American Epilepsy Society/Congress of Neurological Surgeons Clinical Practice Guideline Draft for Public Comment

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Funding Statement: The systematic review and development of this clinical guideline was funded by the American Epilepsy Society.

Disclosures

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Elsevier Publishing (GB, RMB), Springer (RMB), Cleveland Clinic Foundation (RMB), Ceraxis Health (RMB), UpToDate Inc. (JLH), J Kiffin Penry (JLH), Marinus Pharmaceuticals (AMH), LivaNova USA, Inc. (AMH), Merck (AMH), Jazz Pharmaceuticals (AMH), EISAI, Inc. (AMH), PranaQ (AMH), UniQURE (AMH), NEUROPACE, Inc. (BCJ, JDR), Monteris Medical Corporation (RM), SynerFuse (RM), Koh Young (GM), Endostream Medical (GM), NeuroOne Medical Technologies (RM), Synchron (RM), Medtronic (RM), ClearPoint Medical (JDR), Turing Medical (JDR), The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abbreviations: AES-American Epilepsy Society; AHE-amygdalo-hippocampectomy; ATL-anterior temporal lobectomy; CNS-Congress of Neurological Surgeons; DBS-deep brain stimulation; EEG-electroencephalogram; fMRI-functional magnetic resonance imaging; GRADE- Grading of Recommendations Assessment, Development and Education; LITT-laser interstitial thermal therapy; MTLE-mesial temporal lobe epilepsy; MRI-magnetic resonance imaging; NAEC-National Association of Epilepsy Centers; QOL-quality of life; RNS-responsive neurostimulation; SAH-selective amygdalo-hippocampectomy; SRS-stereotactic radiosurgery; SUDEP-sudden unexplained death in epilepsy; TLE-temporal lobectomy; VNS-vagus nerve stimulation

Abstract

This practice guideline from the American Epilepsy Society (AES) and the Congress of Neurological Surgeons (CNS) provides evidence-based recommendations for surgical treatment of epilepsy for adults and children. It is an update to previous practice parameters published by the Academy of Neurology in 2003. The multidisciplinary panel addressed resective procedures for mesial temporal epilepsy, neocortical epilepsy, and resection/disconnection of hypothalamic hamartoma. It also examined evidence for callosotomy in developmental and epileptic encephalopathies. It did not address neurostimulation treatment. A comprehensive, literature review was conducted using Grading of Recommendations Assessment, Development and Education (GRADE) methodology, and GRADE was also used for decision-making. This guideline considers not only seizure outcomes but also other critical and important outcomes. Seizures, quality of life, mortality, adverse events and verbal memory loss were considered critical outcomes, while other neuropsychological deficits besides verbal memory loss (i.e., naming, fluency), neuropsychiatric and social outcomes were considered important outcomes.

Following the GRADE process, the following strong recommendation was made based on moderate level of evidence: (1) temporal lobectomy is recommended for people with mesial temporal sclerosis at low risk for cognitive decline. Due to very low to low certainty of evidence the panel suggested the following conditional recommendations: (1) temporal lobectomy (TLE) for people with mesial temporal sclerosis at high risk for cognitive decline, (2) amydalo-hippocampectomy (AHE) in mesial temporal epilepsy, (3) laser interstitial thermal therapy (LITT) in mesial temporal epilepsy, (4) neocortical resection in neocortical epilepsy, and (5) callosotomy in people with drop attacks, Lennox-Gastaut syndrome or developmental and epileptic encephalopathies. The panel recognized that conditional recommendations need to account for individual patient circumstances and mandates shared decision-making to ensure that decisions align with each person's values and preferences. For hypothalamic hamartoma, the panel strongly recommended LITT despite low levels of evidence due to a paradigmatic situation that open surgery has significant risks that outweigh the benefits. If LITT is not available, the panel suggested radiosurgery for hypothalamic hamartoma (conditional recommendation).

The panel highlighted that every person with drug-resistant epilepsy should have access to a tertiary epilepsy care center that performs surgical procedures and advanced epilepsy diagnostics (good practice statement).

Introduction

Resective epilepsy surgery has been a well-established treatment for drug-resistant epilepsy since the early 20th century.[1] Over recent decades, diagnostic and surgical techniques have evolved significantly, with the development of less invasive procedures such as selective amygdalo-hippocampectomy (SAH), laser interstitial thermal therapy (LITT), and stereotactic radiosurgery (SRS). These advancements have necessitated updated guidelines to incorporate these new approaches.

Despite these technological and procedural improvements, the overall rate of seizure freedom has not markedly increased. Retrospective studies and meta-analyses[2] indicate that the percentage of patients achieving seizure freedom remains at approximately 64%, even with ongoing progress.[3] Multidisciplinary epilepsy conferences consistently highlight that each patient presents unique challenges, and clinical decision-making is often complex due to the wide array of therapeutic options available. In this rapidly evolving landscape, it is essential for professionals to stay informed about the comparative efficacy, risks, and long-term outcomes of various interventions to guide patients toward the most suitable treatment pathways.

Additionally, neuromodulation therapies—such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS)—provide alternative options for patients who may not be ideal candidates for resective surgery. While there is evidence supporting the potential for seizure freedom with these modalities, their effectiveness is generally lower than that of resective procedures.[4] This guideline intentionally does not compare resective surgery to neuromodulation, due to a lack of robust comparative studies that could reliably address this question.

In this rapidly evolving landscape, evidence-based clinical practice guidelines play a critical role in translating the expanding and heterogeneous literature into actionable recommendations. By systematically appraising the certainty of evidence and explicitly weighing benefits, harms, feasibility, and patient values, guidelines Enhance consistency and transparency in clinical decision-making by systematically evaluating the strength of evidence and carefully considering benefits, risks, feasibility and patient values. This process also aids clinicians in advising patients about expected outcomes and potential trade-offs. Beyond bedside care, guideline statements provide a common framework for multidisciplinary teams, define minimum standards for evaluation and treatment pathways, and identify priority evidence gaps that should shape the next generation of prospective studies and comparative effectiveness research. Importantly, guidelines also inform health policy by supporting coverage determinations, reimbursement structures, and procedure coding, thereby helping to reduce financial barriers and improve equitable access to specialized epilepsy services across diverse healthcare settings.

Rationale

The last published practice parameter[5] provided a foundation for recommendations and since then, the field has expanded significantly in scope and sophistication so that an

update to the recommendations is necessary. Despite the existence of previous practice parameters, the proportion of patients undergoing surgical procedures has not increased.[6] Of the 3.4 million individuals living with active epilepsy in the United States,[7] it is estimated that between 14% and 36% have drug-resistant epilepsy,[8] to approximately 476,000 to 1,224,000 people. Nevertheless, procedure volumes remain low; for example, in 2019, only 1,508 temporal lobectomies and 877 extratemporal resections were performed across 256 U.S. epilepsy centers.[9] Multiple factors contribute to this, with access to care and health disparities likely representing the most significant barriers.[10] Updated recommendations are therefore needed to better inform healthcare providers and patients, enabling them to pursue appropriate care.

Historically, many studies have focused only on seizure outcomes. In contrast, this guideline also considers additional outcomes, including all-cause mortality such as sudden unexplained death in epilepsy (SUDEP), quality of life, neuropsychological, psychiatric, and social outcomes, as well as permanent neurological deficits and medical or surgical adverse events. By incorporating these aspects, the guidelines aim to provide a more comprehensive decision-making tool for people with epilepsy and medical providers who provide epilepsy care.

The evidence base for many surgical procedures relies heavily on retrospective observational data subject to selection bias. When applying strict GRADE methodology to evaluate this literature, the resulting evidence is frequently classified as low quality due to this inherent study limitations. The recommendations are made after intensive discussions of the diverse panel of experts, including a patient representative. The patient's perspective, as well as the insights of neuropsychological and ethical experts, added significantly to the discussion.

The development of these guidelines required considerable time and collaboration. A key objective was to achieve consistency in recommendations across multiple professional societies, as guidelines have not always aligned in the past.[11] As a joint effort of the American Epilepsy Society (AES) and the Congress of Neurological Surgeons (CNS), we hope this work exemplifies multidisciplinary collaboration, united by the goal of providing the best possible care for patients.

These guidelines aim to equip clinicians with updated, evidence-based approaches for evaluating and managing epilepsy surgery candidates, while also serving as a robust resource for epilepsy surgeons, epileptologists, and other healthcare professionals involved in the care of patients with drug-resistant epilepsy

Guideline Recommendations Summary

The panel makes a strong recommendation for anterior temporal resection compared to best medical therapy for people with mesial temporal lobe epilepsy and low risk for cognitive decline after resection. For people with greater than low risk of cognitive decline after a resection, the panel suggests anterior temporal lobectomy (ATL) (conditional

recommendation). A conditional recommendation needs to account for individual patient circumstances and mandates shared decision-making.

Based on very low quality of evidence, it is suggested that LITT or SAH can be performed as an alternative to a temporal lobectomy in mesial temporal lobe epilepsy (conditional recommendation). The panel suggests against radiosurgery for temporal lobe epilepsy (conditional recommendation).

Resective epilepsy surgery is suggested in neocortical epilepsy compared to best medical therapy (conditional recommendation).

For drop attacks in Lennox-Gastaut Syndrome and developmental and epileptic encephalopathies, callosotomy is suggested for better seizure outcomes as compared to VNS (conditional recommendation). VNS can be an alternative if a lower risk is preferred.

In epilepsy associated with hypothalamic hamartomas, LITT is recommended over open resection due to the associated higher risk of injury with open surgery despite low levels of evidence (paradigmatic situation). Full recommendations are provided in Table 1.

Methods

Overview of Guideline Development Process

The guideline development process was guided by AES policies and procedures and overseen by the AES Guidelines and Assessment Committee.[12] Informed by systematic reviews evaluating treatment effectiveness, comparative effectiveness, and harms, this clinical practice guideline was developed by a panel of topic experts for each treatment category, with input from patients, family members, caregivers, or advocates (Supplement 1). The panel used the GRADE approach to assess the supporting evidence contained in the reviews and develop the guideline recommendations.[13] This clinical practice guideline was developed with financial support from the AES.

Formulating Specific Clinical Questions and Determining Outcomes of Interest

The previous practice parameter[5] reported evidence for effectiveness of epilepsy surgery. Only temporal lobe epilepsy surgery was supported by Class I evidence in the practice parameter. The current guideline is meant to examine additional evidence for epilepsy surgery since the 2003 practice parameter and develop recommendations for practice based on updated evidence. Since 2003, new surgical procedures, such as laser surgery, have been introduced and need to be incorporated into clinical guidance. The previous guideline was not inclusive of procedures frequently employed in pediatric practice, such as callosotomy and surgical treatment of hypothalamic hamartomas. The question of reduced mortality with surgical treatment is relevant to surgical decision-making and should be part of recommendations for clinical practice.

Each PICO question addressed in this guideline identifies a specific population (P), intervention (I), comparator (C), and the corresponding patient-important outcomes (O).

The purpose of this clinical practice guideline was to assess systematically, with documentation consistent with current globally accepted standards, the best available evidence that evaluates the efficacy of epilepsy surgery, as specified in the PICO questions (Appendix A).

Evidence Review and Development of Recommendations

Rigorous, high-quality systematic reviews were conducted to address each PICO question. A thorough literature search was performed using MEDLINE, Embase, and the Cochrane Library.[14,15] The methodology team completed dual independent literature screening, data extraction, and risk of bias assessments of included studies for the update. Methodologists assessed the certainty of evidence and developed concordant recommendations using the GRADE evidence-to-decision framework.[14]

Evidence synthesis included best available evidence hierarchically by study type, where available: comparative, including randomized control trials (RCTs); prospective and retrospective cohorts; crossover studies; and case control studies. If these study types were not available, cross-sectional observational studies and case series were included with stringent criteria for sample size. Systematic reviews and meta-analyses were excluded from this data analysis but used to identify potentially relevant resources.[15]

The literature identified encompassed 28,942 studies from which 2,028 were selected for full-text review. Of those articles, 65 were identified as relevant to the study questions (Figure 1). Recommendations were informed by data presented in the evidence profiles, certainty of evidence ratings, the balance of benefits and harms of the intervention and comparator, and patient values and preferences.

