3) [B] (mean 6.3 months +/- SD 4.8 months f/u)									
1 case series Xu et al 2018	Very serious limitations [3]	Serious indirectness [4]	Not applicable	Not calculable	15	No comparator	73% CI not reported	Critical	Very low
Rate of freedom from gelastic seizures (not defined) (less than one year f/u)									
1 case series Curry et al 2018	Very serious limitations [5]	Very serious indirectness [6]	Not applicable	Not calculable	Not stated	No comparator	78% CI not reported.	Critical	Very low
Rate of freedom from gelastic seizures (not defined) (one year f/u)									
1 case series Curry et al 2018	Very serious limitations [5]	Very serious indirectness [6]	Not applicable	Not calculable	Not stated	No comparator	93% CI not reported.	Critical	Very low

Seizure free rate (gelastic seizures) (ILAE class 1) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [5]	Serious indirectness [4]	Not applicable	Not calculable	15	No comparator	80% CI not reported	Critical	Very low
Rate of well-sustained seizure control (gelastic seizures) (ILAE class 1-2) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [5]	Serious indirectness [4]	Not applicable	Not calculable	15	No comparator	93% CI not reported	Critical	Very low
Seizure free rate (non-gelastic seizures) (ILAE class 1) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [5]	Serious indirectness [4]	Not applicable	Not calculable	9	No comparator	56% CI not reported	Critical	Very low
Rate of well-sustained seizure control (non-gelastic seizures) (ILAE class 1-2) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [5]	Serious indirectness [4]	Not applicable	Not calculable	9	No comparator	67% CI not reported	Critical	Very low
ILAE class 4 (non-gelastic seizures) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [5]	Serious indirectness [4]	Not applicable	Not calculable	9	No comparator	11% CI not reported	Critical	Very low
ILAE class 5 (non-gelastic seizures) (mean >17.5 months +/- SD 7.5 months f/u)									
1 case series	Very serious	Serious indirectness [4]	Not applicable	Not calculable	9	No comparator	22% CI not reported	Critical	Very low

Xu et al 2018	limitations [5]								
Need for medical therapy									
Rate of being free from seizures and free of antiepileptic medicines (f/u duration not stated)									
1 case series Curry et al 2018	Very serious limitations [5]	Very serious indirectness [6]	Not applicable	Not calculable	71	No comparator	12% CI not reported	Important	Very low
Safety. For safety outcomes, lower rates or numbers are better.									
Immediate postoperative complications									
1 case series Xu et al 2018	Very serious limitations [3]	Serious indirectness [4]	Not applicable	Not calculable	18	No comparator	New neurological deficit: 7 (39%) (CI not reported); Of which: Strength deficit: 5 Unilateral Horner's syndrome: 1 Strength deficit and unilateral Horner's syndrome: 1	Important	Very low
Intermediate complications (mean 6.3 months +/- SD 4.8 months f/u)									
1 case series Xu et al 2018	Very serious limitations [3]	Serious indirectness [4]	Not applicable	Not calculable	18	No comparator	Neurological deficit: 5 (28%), two of which were new deficits. Short-term memory deficit: 5 (28%), three of which were new. Newly diagnosed hypothyroidism: 2 (11%). Weight gain from increased appetite: 4 (22%). CI not reported	Important	Very low
Longer term complications (mean 17.5 months +/- SD 7.5 months f/u)									
1 case series Xu et al 2018	Very serious limitations [3]	Serious indirectness [4]	Not applicable	Not calculable	18	No comparator	Persistent neurological deficit: 4 (22%) Hypothyroidism: 2 (11%).	Important	Very low

							Short-term memory issues: 4 (22%). Persistent weight gain: 4 (22%). CI not reported		
Complications (follow-up duration not stated)									
1 case series Curry et al 2018	Very serious limitations [5]	Very serious indirectness [6]	Not applicable	Not calculable	71	No comparator	Delayed wound healing: 4 Single episode of hyponatremia: 3 Worsening diabetes insipidus: 1 Temporary increase in non-gelastic seizures that resolved at 4 months post-surgery: 9 Severe deficit in short-term memory which did not resolve: 1	Important	Very low
Abbreviations: CI: Confidence interval; f/u: follow-up; ILAE: International League Against Epilepsy; MRgLITT: MR-guided laser interstitial thermal therapy; SD: standard deviation									

1. Serious risk of bias due to unclear reporting of study participants.
2. Serious indirectness as only non-comparative evidence was identified for inclusion in this SRMA.
3. Very serious risk of bias due to unclear reporting of study participants and lack of statistical analysis.
4. Serious indirectness due to lack of comparator.
5. Very serious risk of bias due to unclear reporting of study participants, unclear reporting of follow-up and lack of statistical analysis.
6. Very serious indirectness due to limited information on inclusion criteria and lack of comparator.

A Engel seizure classification: *Class I: Free of disabling seizures* (IA: Completely seizure-free since surgery; IB: Non disabling simple partial seizures only since surgery; IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years; ID: Generalized convulsions with antiepileptic drug withdrawal only): *Class II: Rare disabling seizures* ("almost seizure-free") (IIA: Initially free of disabling seizures but has rare seizures now; IIB: Rare disabling seizures since surgery; IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years; IID: Nocturnal seizures only) *Class III: Worthwhile improvement* (IIIA: Worthwhile seizure reduction; IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years): *Class IV: No worthwhile improvement* (IVA: Significant seizure reduction; IVB: No appreciable change; IVC: Seizures worse

B ILAE Classification: 1: Completely seizure free, no auras; 2: Only auras, no other seizures; 3: one to three seizure days per year: +/- auras; 4: Four seizure days per year to 50% reduction of baseline seizure days; ± auras; 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras; 6: More than 100% increase of baseline seizure days; ± auras

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is

	extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. Epilepsy Res. 2018;142: 131-134.
- Wang Y, Xu J, Liu T, Chen F, Chen S, Xie Z, et al. Magnetic resonance-guided laser interstitial thermal therapy versus stereoelectroencephalography-guided radiofrequency thermocoagulation for drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsy Res. 2020;166 (no pagination). http://dx.doi.org/10.1016/ j.eplepsyres.2020.106397
- Xu DS, Chen T, Hlubek RJ, Bristol RE, Smith KA, Ponce FA, et al. Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for the Treatment of Hypothalamic Hamartomas: A Retrospective Review. Neurosurgery. 2018;83(6):1183-92. 10.1093/neuros/nyx604

Other references

- Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, et al. ILAE Commission Report: proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia. 2001;42(2):282-286. https://www.ilae.org/files/ilaeGuideline/New-Classification-of-OutcomeFollowing-Epilepsy-Surgery-2001.pdf

NHS England and NHS Improvement
Skipton House
80 London Road
London
SE1 6LH

This publication can be made available in a number of other formats on request.