Interpretation of Strong and Conditional Recommendations

Recommendations are classified as either "strong" or "conditional." The phrase "the guideline panel recommends" indicates a strong recommendation; the phrase "the guideline panel suggests" indicates a conditional recommendation.

Summary of the Evidence

I. Drug-Resistant Mesial Temporal Epilepsy

Good Practice Statement

Every patient with drug-resistant epilepsy should have access to a tertiary epilepsy center for evaluation of epilepsy surgery. In the United States tertiary epilepsy care is delivered at Level 3 and Level 4 epilepsy centers as defined by the National Association Epilepsy Centers (NAEC).[16] Drug-resistance is defined as not being seizure-free after two antiseizure medications at therapeutic doses.[17]

> **Overarching recommendation for mesial temporal lobe epilepsy:** The AES/CNS guideline panel suggests one of the three surgical interventions including ATL, SAH,

and LITT in people with drug-resistant mesial temporal lobe epilepsy through a shared decision-making process considering appropriate risk assessment, values and preferences. The panel suggests not considering radiosurgery in this population.

Remarks for all PICO 1 recommendations:

- Mesial temporal lobe epilepsy is rare in patients less than 12 years old. The panel did not address this question in people under 12 years old.

Summary of Recommendations Related to Anterior Temporal Lobectomy vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy

Recommendation I-A-1: The AES/CNS guideline panel recommends the use of ATL compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy who are at low risk of cognitive decline.
(**Strong** Recommendation, **Moderate** Certainty of Evidence)

Recommendation I-A-2: The AES/CNS panel suggests the use of ATL compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy at greater than low risk for cognitive decline. (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Remarks for Recommendations I-A-1 and I-A-2:

- Risk assessment for cognitive decline can be done using known and validated approaches, including but not limited to neuropsychological testing, fMRI, intra-carotid testing with anesthetics and multivariable prediction models.
- The evaluation of risk-benefit ratio should consider the extent and type of resection.
- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.

Summary of the evidence

Only six studies met inclusion criteria. Two were randomized controlled trials,[18,19] two prospective,[20,21] and two retrospective studies.[22,23] Most studies regarding the outcomes of temporal lobectomies are non-randomized, retrospective, observational, without control groups or of small sample size.

The two randomized controlled studies provide moderate certainty of evidence.[18,19] Both studies report superiority of being free of disabling seizures after surgery at 1 or 2 years compared to best medical treatment with a large effect size. On average

500-838 more per 1000 people are seizure-free with temporal lobectomy in the RCTs as compared to best medical therapy. Both studies are of small sample size with 23/40 (57%) being free of disabling seizure at 1 year follow-up[18] and 11/15 (73%) being free of disabling seizures at 2 years.[19] The proportion of seizure freedom was 1/40 (2.5%) and 0/23 (0%) in the medical group. This is similar to non-randomized studies with low certainty of evidence.[20] In addition, temporal lobectomy significantly improved quality of life in both randomized controlled trials with moderate certainty and a median improvement on the Quality of Life in Epilepsy Inventory–89 (QOLIE-89) of 17.53 points in the surgical cohort compared to the medical cohorts.

Long-term studies beyond 2 years are non-randomized and of low certainty due to serious risk of bias, but superiority of temporal lobectomy for seizure outcomes persists.[20,22,23] The evidence is very uncertain about its effects on quality of life at longer follow–up periods, employment and driving.

All-cause mortality, including SUDEP, is reduced with temporal lobectomy compared to best medical treatment.[18,20,23] Reported mortality in above studies has very low certainty of evidence due to imprecision/rarity of the event and extremely serious risk of bias in non-randomized studies.

In randomized trials, neuropsychological outcomes are either reported as a decline in verbal memory that interfered with the patient's occupation[18] or as a loss of verbal memory with objective neuropsychological measures.[19] There is very low certainty of evidence due to imprecision and risk of bias due to missing data of neuropsychological outcomes in the Early Randomized Surgical Epilepsy Trial (ERSET) study.[19]

Depression as an outcome had a very low level of evidence and was reported in both directions. Psychosis outcomes had similarly low levels of evidence.

Benefits, harms, and burden

Discussing the benefits and harms of epilepsy surgery, the panel concluded that benefits and harms are not equal in people with dominant and non-dominant temporal lobe epilepsy due to the differential risk of cognitive decline after temporal lobectomy. Therefore, the panel addressed the question in two different subgroups: people with low risk of cognitive decline and people with all other risk levels of cognitive decline. Risk assessment was based on standard diagnostic methods including but not limited to neuropsychological testing, fMRI and intra-carotid testing with anesthetics such as amytal, etomidate, pentobarbital, methohexital or propofol.

The critical outcomes for patients at low risk of cognitive decline included seizure freedom and quality of life at 1- and 2-years follow-up. The panel determined that

there is moderate certainty in the evidence for a net health benefit from conducting ATL compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy at low risk of cognitive decline. The negative effects were considered small. Other evidence-to-decision criteria, specifically values and preferences and feasibility and acceptability, were in favor of ATL in the low-risk population so that the desirable consequences were found to be greater than the undesirable consequences and a strong recommendation for temporal lobectomy was made.

The panel determined that in people at greater than low risk for cognitive decline there is a large benefit in terms of seizure freedom with moderate level of evidence but very low certainty of evidence regarding the cognitive harms, so the net-health benefit remains of very low certainty. Other evidence-to-decision criteria, specifically feasibility and acceptability, were in favor of ATL in this population while values and preferences were found to probably vary from patient to patient. The desirable consequences were found to be greater than the undesirable consequences, and a conditional recommendation for temporal lobectomy was made.

Additional considerations by the panel not included in the evidence
The population of people with mesial temporal lobe epilepsy was divided into two subgroups due to different values and preferences that patients may place on potential cognitive decline that is associated with temporal lobe resections. For some patients, verbal memory loss may be acceptable, and for others it may not be acceptable.

Risk can also be stratified using multivariable prediction models.[24] In general, people with seizures arising from the non-dominant temporal lobe are at lower risk for cognitive decline than in those whose seizures originate from the language-dominant hemisphere. Further, those already experiencing cognitive impairment (e.g., memory, language) are at less risk for cognitive decline than those with intact cognitive function. The panel did not examine evidence in children less than 12 years old but determined that similar principles apply in the pediatric population, although enhanced plasticity in the young is an additional important factor to consider.

A systematic review by Al-Aqeel et al[25] performing primary discrete-choice experiments found that people with epilepsy have strong preferences for improving seizure control, which was ranked as the top priority in all studies and that patients also have a strong preference for the reduction of adverse effects and may be willing to make trade-offs between improved seizure control and reduction of long-term side effects that may impact their quality of life. Therefore, a careful shared decision-making process is vital that should also include discussion of cognitive and psychiatric adverse events.

Other considerations

The panel discussed whether epilepsy surgery itself increases or decreases health disparities and could not come to final conclusions. Some panel members emphasized that disparities stem from systemic barriers such as geography, insurance coverage, stigma, healthcare system limitations, and access to specialized centers. These factors disproportionately affect certain populations, leading to lower surgery rates among some racial and socioeconomic groups.[26]

Others noted that if epilepsy surgery remains available under the current healthcare structure, disparities may worsen, particularly for underprivileged communities with limited access to specialized care. However, it was also highlighted that more people are accepting surgery now than in the past, suggesting that the intervention itself does not widen disparities; rather, the healthcare system determines who can access it. The panel acknowledged disagreements on how to interpret these judgments. Ultimately, there was consensus that the barriers to epilepsy surgery are not due to the procedure itself but rather the broader structural challenges within the healthcare system.

The panel also noted that temporal lobectomies are not standardized, can be performed with different resection margins and the extent of the resection can vary by surgeon. This guideline does not specify the extent of a temporal lobectomy.

Conclusions and research needs for this recommendation

The only randomized controlled evidence for epilepsy surgery with a moderate level of certainty exists for temporal lobe resections. There is a lack of randomized controlled trials, and adverse events are mainly documented in retrospective observational studies. As temporal lobectomy is a well-established and widely available therapy, it is not feasible or practical to perform future large randomized controlled trials; this is evidenced by previous difficulties investigators encountered enrolling patients in such studies.[19]

Summary of Recommendations Related to Selective Amygdalo-Hippocampectomy vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy

Recommendation I-B: The AES/CNS guideline panel suggests the use of selective amygdalo-hippocampectomy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Remarks for Recommendation I-B:

- A prerequisite for this recommendation is that the facility is equipped to offer SAH and that healthcare professionals have the proper training to perform the procedure.
- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-

making to ensure that clinical decisions align with each patient's values and preferences.

Summary of the evidence

There is only one retrospective, non-randomized study that compares SAH to medical treatment.[27] In this study, 9/11 (82%) people became seizure-free with SAH, none with medical therapy. Composite memory scores were not significantly different between groups at baseline and at follow up, but a significant decline in verbal memory was noted in 73% of the surgical group and 25% of the medical group at follow up. The study has a serious risk of bias and imprecision due to the retrospective nature and sample size, and the level of evidence is very low.

Benefits, harms, and burden

Potential benefits of SAH include an increased likelihood of seizure freedom, which the panel identified as a critical outcome, as well as possible improvements in quality of life, mood, and social functioning. Despite the very low certainty of evidence, the panel judged the magnitude of desirable effects to be large, based on the direction of effect and consistency with clinical experience in appropriately selected patients. Potential harms include cognitive decline, particularly for procedures involving the dominant temporal lobe. While available evidence suggests these harms are generally small on average, estimates are imprecise and vary across individuals. The burden of surgery includes perioperative risks, recovery time, and the need for specialized follow-up care, but the panel judged the overall undesirable effects to be small relative to the anticipated benefits.

Additional considerations by the panel not included in the evidence

The panel noted substantial variability in patient values and preferences, particularly regarding trade-offs between seizure freedom, cognitive outcomes, mood, and quality of life. While many patients prioritize seizure freedom, others place greater importance on cognitive preservation, emotional well-being, or functional independence, especially when surgery involves the dominant hemisphere. Feasibility and acceptability of SAH depend on institutional expertise, surgeon training, and access to comprehensive epilepsy centers. Surgical approach and regional training patterns may influence outcomes and adoption. The panel also emphasized the importance of shared decision-making, clear communication of uncertainties, and timely referral to specialized centers, particularly given barriers such as delayed referral, limited access to care, and patient concerns or misconceptions about surgery.

Other considerations

Other considerations discussed by the panel include delays in referral for epilepsy surgery, variability in definitions of drug-resistant epilepsy, and structural barriers to accessing specialized care. These factors may contribute to underutilization of surgical options and disparities in care. The panel emphasized that timely referrals

to a comprehensive epilepsy center and standardized presurgical evaluation are critical to ensuring appropriate patient selection and informed decision-making. Equity considerations remain uncertain and are likely driven by broader healthcare system factors rather than the procedure itself.

Conclusions and research needs for this recommendation

The panel determined that there is very low certainty in the evidence for a net health benefit from conducting SAH compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy. Other evidence-to-decision criteria, specifically feasibility and acceptability, were in favor of SAHin this population while values and preferences were found to probably vary from patient to patient. The desirable consequences were found to be greater than the undesirable consequences, and a conditional recommendation was made.

Summary of Recommendations Related to Laser Interstitial Thermal Therapy (LITT) vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy

Recommendation I-C: The AES/CNS guideline panel suggests the use of laser interstitial thermal therapy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks for Recommendation I-C:

- A prerequisite for this recommendation is that the facility is equipped to offer LITT and that healthcare professionals have the proper training to perform the procedure.
- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.

Summary of the evidence

All studies reporting on LITT in mesial temporal lobe epilepsy are observational, non-randomized and have extremely serious risk of bias or imprecision. In three studies with 434 participants, 225/434 (51.85%) reported seizure freedom Engel I classification at 1 year follow-up.[28,29,30] After 4 years, 268 participants in one study, 132/268 (49.25%) still were considered seizure free Engel Class I.[29]

In a comparative study comparing LITT to temporal lobe resections, 22 of 33 participants with LITT (66.67%) reported seizure freedom (ILAE class I) after 3 years and propensity score matching to participants with temporal lobectomies did not find difference in outcome between LITT and temporal lobectomy.[31] Another study comparing 40 participants with LITT to 40 with temporal lobectomy reported statistically significant differences in verbal memory (Rey Auditory Verbal Learning Test) outcome with LITT at 1 year follow-up.[28] Better verbal memory outcomes were observed with LITT in this study.

All-cause mortality in two studies was reported as 1.94% (8/412) in two studies[29,30] with a median follow up of 3.75 years. SUDEP was reported 1/227 (0.4%) at 1 year and 4/135 (2.9%) at 3.5 years.[29,30] All evidence regarding LITT was of very low certainty.

Benefits, harms, and burden
The benefits of LITT to achieve seizure freedom compared to best medical therapy were considered large by the committee based on the low seizure freedom rate of best medical therapy (7.5%) reported in randomized studies.[18] However, seizure freedom rates of LITT based on observational studies were felt to be slightly lower compared to open temporal lobe resection and tolerability of the procedure may outweigh the slightly lower effectiveness. The harm of LITT was considered small. Neuropsychological deficits occur, and the overall effects of those declines are difficult to estimate. Complications such as visual changes are reported but very considered small. The risk of cognitive decline is stratified similar to the risk of cognitive decline after temporal lobectomy that verbal memory and naming declines are more likely after LITT in the dominant temporal lobe. The panel agreed that LITT is well tolerated and requires short hospitalizations.

Additional considerations by the panel not included in the evidence
There are multiple metanalysis of smaller observational studies that compare outcomes of LITT to temporal lobectomy.[32-35] There seems to be concordance that with dominant procedures naming is better preserved with LITT than temporal lobectomy. Verbal memory outcomes were inconclusive.

Other considerations
Patients place high value on short hospitalization times and post-operative care and return to daily activities, including work, provided by LITT. They also place high value on seizure freedom although they value avoiding long term effects that may impact their quality of life. LITT is often only offered in specialized centers and requires specialized training. The feasibility of performing LITT may vary depending on the region.

Conclusions and research needs for this recommendation
The panel determined that there is very low certainty in the evidence for a net health benefit from conducting Laser Interstitial Thermal Therapy (LITT) compared to medical therapy in patients with drug resistant mesial temporal lobe epilepsy. The desirable consequences were found to be greater than the undesirable consequences, and a conditional recommendation was made.

There is a significant beneficial effect of reaching seizure freedom. However, the risk for cognitive decline is present, especially in high-risk populations. Values and

preferences of patients, including short hospitalizations, may influence the decision for LITT.

The panel emphasizes the importance of exploring in future research the difference between the seizure free and cognitive decline rates in LITT compared to rates in ATL. This can only be studied in large randomized controlled cohorts that may not be realistically feasible.

Summary of Recommendations Related to Radiosurgery vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy

Recommendation I-D: The AES/CNS guideline panel suggests against the use of radiosurgery compared to medical therapy in people aged 12 years or older with drug-resistant mesial temporal lobe epilepsy.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks for Recommendation I-D:

- Healthcare professionals should consider the other assessed surgical approaches in this guideline, including ATL, SAH, and LITT when making this decision with their patients (refer to related recommendations).
- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.

Summary of the evidence

In addition to isolated case reports, there is one prospective, single-blind, controlled multicenter trial.[36] Outcomes were seizure remission (absence of disabling seizures between 25 and 36 months after treatment), verbal memory and quality of life at 36-month follow-up. Because of reduced recruitment, only 58 patients were treated: 31 with stereotactic radiosurgery (SRS) and 21 with ATL. There was no arm with medical treatment only; all patients were on antiseizure medications. This reduced recruitment resulted in early termination of the study, and noninferiority of SRS to ATL could not be demonstrated.

Sixteen (52%) of the patients receiving SRS became seizure-free compared with 21 (78% of patients who received ATL). 81% of patients receiving ATL became seizure-free by the first assessment period (after 3 months) while at 3 months only 6% of patients who ultimately were seizure-free after SRS had achieved seizure freedom. There was a gradual increase in the seizure-free cohort among those patients receiving SRS over the 36-month monitoring period; however, only 4 of 13 (13%) reported seizure-freedom (Engel 1b classification) at one year.[36]

Analysis including 23 participants revealed an increase in quality of life one year after radiosurgery [mean change (95% CI) 0.57 (-0.05, 7.19)] and three years after

radiosurgery [mean change (95% CI) 7.61 (-0.30, 15.47)]. Both the stereotactic radiosurgery and ATL groups showed QOL improvements; this correlated with the number of patients who were free of disabling seizures. Early improvements appeared sooner after ATL, whereas stereotactic radiosurgery group improvements emerged more gradually. The authors also noted an increase in verbal memory one year after radiosurgery in an analysis of 14 participants [mean change (95% CI) 0.6 (-1.32, 2.53)] and three years after radiosurgery [mean change (95% CI) -0.38 (-2.00, 1.23)] (Barbaro et al 2018), but this change was not significant in English-speaking patients with dominant temporal lobe resections.[36]

In the same study (n = 31), no permanent, unexpected neurological deficits were reported three years after undergoing radiosurgery, and 5/31 (16.13%) reported serious adverse events, including headache (n = 1), cerebral edema (n = 1), seizure exacerbation (n = 2), or new neurological event (n = 1) years after undergoing radiosurgery. Adverse events in the ATL arm occurred in the first 3 postoperative months with 3 total adverse events deemed serious reported (wound infection, cerebritis, depression). The degree of cerebral edema was difficult to ascertain from the records. Sixty-five percent of patients in the SRS arm received steroids per protocol; 26% of patients in the ATL arm received steroids. From SRS studies in all disorders, focal edema is known to accompany SRS therapy.[36]

Benefits, harms, and burden

The panel determined that in the very low certainty evidence the balance of effects does not favor radiosurgery or medical therapy in patients with drug-resistant mesial temporal lobe epilepsy. Despite radiosurgery being probably feasible, the panel judged that it was probably not acceptable in part due to the delay (in years) for measurable benefit and the increase in side effects (e.g., focal edema requiring steroids), and values and preferences are likely to vary. Thus, the panel judged that the undesirable consequences were greater than the desirable consequences, which informed the conditional recommendation against radiosurgery.

Additional considerations by the panel not included in the evidence

A report of visual field defects after radiosurgery compared with temporal lobectomy in the ROSE trial did not reveal any significant differences in incidence or severity of visual field defects between the two treatment arms.[37]

Other considerations

Comments from the panel, based on clinical experience, noted that data from the study likely underestimates cognitive decline, serious adverse events, and even mortality after radiosurgery.

Conclusion and research needs for this recommendation

There is no reliable evidence that compares radiosurgery to medical therapy, but there is randomized controlled evidence that compares radiosurgery to temporal

lobectomy. Radiosurgery should not be performed unless resective surgery is absolutely unavailable. The panel did not recommend any further studies for radiotherapy in epilepsy surgery.

II. Drug-Resistant Neocortical Epilepsy

Summary of Recommendations Related to Resective or Ablative Surgery vs. Medical Therapy in Patients with Drug-Resistant Neocortical Epilepsy

Recommendation II: The AES/CNS guideline panel suggests the use of resective or ablative surgery compared to medical therapy in people aged 2 years and older with drug-resistant neocortical epilepsy.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Remarks for Recommendation II:

- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences (e.g., physicians should account and discuss with patients the outcome differences between lesional versus non lesional epilepsy).
- The consideration of functional proximity or overlap of epileptogenic zone with functional cortex should be considered in decision-making.

Summary of the evidence

There were no randomized controlled trials that compared resective surgery in neocortial resections to best medical therapy.

In two observational studies with 446 participants, with about 80% pediatric population, at 1-year follow-up, 255 (57.17%) had achieved seizure freedom Engel Ia classification after undergoing resective surgery.[38,39] In one study with 110 adult participants, at 1-year follow-up, 72 (65.4%) achieved seizure-freedom Engel I after undergoing resective surgery.[40]

In one study with 105 participants (87% belong to pediatric population), at 2-year follow-up, 59 (56.19%) achieved seizure-freedom Engel I classification after undergoing resective surgery.[38] One study included 188 participants (around 50% adults and 50% children) and reported that 124 (66%) achieved seizure-freedom Engel I classification after undergoing resective surgery, at 2-year follow-up.[41] One study included 788 participants, of which 574 were pediatric (73%). This study reported that 544 (69%) achieved seizure-freedom Engel I classification after undergoing resective surgery, at 2-year follow-up.[42]

Four studies with 591 participants providing outcome data (>80% under 18 years) reported that 304 (51.44%) achieved seizure-freedom Engel Ia after undergoing

resective surgery.[38,39,43,44] Two studies with 124 participants providing outcome data reported that 61 (49.19%) achieved seizure-freedom Engel Ia after undergoing resective surgery[44,45] Two studies with 164 participants, reported that 118 (71.95%) achieved seizure-freedom Engel I at the longest follow-up after undergoing resective surgery. One of the studies included reported no difference in the proportion of participants achieving seizure-freedom (Engel I classification) between children <6 years of age (32/40, 80%) and adults >20 years of age (53/66, 80%).[44]

Permanent unexpected neurological deficits were uncommon. Two studies reported low rates of permanent deficits among those <18 years of age attributed to surgical injury or resection involving eloquent cortex.[43,44] In adults, permanent neurological deficits or death were rare.[41,43-45] Evidence included all cortical regions.

Benefits, harms, and burden

The panel determined that there are benefits to resective or ablative surgery for neocortical epilepsy. Based on available evidence, resective surgery appears to offer meaningful and durable seizure control for patients with drug-resistant neocortical epilepsy, with acceptable rates of adverse events. Evidence quality is limited by study design heterogeneity and lack of randomized controlled trials. Resective epilepsy surgery demonstrated a substantial and durable benefit in achieving seizure freedom, with approximately 50–70% of patients achieving Engel I outcomes across time points. Benefits were observed in both pediatric and adult populations, with seizure outcomes maintained at long-term follow-up. Harms were infrequent but present, including permanent neurological deficits and surgical complications, though reporting was inconsistent and often incomplete. Most evidence derives from observational studies with heterogeneous populations, surgical techniques, and follow-up durations.

Other considerations

Appropriate referral to a NAEC Level 4 epilepsy center is needed for the evaluation and treatment of drug-resistant neocortical epilepsy as intracranial EEG is typically required and assessment through a multidisciplinary epilepsy surgical team is warranted. NAEC Level 3 centers are required to have a referral agreement with a Level 4 center. Some patients may not have access to a Level 4 center either through geographic or other reasons, and this should be considered in future work to reduce barriers to epilepsy surgery.

Conclusions and research needs for this recommendation

A conditional recommendation was made for resective or ablative surgery compared to medical therapy in patients with drug-resistant neocortical epilepsy. Although the evidence provides only very low certainty for a net health benefit for surgery, the expert panel concluded that other evidence-to-decision criteria including acceptability, overall risk, and general benefit and advises shared decision-making between physician and patient. Values and preferences of

physicians and patients probably vary, but outcomes were felt to be desirable and supported by the overall recommendation. Future research should include high quality comparative studies comparing surgical techniques.

III. Drug-Resistant Drop Attack and Lennox-Gastaut Syndrome

Summary of Recommendations for Drug-Resistant Drop-Attacks, Lennox-Gastaut Syndrome, or Developmental Epileptic Encephalopathy

Recommendation III-A: The AES/CNS guideline panel suggests the use of callosotomy compared to VNS in adults with drug-resistant drop-attack, Lennox-Gastaut Syndrome, or epileptic encephalopathy.
(**Conditional** Recommendation, **Very Low** Certainty of Evidence).
Recommendation III-B: The AES/CNS guideline panel suggests the use of Callosotomy compared to VNS in children with drug-resistant drop-attack, Lennox-Gastaut Syndrome, or epileptic encephalopathy.
(**Conditional** Recommendation, **Very Low** Certainty of Evidence).
Remarks for Recommendation III-A and B:

- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.
- VNS is also an acceptable option. It is slightly less effective in terms of seizure outcomes but often a safer alternative. Patients and caregivers may place higher value on safety than effectiveness.
- There is not sufficient evidence what type of callosotomy (anterior, posterior or complete callosotomy) should be performed.

Summary of the evidence
Both open and LITT callosotomies were considered in evidence. There were no prospective randomized studies that compared callosotomy to VNS, neither in adult nor pediatric populations. Twenty-four observational studies were included: 7 prospective cohort, 9 retrospective cohort, and 8 before/after studies. Eight studies included adult patients,[46-53] and 16 studies included pediatric patients.[54-] Of the 8 adult studies, the number of participants per study ranged from 15 to 52. Corpus callosotomy was performed in various ways among the studies, and it was not possible to evaluate potential differential efficacy of technique (complete verses partial or selective callosotomy). Of the 16 pediatric studies, the number of participants ranged from 10 to 60. Some studies compared cohorts receiving callosotomy vs. VNS,[57,59,53,69] while the rest evaluated corpus callosotomy alone. Medication strategy prior to surgery and patient population was varied among studies, as was duration of follow-up and the strategy the authors used to evaluate the efficacy of the intervention (serial EEG, seizure diary, parent or caregiver report, or other method).

One study reported 13/24 (54%) seizure-freedom at 1-year,[46] 3-year seizure freedom was 6/68 (9%) in two studies,[47,48] and two additional studies found > 90% seizure reduction at 5.5 years.[49,52] Long-term (10- year) seizure freedom was evaluated in two studies to be 17% (8/46),[51,53] and long-term freedom from drop attacks 45% (28/62).[50,51] Seizures outcomes included all types of seizures and not only drop attacks.

After callosotomy, multiple studies showed between 45 and 55% improvement in QoL/daily function.[47,50-52]

In patients undergoing callosotomy, some patients had worsening praxis and visuospatial skills, with 3 to 5% having new focal neurologic deficits.[46,47,50,52] Two studies reported 1 death after callosotomy.[48,52] One study reported one infection,[48] and one study reported 2 hemorrhages.[47] The rate of transient serious neurologic events ranged from 13 to 20% among the studies, and d speech function was variable after callosotomy. In one study 11/ 52 (21%) had improved speech function, 9/52 (17%) had impaired speech function, the remainder had unchanged speech function.[47] The evidence for efficacy from VNS was less robust in the literature.

Benefits, harms, and burden
The benefit of callosotomy to achieve a meaningful reduction in seizures including drop attack was found to be significant compared to continued medical management. Long-term efficacy appeared maintained at 10 years in select studies. While some harms were identified in select studies, overall harm appeared low based on this evidence. Most studies were retrospective, and not all studies evaluated for harm from surgery, making these data difficult to interpret. The extent of callosotomy varied (partial vs complete), and not all studies confirmed the extent of callosotomy with post-surgery imaging. Most studies evaluated open surgery instead of LITT-based callosotomy. Current risk profile needs to be evaluated at a center level when weighing risks and benefits for a patient.

Additional considerations by the panel not included in the evidence
No additional evidence was discussed by the panel.

Other considerations
Quality of life (QoL) and neuropsychological outcomes appeared improved in the limited studies that evaluated these outcomes. Most patients in these studies had developmental delays, and none were employed. Benefit from intervention was seen both by patients (e.g., less drop attacks/seizures) and by patient caregiver (e.g., easier to care for patient, increased QoL). The panel also discussed the use of both interventions in combination, especially to place a VNS for remaining focal seizures if drop attacks have been addressed with callosotomy.

Conclusions and research needs for this recommendation

Based on the medical evidence, the panel felt there is potential benefit to patients with Lennox-Gastaut Syndrome and drug-resistant drop attacks to undergo callosotomy or VNS in addition to medical therapy. Surgery for callosotomy can result in long-term seizure freedom or seizure reduction. Risk is hard to assess based on current studies, many of which are over 20 years old. Values and preferences of caregiver may more easily be measured because of the developmental delay of these patients; however, evaluation showed improvement in QoL per caregiver assessment. Callosotomy appeared to be more efficacious than VNS, however potential synergy in having both procedures was not evaluated. Future research should include prospective randomized trials of callosotomy and VNS, using validated outcome measures with long-term follow-up, in order to better inform future guidelines and provide better evidence for physicians, patients, and caregivers. Each facility should understand their differential operative risk for these procedures to make informed shared decisions with patients.

IV. Hypothalamic Hamartoma

Summary of Recommendations for Drug-Resistant Epilepsy Associated with Hypothalamic Hamartoma

Recommendation IV-A: The AES/CNS guideline panel recommends for the use of LITT compared to surgical resection in people with hypothalamic hamartoma (paradigmatic situation due to potential for catastrophic harm)

(**Strong** Recommendation, **Very Low** Certainty of Evidence)

Remarks for Recommendation IV-A:

- Access needs to be at a Level 4 epilepsy center that has access to LITT
- In some rare cases, LITT may not be feasible based on the anatomy

Summary of the evidence

The five studies reporting on laser interstitial thermal therapy (LITT) in the treatment of hypothalamic hamartomas consist of retrospective cohorts (3), case study (1), and prospective cohort (1). All of these studies evaluate LITT therapy, but none of the studies compared this treatment to other types of treatment (surgical or radiotherapy). As a result, there is an extremely serious risk of bias and a serious risk of imprecision. Seizure freedom was evaluated in all these studies at 1 year or greater with Engel I in 71.79% at 2-years in a pediatric only cohort.[70-72] In mixed adult and pediatric cohorts, seizure freedom of 61.1% ILAE 1 at 4 years[73] and 93% Engel I at 1-year[74] was reported. Permanent, unexpected neurological deficit was reported in 2 studies (pediatric) of 2% at 2 years[70,71]) and in one mixed population at 22% at 4 years[73] note there was no further description of the neurological deficit included). All-cause mortality was reported in 2 studies of 0%.[71,72] Other medical or surgical complications in the pediatric patients included weight gain (4.25%),[70]

endocrinological side effects (2.04%),[72] sodium disturbances (6.9%),[71] and psychiatric side effects (1.72%).[72] In the mixed population, 2 studies found 1 patient with newly diagnosed hypothyroidism (5.6%),[70] and 1 patient with worsened diabetes insipidus (1.41%).[74] Of note, one study reported none of the 18 patients had short-term memory issues, weight gain or increased appetite.[70] All studies are observational and retrospective, and the certainty of evidence is very low.

Benefits, harms, and burden
The benefits of LITT ablation of the hypothalamic hamartoma to achieve seizure freedom (61-93%) were unable to be compared to surgical treatment in this review due to the lack of papers including this comparison. However, in the setting of a low risk of morbidity and mortality with this procedure coupled with the complexity of an open surgical or endoscopic procedure to resect or disconnect a hypothalamic hamartoma makes LITT a feasible option.

The panel unanimously agreed, based on clinical experience, that LITT offers better outcomes and fewer harms than open surgery. The panel members noted that in current practice, clinicians will offer LITT for hypothalamic hamartoma over open resection. Open resection is more invasive, carries higher complication risk, and requires specialized surgical expertise that is not widely available.

This is a paradigmatic situation in which a strong recommendation is warranted despite very low certainty of evidence. Very low certainty evidence suggests that LITT provides a benefit in seizure control (seizure freedom ~74–75%) with low risk of serious complications or mortality. Although all evidence comes from non-comparative studies and is rated very low certainty, the direction and magnitude of effect are consistent, and the known harms of open resection are greater, based on clinical experience.

Additional considerations by the panel not included in the evidence
No additional evidence was discussed by the panel.

Other considerations
Patients place high value on short hospitalization times and post-op care and return to daily activities including school or work as provided by LITT. They also place high value on seizure freedom although they also value avoiding long-term effects that may impact their quality of life. Physicians (and patients) recognize that due to the minimally invasive approach and short hospitalization, a conservative ablation can be completed and repeated if complete disconnection is not obtained. However, as LITT is often only offered in specialized centers and requires specialized training, the feasibility of performing LITT may vary depending on the region and should be undertaken only in centers with appropriate expertise.

Conclusions and research needs for this recommendation

The discussion of the panel was that while there are no direct comparisons of open or endoscopic hypothalamic disconnection/resection with LITT ablation, a direct comparison is not feasible due to the complexity of open surgery. As there is acceptable seizure control with low complication rates, the panel determined that LITT should strongly be considered as the first line surgical intervention in the treatment hypothalamic hamartoma in appropriate patients (gelastic seizures with favorable anatomy) at centers with experienced training in this technique. The panel recommended future research to focus on the differing anatomic types of hypothalamic hamartoma and the effectiveness of seizure control from LITT as well as characterizing the post-treatment seizure-freedom rates between patients with gelastic or non-gelastic seizures.

Recommendation IV-B: The AES/CNS guideline panel suggests either the use of radiosurgery or surgical resection in people with hypothalamic hamartoma compared to medical therapy.

(**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Remarks for Recommendation IV-B:

- If LITT is not available, then the panel suggest radiosurgery. Decision-making between patient and clinician is important.
- A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.

Summary of the evidence

Ten studies reported on radiosurgery in the treatment of hypothalamic hamartomas.[75-84] These consist of retrospective cohorts (5), case series (2), prospective cohort (2), and one before-after study. All these studies evaluated radiosurgery, and two of these papers compared radiosurgery to another form of treatment such as surgical or endoscopic disconnection. As a result, there is an extremely serious risk of bias and a serious risk of imprecision. Seizure-freedom was compared between radiosurgery and surgical intervention in 2 papers. In pediatric patients, 0/4 radiosurgery and 4/10 (40%) surgical patients were seizure-free at 2.28 years.[75] In adult patients, 2/4 (50%) radiosurgery and 8/29 (27.6%) patients were seizure free at 4.8 years.[76] In non-comparative studies, 0/26 adult patients (at 1.2 years),[77] 11/24 (46%) adult patients (at 2 years),[78] 3/10 (30%) adult patients (at 9.8 years),[79] and 10/34 (29.41%) pediatric patients (2.35 years)[78,80] were seizure-free. In mixed populations of adults and pediatric patients, 15/48 (31.25%) were seizure-free at 3 years.[81] Permanent, unexpected neurological deficit was reported in a comparison study that showed 0/4 deficits in the radiosurgery group compared to 1/32 (3.1%) in the surgical group.[76] The remainder of the non-comparison studies demonstrated a permanent, unexpected neurological deficit in 0/15 pediatric,[78] 0/10 pediatric,[80] 0/24 mixed population,[82] and 0/48 mixed

population.[79,81] All-cause mortality in the comparison paper reported 0/4 in the radiosurgery group and 4/36 (11.1%) in the surgical group (4.8 years)[76] and in pediatric patients 0/15.[78] In the mixed population, 2/63 patients died at 3.5 years following radiosurgery[82,83] 0/48 deaths at 5.9 years.[81] All evidence is observational and retrospective and of low certainty.

Benefits, harms, and burden

The benefits of radiosurgery of the hypothalamic hamartoma to achieve seizure-freedom is low (0-50%) when compared to open surgical treatment in this review (27-40%); however, the extremely low risk of morbidity and mortality with this procedure coupled with the complexity of an open surgical or endoscopic procedure to resect or disconnect a hypothalamic hamartoma makes radiosurgery a feasible option in cases that are not amenable to LITT. The panel judged that they do not know what the balance of effects is, based on the very low certainty evidence of trivial benefits and unknown harms.

Other considerations

Patients place high value on short recovery times and minimal post-op care with rapid return to daily activities including school or work as provided by radiosurgery. They also place high value on seizure-freedom. Although radiosurgery has a lower seizure freedom rate, it may be appropriate in otherwise difficult to treat LITT cases or when barriers of access to LITT centers/expertise exist. Physicians and patients should participate in shared decision-making when in these challenging situations.

Conclusions and research needs for this recommendation

The discussion of the panel focused on LITT ablation as the best option for treatment of hypothalmic hamartoma. However, if there is limited access to this treatment or challenging complexities in the anatomy, radiosurgery can play a role. While radiosurgery has a low morbidity and mortality profile, it also has a lower surgical-freedom rate. The panel recommends future research to focus on the differing anatomic types of hypothalamic hamartoma and the effectiveness of seizure control from radiosurgery in comparison to LITT as well as characterizing the post-treatment seizure freedom rates between patients with gelastic or non-gelastic seizures.

Discussion

These guidelines address a central tension in contemporary epilepsy surgery: technical capabilities and procedural diversity have expanded substantially, yet population-level seizure-freedom and equitable access to definitive therapy have not improved in parallel. The evidence synthesis confirms that resective surgery remains the most effective intervention for carefully selected patients with focal drug-resistant epilepsy, particularly mesial temporal lobe epilepsy (MTLE), where ATL continues to have the most mature comparative evidence base. At the same time, the guideline process highlights how rapidly

evolving surgical and ablative approaches have outpaced the strength of comparative data needed to confidently individualize treatment selection, quantify trade-offs, and harmonize recommendations across centers.

Mesial temporal lobe epilepsy: ATL remains the benchmark, with cognitive risk as the decisive modifier

Across the body of evidence, ATL stands out as the only intervention supported by randomized data demonstrating superiority over continued medical therapy for seizure-freedom and patient-reported outcomes. The panel's strong recommendation for ATL in individuals aged 12 years or older who are at low risk for postoperative cognitive decline reflects moderate certainty that the net health benefit is substantial and clinically meaningful. In practice, this subgroup corresponds to patients in whom the anticipated incremental seizure-control benefit of ATL is not offset by an unacceptable probability of disabling memory or language decline. Importantly, "risk for cognitive decline" is not a binary attribute but the output of an integrated presurgical evaluation incorporating lateralization of language and memory networks, baseline neuropsychological performance, imaging markers (including hippocampal integrity and contralateral reserve), and individualized estimates derived from validated assessment strategies. The guideline therefore positions cognitive risk stratification not as an ancillary consideration but as the central determinant of recommendation strength.

For people who do not meet "low cognitive risk" criteria, the evidence supporting ATL over medical therapy becomes very low certainty, largely because observational studies are susceptible to selection effects that are tightly coupled to cognitive risk. In this setting, the conditional recommendation appropriately acknowledges that the decision is preference-sensitive and highly contingent on baseline function, dominance, occupational and educational priorities, and the patient's tolerance for cognitive trade-offs relative to seizure burden. The guideline's practical implication is that the role of ATL remains prominent, but that counseling should be explicitly framed around individualized risk, the realistic magnitude of seizure-control benefit, and the range of acceptable outcomes to the patient.

Selective amygdalo-hippocampectomy and LITT: clinically established, evidence-limited alternatives that require transparent counseling

The expansion of SAH and the more recent LITT reflects a shared clinical objective: preserve seizure-control efficacy while reducing cognitive and perioperative morbidity, shortening recovery, and improving acceptability. However, the evidence base for both SAH and LITT is predominantly retrospective, heterogeneous in-patient selection, and variable in follow-up duration and outcome definitions, resulting in very low certainty in comparative benefit estimates against medical therapy. The guideline's conditional support for SAH and LITT as alternatives to ATL should therefore be interpreted as an endorsement of their pragmatic role in modern practice rather than evidence of equivalence.

A key interpretive point is that apparent differences in seizure-freedom rates across procedures may reflect confounding by indication as much as procedural efficacy. For example, LITT cohorts may include patients selected because of perceived higher cognitive risk, medical comorbidity, or preferences favoring minimal invasiveness—factors that can simultaneously influence seizure outcomes and post-operative recovery trajectories. Consequently, procedure choice should be presented to patients as a balance among expected seizure-control probability, cognitive risk and uncertainty, recovery time, and the feasibility of staged or salvage strategies if seizures persist. From a guideline perspective, the priority is not to declare procedural parity but to standardize how clinicians communicate uncertainty and how centers track outcomes to progressively reduce it.

To proceed to procedures such as SAH or LITT where only the mesial temporal structures are removed, it needs to be ascertained that seizure onset is truly located in the hippocampal structures and not in the lateral temporal structures, so the underlying disease may influence the choice of procedure. Clearly visible mesial temporal sclerosis on MRI with non-divergent video-EEG or neuropsychological data seems to be the ideal indication for more limited procedures such as SAH or LITT.

Radiosurgery for MTLE: delayed and uncertain benefit with non-trivial risk and limited clinical role

The evidence for radiosurgery in MTLE does not support its routine use.

Although seizure-freedom can occur, benefit appears delayed relative to open surgery, and adverse effects related to radiation-induced changes remain a concern. With very low certainty evidence and limited contemporary clinical uptake, the conditional recommendation against radiosurgery is best understood as an application of precaution under uncertainty: when more established options exist that provide earlier seizure control and more predictable risk profiles, radiosurgery should not be prioritized outside specialized contexts, research protocols, or situations where other options are infeasible. This recommendation also underscores a broader guideline theme: minimally invasive does not inherently mean lower risk, and delayed therapeutic latency can be clinically consequential in a population with ongoing SUDEP risk, injury risk, and cumulative psychosocial burden.

Neocortical epilepsy: heterogeneity drives low-certainty evidence and reinforces the need for network-informed, center-based evaluation

For drug-resistant neocortical epilepsy, the panel's conditional recommendation favoring resective or ablative procedures over medical therapy reflects a consistent signal that surgery can provide meaningful seizure benefit but also reveals the methodological limits of the literature. Neocortical epilepsies encompass diverse etiologies (lesional and non-lesional), seizure-onset organizations, and degrees of overlap with eloquent cortex; these sources of heterogeneity complicate generalizable estimates of benefit, cognitive outcomes, and risk of permanent deficit. The guideline appropriately emphasizes that treatment selection in this population is inseparable from high-quality presurgical localization, risk mapping, and the ability to deploy intracranial EEG and functional

mapping when noninvasive data is insufficient. Practically, this reinforces the requirement for referral to Level 4 epilepsy centers and supports a standardized approach to counseling that explicitly addresses the probability of incomplete resection due to eloquent overlap, the impact of epileptogenic zone extent, and the realistic expectations for seizure control and cognitive and functional outcomes.

Drop attacks in Lennox–Gastaut syndrome and developmental and epileptic encephalopathies: palliative goals, safety priorities, and shared decision-making

In generalized developmental and epileptic encephalopathies, the guideline's conditional preference for callosotomy over VNS for drop attacks reflects a pragmatic prioritization of immediate injury reduction and seizure-type–specific benefit. The evidence remains very low certainty, but the direction of effect across observational comparisons consistently suggests greater reduction in drop attacks with callosotomy at the cost of higher perioperative and neurobehavioral risks in some patients. The guideline therefore frames callosotomy and VNS not as competing "definitive" therapies but as palliative strategies selected according to caregiver priorities, acceptable risk, and system capacity. A key message for implementation is that counseling should be explicit about goals (injury reduction, seizure-type targeting, function, caregiving burden), expected time course of benefit, and uncertainty around optimal callosotomy extent.

Hypothalamic hamartoma: a paradigmatic decision under very low certainty where harm avoidance justifies a strong recommendation

The hypothalamic hamartoma recommendations illustrate an important principle within GRADE-based guideline development: strong recommendations can be justified even when certainty is very low if the balance of consequences is compelling and the alternative carries a credible risk of catastrophic harm. Although direct comparative trials are lacking, the accumulated clinical experience and consistency of observational outcomes support LITT as a less invasive approach with favorable seizure outcomes and a lower risk profile than open resection in many hypothalamic hamartoma presentations. The guideline's "paradigmatic situation" framing is pragmatic and defensible: when the anatomy is suitable and expertise is available, LITT should be the default approach, with open procedures reserved for selected cases where LITT is infeasible or incomplete, and radiosurgery considered in constrained settings when LITT is unavailable. This also highlights the necessity of transparent documentation of feasibility constraints, technical endpoints (extent of disconnection/ablation), and standardized complication reporting in HH care pathways.

Cross-cutting themes: the evidence gap is not only procedural, but structural

Several consistent themes emerge across PICOs. First, the evidence base is dominated by nonrandomized studies, with pervasive confounding from indication and inconsistent outcome definitions. Second, the outcomes that matter most to patients—cognition, psychiatric health, quality of life, social functioning, and long-term mortality including SUDEP—are underreported, heterogeneously measured, and rarely integrated into comparative effectiveness frameworks. Third, system-level barriers continue to suppress

procedure uptake: delayed referral, limited access to Level 4 centers, geographic maldistribution of services, and disparities in evaluation and treatment pathways. The implication is that future progress requires not only better procedures but also better implementation science, equitable referral pathways, and standardized outcome ecosystems that permit reliable cross-center benchmarking.

Directions for the future: a research agenda aligned with decision-making

To meaningfully advance guideline certainty and clinical personalization, the field needs a coordinated strategy that produces high-level, generalizable evidence. Several priorities are immediate:

Comparative effectiveness trials and pragmatic registries

Randomized trials will remain difficult for many surgical questions, but pragmatic trial designs, prospective multicenter cohorts, and registry-based comparative analyses can substantially improve certainty if executed with rigorous confounding control, predefined endpoints, and transparent missing-data handling. For MTLE, direct comparisons of ATL, SAH, and LITT with harmonized inclusion criteria and standardized seizure, cognitive, psychiatric, and quality-of-life outcomes are a high priority. For neocortical epilepsy, studies stratified by lesional status, localization confidence, and eloquent overlap are essential to convert heterogeneous observational signals into clinically actionable estimates.

Standardized, patient-centered outcomes and long-term follow-up

Future studies should routinely include validated measures of memory, language, mood, and health-related quality-of-life, along with structured reporting of employment/schooling, driving, and caregiver burden. Long-term follow-up is not optional: delayed seizure-recurrence and late cognitive or psychiatric effects meaningfully change the net benefit profile. Mortality outcomes, including SUDEP and epilepsy-related deaths, should be systematically captured in cohorts and registries.

Risk stratification and prediction models that are externally validated

Because recommendation strength hinges on cognitive risk, the field needs validated prediction tools that integrate multimodal data (e.g., neuropsychology, imaging, language/memory lateralization, electrophysiology) and are portable across centers. These models should be prospectively validated and should support counseling that quantifies the probability distribution of various clinical outcomes that are important to patients (e.g., language, memory, mood, QoL), not simply categorical “risk” labels.

Procedure-specific technical standards and reporting

For minimally invasive approaches, technical variability is a major unmeasured confounder. Standardized reporting of ablation targets, volumetric endpoints, disconnection completeness, and salvage strategies is necessary to interpret outcomes and compare across techniques. Uniform definitions for “serious adverse events,”

permanent deficits, and transient complications should be adopted to allow robust synthesis in future guideline iterations.

Implementation and equity as core outcomes

Given persistently low utilization despite strong evidence in specific populations, future work must evaluate referral delays, pathway bottlenecks, and disparity drivers. Interventions such as standardized drug-resistant epilepsy referral triggers, tele-epilepsy surgery pathways, and regional hub-and-spoke models should be tested with measurable endpoints (time-to-evaluation, procedure uptake, outcomes) and published in high-impact venues to accelerate adoption.

Summary

Resective epilepsy surgery remains the most effective treatment for eligible patients with focal drug-resistant epilepsy, and ATL retains its role as the reference standard for MTLE. Newer approaches such as SAH and LITT are important components of modern practice, but their evidence base does not yet match their clinical adoption; they should be offered with explicit communication of uncertainty and systematic outcome tracking. Radiosurgery has a limited role in MTLE given delayed and uncertain benefit and potential harms. In neocortical epilepsies and generalized encephalopathies, heterogeneity and palliative goals demand individualized decision-making supported by Level 4 center expertise and shared decision-making. For patients with drop attacks, Lennox-Gastaut Syndrome and epileptic encephalopathy, callostomy is suggested, but vagal nerve stimulation is an alternative, if less risk is desired. Callostomy and VNS can also be used in combination. For hypothalamic harmatoma, LITT is recommended, and radiotherapy only if LITT is not available.

The next leap forward will not come from incremental technical innovation alone, but from high-quality comparative evidence, standardized patient-centered outcomes, validated risk prediction, and implementation strategies that close the access gap.

References

1. Engel J Jr. Evolution of concepts in epilepsy surgery. Epileptic Disord. 2019;21(5):391-409. doi: 10.1684/epd.2019.1091. PMID: 31708489.
2. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA. 2015;313(3):285-293. doi:10.1001/jama.2014.17426.
3. West S, Nevitt SJ, Cotton J, Gandhi S, Weston J, Sudan A, Ramirez R, Newton R. Surgery for epilepsy. Cochrane Database Syst Rev. 2019;6(6):CD010541. doi: 10.1002/14651858.CD010541.pub3.
4. Touma L, Dansereau B, Chan AY, Jetté N, Kwon CS, Braun KPJ, Friedman D, Jehi L, Rolston JD, Vadera S, Wong-Kisiel LC, Englot DJ, Keezer MR. Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission. Epilepsia. 2022;63(6):1314-1329. doi: 10.1111/epi.17243.
5. Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, Gumnit R, Zahn C, Westbrook E, Enos B; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society; American Association of Neurological Surgeons. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology. 2003;60(4):538-47. doi: 10.1212/01.wnl.0000055086.35806.2d.
6. Haneef Z, Stern J, Dewar S, Engel J Jr. Referral pattern for epilepsy surgery after evidence-based recommendations: a retrospective study. Neurology. 2010;75(8):699-704. doi:10.1212/WNL.0b013e3181eee457.
7. Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy - United States, 2015. MMWR Morb Mortal Wkly Rep. 2017;66:821-825.
8. Sultana B, Panzini MA, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, Bauer PR, Kwon CS, Jette N, Josephson CB, Keezer MR. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. Neurology. 2021;96:805-817.
9. Ostendorf AP, Ahrens SM, Lado FA, Arnold ST, Bai S, Bensalem Owen MK, Chapman KE, Clarke DF, Eisner M, Fountain NB, Gray JM, Hopp JL, Riker E, Schuele SU, Small BV, Herman ST. United States epilepsy center characteristics: a data analysis from the National Association of Epilepsy Centers. Neurology. 2022;98:e449-e458.
10. Kapur J, Clarke D, Etienne M, Gutierrez C, Jobst BC, Johnson E, Joshi S, Kiriakopoulos ET, Labiner DM, Lado FA, Lekoubou A, Lowenstein DH, Parko K, Riker E, Shellhaas RA, Sirven JI, Skjei K, Stern JM, Welty TE, Eickmeyer AB, Strickland SL. American Epilepsy Society/International League Against Epilepsy-North America Joint Task Force for Epilepsy Health Care Disparities in the United States. Epilepsy Curr. 2025;15357597251342227.
11. Mazanec MT, Lu E, Sajatovic M, Jobst BC. A systematic literature review of recommendations for referral to specialty care for patients with epilepsy. Epilepsy Behav. 2021;116:107748.

12. Gloss D. American Epilepsy Society clinical practice guideline development manual. American Epilepsy Society; 2020. Available from: https://www.aesnet.org/docs/default-source/pdfs-clinical/aes_guideline_manual.pdf?sfvrsn=9a9ae64b_2
13. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. Jun 28 2016;353:i2016. doi:10.1136/bmj.i2016
14. Roldán-Benítez YM, Bergey G, Jobst BC, Gonzalez-Martinez J, Darzi A. Epilepsy surgery systematic review (in progress).
15. Jobst B, Bergey G, Gonzalez-Martinez J, Bauer D, Bernat J, Busch R, Engel J, Gedela S, Gloss D, Hopp J, Husain A, McKhann G, McGovern R 3rd, Nordli D, O'Neill B, Pouratian N, Price A, Sharan A, Spencer D, Shane R, Darzi A, Sharma S, Roldan Y, Duda T, Eid A, Ghandour D, Hart S, Lannon M, Rehring P, Keller J, Skidmore B, Brackett A. American Epilepsy Society (AES)/Congress of Neurological Surgeons (CNS) epilepsy surgery systematic review and clinical practice guideline. PROSPERO; 2024. Available from: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024494990
16. Lado FA, Ahrens SM, Riker E, Muh CR, Richardson RM, Gray J, Small B, Lewis SZ, Schofield TJ, Clarke DF, Hopp JL, Lee RR, Salpekar JA, Arnold ST; National Association of Epilepsy Guidelines for Specialized Epilepsy Centers Panel. Guidelines for Specialized Epilepsy Centers: executive summary of the report of the National Association of Epilepsy Centers Guideline Panel. Neurology. 2024;102(4):e208087. doi:10.1212/WNL.0000000000208087.
17. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x.
18. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345(5):311-318. doi:10.1056/NEJM200108023450501.
19. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, Sperling MR, Gardiner I, Erba G, Fried I, Jacobs M, Vinters HV, Mintzer S, Kieburtz K; Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307(9):922-930. doi:10.1001/jama.2012.220.
20. Gilliam F, Kuzniecky R, Meador K, Martin R, Sawrie S, Viikinsalo M, Morawetz R, Faught E. Patient-oriented outcome assessment after temporal lobectomy for refractory epilepsy. Neurology. 1999;53(4):687-694. doi:10.1212/WNL.53.4.687.
21. Jones JE, Blocher JB, Jackson DC. Life outcomes of anterior temporal lobectomy: serial long-term follow-up evaluations. Neurosurgery. 2013;73(6):1018-25. doi: 10.1227/NEU.0000000000000145.
22. Kumlien E, Doss RC, Gates JR. Treatment outcome in patients with mesial temporal sclerosis. Seizure. 2002;11(7):413-417. doi:10.1053/seiz.2001.0614.

23. Jayalakshmi S, Vasireddy S, Sireesha J, Vooturi S, Patil A, Sirisha S, Vadapalli R, Chandrasekhar YBVK, Panigrahi M. Long-term seizure freedom, resolution of epilepsy and perceived life changes in drug resistant temporal lobe epilepsy with hippocampal sclerosis: comparison of surgical versus medical management. Neurosurgery. 2023;92(6):1249-1258. doi:10.1227/neu.0000000000002358.
24. Busch RM, Hogue O, Kattan MW, Hamberger M, Drane DL, Hermann B, Kim M, Ferguson L, Bingaman W, Gonzalez-Martinez J, Najm IM, Jehi L. Nomograms to predict naming decline after temporal lobe surgery in adults with epilepsy. Neurology. 2018;91(23):e2144-e2152. doi: 10.1212/WNL.0000000000006629.
25. Al-Aqeel S, Alotaiwi R, Albugami B. Patient preferences for epilepsy treatment: a systematic review of discrete choice experimental studies. Health Econ Rev. 2023 Mar 18;13(1):17. doi: 10.1186/s13561-023-00431-0.
26. Karakas C, Alam MC, Ferreira LD, Nair S, Kovalev D, Haneef Z. Sociodemographic barriers in epilepsy surgery in the United States: A systematic review and meta-analysis. Epilepsy Behav. 2025;167:110391. doi: 10.1016/j.yebeh.2025.110391.
27. Vogt VL, Witt JA, Malter MP, Schoene-Bake JC, von Lehe M, Elger CE, Helmstaedter C. Neuropsychological outcome after epilepsy surgery in patients with bilateral Ammon's horn sclerosis. J Neurosurg. 2014;121(5):1247-1256. doi:10.3171/2014.7.JNS132037.
28. Drane DL, Willie JT, Pedersen NP, Qiu D, Voets NL, Millis SR, Soares BP, Saindane AM, Hu R, Kim MS, Hewitt KC, Hakimian S, Grabowski T, Ojemann JG, Loring DW, Meador KJ, Faught E, Miller JW, Gross RE. Superior verbal memory outcome after stereotactic laser amygdalohippocampotomy. Front Neurol. 2021;12:779495. doi:10.3389/fneur.2021.779495.
29. Youngerman BE, Banu MA, Khan F, McKhann GM, Schevon CA, Jagid JR, Cajigas I, Theodotou CB, Ko A, Buckley R, Ojemann JG, Miller JW, Laxton AW, Couture DE, Popli GS, Buch VP, Halpern CH, Le S, Sharan AD, Sperling MR, Mehta AD, Englot DJ, Neimat JS, Konrad PE, Sheth SA, Neal EG, Vale FL, Holloway KL, De H'aese PF, Wu C. Long-term outcomes of mesial temporal laser interstitial thermal therapy for drug-resistant epilepsy and subsequent surgery for seizure recurrence: a multi-centre cohort study. J Neurol Neurosurg Psychiatry. 2023;94(11):879-886. doi:10.1136/jnnp-2022-330979.
30. Esmaeili B, Hakimian S, Ko AL, Hauptman JS, Ojemann JG, Miller JW, Tobochnik S. Epilepsy-related mortality after laser interstitial thermal therapy in patients with drug-resistant epilepsy. Neurology. 2023;101(13):e1359-e1363. doi:10.1212/WNL.0000000000207405.
31. Mo J, Guo Z, Wang X, Zhang J, Hu W, Shao X, Sang L, Zheng Z, Zhang C, Zhang K. Magnetic resonance-guided laser interstitial thermal therapy vs. open surgery for drug-resistant mesial temporal lobe epilepsy: a propensity score matched retrospective cohort study. Int J Surg. 2024;110(1):306-314. doi:10.1097/JS9.0000000000000811.
32. Alomar SA, Moshref RH, Moshref LH, Sabbagh AJ. Outcomes after laser interstitial thermal ablation for temporal lobe epilepsy: a systematic review and meta-analysis. Neurosurg Rev. 2023;46(1):261. doi: 10.1007/s10143-023-02164-4.
33. Kohlhase K, Zöllner JP, Tandon N, Strzelczyk A, Rosenow F. Comparison of minimally invasive and traditional surgical approaches for refractory mesial temporal lobe

epilepsy: A systematic review and meta-analysis of outcomes. Epilepsia. 2021;62(4):831-845. doi: 10.1111/epi.16846.
34. Ekman FR, Bjellvi J, Ljunggren S, Malmgren K, Nilsson D. Laser Interstitial Thermal Therapy versus Open Surgery for Mesial Temporal Lobe Epilepsy: A Systematic Review and Meta-Analysis. World Neurosurg. 2024;192:224-235.e15. doi: 10.1016/j.wneu.2024.09.090.
35. Stavrogianni K, Poprelka K, Fasilis T, Giannopapas V, Hahn W, Gorny I, Kalyvas A, Stavrinou L, Giannopoulos S, Boviatsis E, Tsivgoulis G, Bonakis A, Knake S, Tsalouchidou PE. Neuropsychological outcomes comparing traditional surgical approaches and laser interstitial thermal therapy for refractory mesial temporal lobe epilepsy: A systematic review and meta-analysis. Epilepsia. 2026;67(2):588-605. doi: 10.1111/epi.18687.
36. Barbaro NM, Quigg M, Ward MM, Chang EF, Broshek DK, Langfitt JT, Yan G, Laxer KD, Cole AJ, Sneed PK, Hess CP, Yu W, Tripathi M, Heck CN, Miller JW, Garcia PA, McEvoy A, Fountain NB, Salanova V, Knowlton RC, Bagić A, Henry T, Kapoor S, McKhann G, Palade AE, Reuber M, Tecoma E. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: the randomized, controlled ROSE trial. Epilepsia. 2018;59(6):1198-1207. doi:10.1111/epi.14045.
37. Quigg M, Barbaro NM, Ward MM, Chang EF, Broshek DK, Langfitt JT, Yan G, Laxer KD, Cole AJ, Sneed PK, Hess CP, Yu W, Newman SA, Mueller S, Tripathi M, Heck CN, Miller JW, Garcia PA, McEvoy A, Fountain NB, Salanova V, Knowlton RC, Bagić A, Henry T, Kapoor S, McKhann G, Palade AE, Reuber M, Tecoma E. Visual field defects after radiosurgery versus temporal lobectomy for mesial temporal lobe epilepsy: Findings of the ROSE trial. Seizure. 2018;63:62-67. doi: 10.1016/j.seizure.2018.10.017.
38. Xue H, Cai L, Dong S, Li Y. Clinical characteristics and post-surgical outcomes of focal cortical dysplasia subtypes. J Clin Neurosci. 2016;23:68-72. doi:10.1016/j.jocn.2015.04.022.
39. Bulacio JC, Bena J, Suwanpakdee P, Nair D, Gupta A, Alexopoulos A, Bingaman W, Najm I. Determinants of seizure outcome after resective surgery following stereoelectroencephalography. J Neurosurg. 2021;136(6):1638-1646. doi:10.3171/2021.6.JNS204413.
40. Sun Y, Wang X, Che N, Qin H, Liu S, Wu X, Wei M, Cheng H, Yin J. Clinical characteristics and epilepsy outcomes following surgery caused by focal cortical dysplasia (type IIa) in 110 adult epileptic patients. Exp Ther Med. 2017;13(5):2225-2234. doi:10.3892/etm.2017.4315.
41. Jayalakshmi S, Nanda SK, Vooturi S, Vadapalli R, Sudhakar P, Madigubba S, Panigrahi M. Focal cortical dysplasia and refractory epilepsy: role of multimodality imaging and outcome of surgery. AJNR Am J Neuroradiol. 2019;40(5):892-898. doi:10.3174/ajnr.A6041.
42. Yardi R, Morita-Sherman ME, Fitzgerald Z, Punia V, Bena J, Morrison S, Najm I, Bingaman W, Jehi L. Long-term outcomes of reoperations in epilepsy surgery. Epilepsia. 2020;61(3):465-478. doi:10.1111/epi.16452.
43. Bourgeois M, Sainte-Rose C, Lellouch-Tubiana A, Malucci C, Brunelle F, Maixner W, Cinalli G, Pierre-Kahn A, Renier D, Zerah M, Hirsch JF, Goutières F, Aicardi J. Surgery of

epilepsy associated with focal lesions in childhood. J Neurosurg. 1999;90(5):833-842. doi:10.3171/jns.1999.90.5.0833.
44. Ramírez-Molina JL, Di Giacomo R, Mariani V, Deleo F, Cardinale F, Uscátegui-Daccarett AM, Lorenzana P, Tassi L. Surgical outcomes in two different age groups with focal cortical dysplasia type II: any real difference? Epilepsy Behav. 2017;70(Pt A):45-49. doi:10.1016/j.yebeh.2017.02.031.
45. Lazow SP, Thadani VM, Gilbert KL, Morse RP, Bujarski KA, Kulandaivel K, Roth RM, Scott RC, Roberts DW, Jobst BC. Outcome of frontal lobe epilepsy surgery. Epilepsia. 2012;53(10):1746-1755. doi:10.1111/j.1528-1167.2012.03582.x.
46. Kagawa K, Hashizume A, Katagiri M, Seyama G, Okamura A, Kawano R, Iida K. Comparison of seizure outcomes and ADL recovery period after total or anterior corpus callosotomy in adolescent and young adults with drop attacks and severe mental retardation. Epilepsy Res. 2021;176:106706. doi:10.1016/j.eplepsyres.2021.106706.
47. Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia. 2001;42(1):67-71. doi:10.1046/j.1528-1157.2001.081422.x.
48. Mamelak AN, Barbaro NM, Walker JA, Laxer KD. Corpus callosotomy: a quantitative study of the extent of resection, seizure control, and neuropsychological outcome. J Neurosurg. 1993;79(5):688-695. doi:10.3171/jns.1993.79.5.0688.
49. Marino R Jr, Radvany J, Huck FR, De Camargo CH, Gronich G. Selective electroencephalograph-guided microsurgical callosotomy for refractory generalized epilepsy. Surg Neurol. 1990;34(4):219-228. doi:10.1016/0090-3019(90)90132-9.
50. Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L, Saute R, Salles C, Hoefel JR, Soder RB, da Costa JC, Hemb M, Theys T, Palmini A. Selective posterior callosotomy for drop attacks: a new approach sparing prefrontal connectivity. Neurology. 2016;87(19):1968-1974. doi:10.1212/WNL.0000000000003307.
51. Passamonti C, Zamponi N, Foschi N, Trignani R, Luzi M, Cesaroni E, Provinciali L, Scerrati M. Long-term seizure and behavioral outcomes after corpus callosotomy. Epilepsy Behav. 2014;41:23-29. doi:10.1016/j.yebeh.2014.08.130.
52. Rougier A, Claverie B, Marchal C, Pedespan JM, Loiseau P. Social outcome of 20 anterior callosotomies for drug-resistant epilepsy. Neurochirurgie. 1995;41(6):413-418.
53. Sakas DE, Phillips J. Anterior callosotomy in the management of intractable epileptic seizures: significance of the extent of resection. Acta Neurochir (Wien). 1996;138(6):700-707. doi:10.1007/BF01411475.
54. Carmant L, Holmes GL, Lombroso CT. Outcome following corpus callosotomy. J Epilepsy. 1998;11(4):224-228. doi:10.1016/S0896-6974(98)00022-X.
55. Cendes F, Ragazzo PC, da Costa V, Martins LF. Corpus callosotomy in treatment of medically resistant epilepsy: preliminary results in a pediatric population. Epilepsia. 1993;34(5):910-917. doi:10.1111/j.1528-1157.1993.tb02111.x.
56. Chandra SP, Kurwale NS, Chibber SS, Banerji J, Dwivedi R, Garg A, Bal C, Tripathi M, Sarkar C, Tripathi M. Endoscopic-assisted (through a mini craniotomy) corpus callosotomy combined with anterior, hippocampal, and posterior commissurotomy in Lennox-Gastaut syndrome: a pilot study to establish its safety and efficacy. Neurosurgery. 2016;78(5):743-751. doi:10.1227/NEU.0000000000001060.

57. Cukiert A, Cukiert CM, Burattini JA, Lima AM, Forster CR, Baise C, Argentoni-Baldochi M. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. Seizure. 2013;22(5):396-400. doi:10.1016/j.seizure.2013.02.009.
58. Iwasaki M, Uematsu M, Nakayama T, Hino-Fukuyo N, Sato Y, Kobayashi T, Haginoya K, Osawa S, Jin K, Nakasato N, Tominaga T. Parental satisfaction and seizure outcome after corpus callosotomy in patients with infantile or early childhood onset epilepsy. Seizure. 2013;22(4):303-305. doi:10.1016/j.seizure.2013.01.005.
59. Kim HJ, Kim HD, Lee JS, Heo K, Kim DS, Kang HC. Long-term prognosis of patients with Lennox--Gastaut syndrome in recent decades. Epilepsy Res. 2015;110:10-19. doi:10.1016/j.eplepsyres.2014.11.004.
60. Liang S, Li A, Jiang H, Meng X, Zhao M, Zhang J, Sun Y. Anterior corpus callosotomy in patients with intractable generalized epilepsy and mental retardation. Stereotact Funct Neurosurg. 2010;88(4):246-252. doi:10.1159/000315462.
61. Liang S, Zhang S, Hu X, Zhang Z, Fu X, Jiang H, Xiaoman Y. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. Eur J Paediatr Neurol. 2014;18(6):670-676. doi:10.1016/j.ejpn.2014.05.004.
62. Na JH, Kim HD, Lee YM. Effective application of corpus callosotomy in pediatric intractable epilepsy patients with mitochondrial dysfunction. Ther Adv Neurol Disord. 2022;15:17562864221092551. doi:10.1177/17562864221092551.
63. Otsuki T, Kim HD, Luan G, Inoue Y, Baba H, Oguni H, Hong SC, Kameyama S, Kobayashi K, Hirose S, Yamamoto H, Hamano S, Sugai K; FACE Study Group. Surgical versus medical treatment for children with epileptic encephalopathy in infancy and early childhood: results of an international multicenter cohort study in Far-East Asia (the FACE study). Brain Dev. 2016;38(5):449-460. doi:10.1016/j.braindev.2015.11.004.
64. Rathore C, Abraham M, Rao RM, George A, Sankara Sarma P, Radhakrishnan K. Outcome after corpus callosotomy in children with injurious drop attacks and severe mental retardation. Brain Dev. 2007;29(9):577-585. doi:10.1016/j.braindev.2007.03.008.
65. Shim KW, Lee YM, Kim HD, Lee JS, Choi JU, Kim DS. Changing the paradigm of 1-stage total callosotomy for the treatment of pediatric generalized epilepsy. J Neurosurg Pediatr. 2008;2(1):29-36. doi:10.3171/PED/2008/2/7/029.
66. Turanli G, Yalnizoğlu D, Genç-Açikgöz D, Akalan N, Topçu M. Outcome and long term follow-up after corpus callosotomy in childhood onset intractable epilepsy. Childs Nerv Syst. 2006;22(10):1322-1327. doi:10.1007/s00381-006-0045-3.
67. Ukishiro K, Osawa SI, Iwasaki M, Kakisaka Y, Jin K, Uematsu M, Yamamoto T, Tominaga T, Nakasato N. Age-related recovery of daily living activity after 1-stage complete corpus callosotomy: a retrospective analysis of 41 cases. Neurosurgery. 2022;90(5):547-551. doi:10.1227/neu.0000000000001871.
68. Yang PF, Lin Q, Mei Z, Chen ZQ, Zhang HJ, Pei JS, Tian J, Jia YZ, Zhong ZH. Outcome after anterior callosal section that spares the splenium in pediatric patients with drop attacks. Epilepsy Behav. 2014;36:47-52. doi:10.1016/j.yebeh.2014.04.019.
69. You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, Lee JK, Kim DS, Park SK. Comparison of corpus callosotomy and vagus nerve stimulation in children with

Lennox-Gastaut syndrome. Brain Dev. 2008;30(3):195-199. doi:10.1016/j.braindev.2007.07.013.
70. Yao Y, Wang X, Hu W, Zhang C, Sang L, Zheng Z, Mo J, Liu C, Qiu J, Shao X, Zhang J, Zhang K. Magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: surgical approach and treatment outcomes. J Clin Med. 2022;11(21):6579. doi:10.3390/jcm11216579.
71. Gadgil N, Lam S, Pan IW, LoPresti M, Wagner K, Ali I, Wilfong A, Curry DJ. Staged magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: analysis of ablation volumes and morphological considerations. Neurosurgery. 2020;86(6):808-816. doi:10.1093/neuros/nyz378.
72. Boerwinkle VL, Foldes ST, Torrisi SJ, Temkit H, Gaillard WD, Kerrigan JF, Desai VR, Raskin JS, Vedantam A, Jarrar R, Williams K, Lam S, Ranjan M, Broderson JS, Adelson D, Wilfong AA, Curry DJ. Subcentimeter epilepsy surgery targets by resting state functional magnetic resonance imaging can improve outcomes in hypothalamic hamartoma. Epilepsia. 2018;59(12):2284-2295. doi:10.1111/epi.14583.
73. Xu DS, Chen T, Hlubek RJ, Bristol RE, Smith KA, Ponce FA, Kerrigan JF, Nakaji P. Magnetic resonance imaging-guided laser interstitial thermal therapy for the treatment of hypothalamic hamartomas: a retrospective review. Neurosurgery. 2018;83(6):1183-1192. doi:10.1093/neuros/nyx604.
74. Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. Epilepsy Res. 2018;142:131-134. doi:10.1016/j.eplepsyres.2018.03.013.
75. Shim KW, Chang JH, Park YG, Kim HD, Choi JU, Kim DS. Treatment modality for intractable epilepsy in hypothalamic hamartomatous lesions. Neurosurgery. 2008;62(4):847-856. doi:10.1227/01.neu.0000318170.82719.7c.
76. Drees C, Chapman K, Prenger E, Baxter L, Maganti R, Rekate H, Shetter A, Bobrowitz M, Kerrigan JF. Seizure outcome and complications following hypothalamic hamartoma treatment in adults: endoscopic, open, and Gamma Knife procedures. J Neurosurg. 2012;117(2):255-261. doi:10.3171/2012.5.JNS112256.
77. Wagner K, Buschmann F, Zentner J, Trippel M, Schulze-Bonhage A. Memory outcome one year after stereotactic interstitial radiosurgery in patients with epilepsy due to hypothalamic hamartomas. Epilepsy Behav. 2014;37:204-209. doi:10.1016/j.yebeh.2014.06.031.
78. Schulze-Bonhage A, Ostertag C. Treatment options for gelastic epilepsy due to hypothalamic hamartoma: interstitial radiosurgery. Semin Pediatr Neurol. 2007;14(2):80-87. doi:10.1016/j.spen.2007.03.006.
79. Romanelli P, Tuniz F, Fabbro S, Beltramo G, Conti A. Image-guided LINAC radiosurgery in hypothalamic hamartomas. Front Neurol. 2022;13:909829. doi:10.3389/fneur.2022.909829.
80. Savateev AN, Golanov AV, Saushev DA, Osinov IK, Kostyuchenko VV, Dalechina AV, Melikian AG, Vlasov PA, Mazerkina NA, Makashova ES. Stereotaksicheskaya radiokhirurgiya pri epilepsii u patsientov s gamartomoi gipotalamusa [Stereotactic radiosurgery for epilepsy related to hypothalamic hamartoma]. Zh Vopr Neirokhir Im N N Burdenko. 2022;86(4):14-24. Russian. doi:10.17116/neiro20228604114.

81. Régis J, Lagmari M, Carron R, Hayashi M, McGonigal A, Daquin G, Villeneuve N, Laguitton V, Bartolomei F, Chauvel P. Safety and efficacy of Gamma Knife radiosurgery in hypothalamic hamartomas with severe epilepsies: a prospective trial in 48 patients and review of the literature. Epilepsia. 2017;58 Suppl 2:60-71. doi:10.1111/epi.13754.
82. Schulze-Bonhage A, Trippel M, Wagner K, Bast T, Deimling FV, Ebner A, Elger C, Mayer T, Keimer R, Steinhoff BJ, Spreer J, Fauser S, Ostertag C. Outcome and predictors of interstitial radiosurgery in the treatment of gelastic epilepsy. Neurology. 2008;71(4):277-282. doi:10.1212/01.wnl.0000318279.92233.82.
83. Tripathi M, Sheehan JP, Niranjan A, Ren L, Pikis S, Lunsford LD, Peker S, Samanci Y, Langlois AM, Mathieu D, Lee CC, Yang HC, Deng H, Rai A, Kumar N, Sahu JK, Sankhyan N, Deora H. Gamma knife radiosurgery for hypothalamic hamartoma: a multi-institutional retrospective study on safety, efficacy, and complication profile. Neurosurgery. 2025;96(2):426-437. doi:10.1227/neu.0000000000003110.
84. Régis J, Scavarda D, Tamura M, Nagayi M, Villeneuve N, Bartolomei F, Brue T, Dafonseca D, Chauvel P. Epilepsy related to hypothalamic hamartomas: surgical management with special reference to gamma knife surgery. Childs Nerv Syst. 2006;22(8):881-895. doi:10.1007/s00381-006-0139-y.

Appendix A. PICO questions

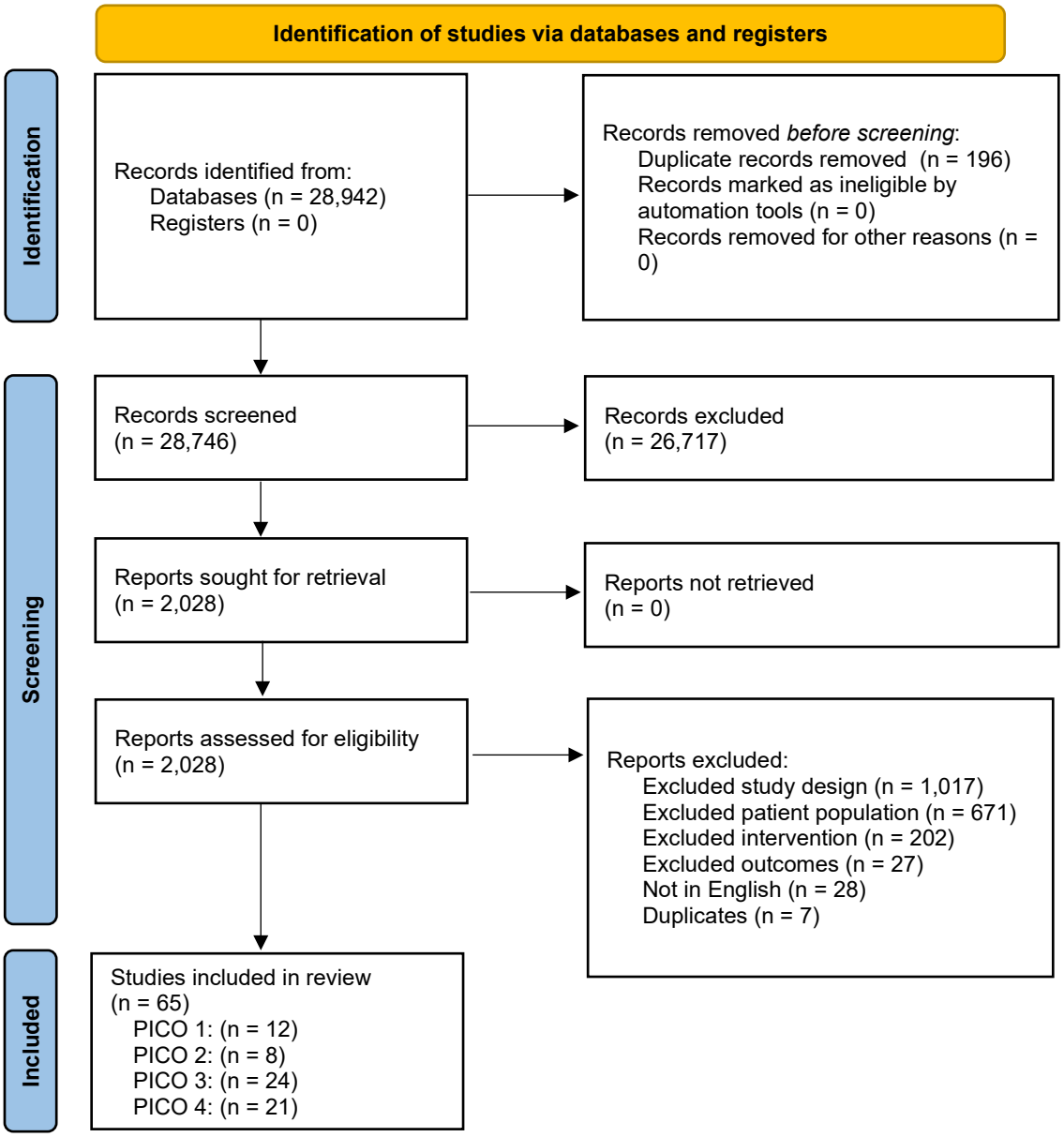
The systematic review for this clinical practice guideline addresses the following questions, all of which are Therapy/Therapeutic/Treatment questions:

1. How do resective or ablative surgical procedures, including standard anterior temporal lobectomy, selective amygdalo-hippocampectomy, laser therapy/laser interstitial thermal therapy (LITT) or radiosurgery, compare to medical therapy for treatment of patients with drug-resistant mesiotemporal epilepsy, including hippocampal sclerosis, in terms of seizure outcome; neuropsychological, neuropsychiatric, social, quality-of-life outcomes; and serious adverse events?
   P: Patients with drug-resistant mesial temporal lobe epilepsy (including hippocampal sclerosis)
   [Excludes infants <2 years and children <10 years of age; Subgroups of interest: Age: adults; pediatric ages 10 through <12 years; and pediatric ages 12 years through adult]
   I: [Comparing each surgical option, independently, against medical therapy]
      a. Standard temporal lobectomy
      b. Selective amygdalo-hippocampectomy
      c. Laser therapy/laser interstitial thermal therapy (LITT)
      d. Radiosurgery
   C: Medical therapy (excludes dietary therapy/ketogenic diet; excludes neurostimulation/neuromodulation)
   O: Seizure outcome; all-cause mortality (including SUDEP); neuropsychological, neuropsychiatric, social, quality of life outcomes; and serious adverse events
2. How does resective or ablative epilepsy surgery compare to medical therapy for treatment of patients with drug-resistant neocortical epilepsy, in terms of seizure outcome; neuropsychological, neuropsychiatric, social, and quality-of-life outcomes; and serious adverse events?
   P: Patients with drug-resistant neocortical epilepsy (Subgroups – adult, pediatric, infants <2 years of age)
   I: Resective or ablative epilepsy surgery
   C: Medical therapy (excludes dietary therapy/ketogenic diet; excludes neurostimulation/neuromodulation)
   O: Seizure outcome; all-cause mortality (including SUDEP); neuropsychological, neuropsychiatric, social, quality of life outcomes; and serious adverse events
3. How does callosotomy (complete or partial) compare to vagus nerve stimulation (VNS) for treatment of patients with drug-resistant drop attack or Lennox-Gastaut syndrome (LGS) (adult, pediatric, and infants <2 years of age as subgroups), in terms of seizure outcome; neuropsychological, neuropsychiatric, social, and quality-of-life outcomes; and serious adverse events?
   P: Patients with drug-resistant drop attack or Lennox-Gastaut syndrome (LGS), inclusive of all related conditions/syndromes/recently evolving nomenclature (Population subgroups: a) Ages – adult, pediatric, infants <2 years;
   b) Seizure types – drop attack/drop seizures, and atonic seizures; and

c) Patients with epileptic encephalopathy (EE)/developmental epileptic encephalopathy (DEE), and West syndrome/Infantile spasms, and Ohtahara syndrome, with LGS)
I: Callosotomy, complete or partial
C: Vagus nerve stimulation (VNS)
O: Seizure outcome; all-cause mortality (including SUDEP); neuropsychological, neuropsychiatric, social, quality-of-life outcomes; and serious adverse events

4. How does laser therapy/laser interstitial thermal therapy (LITT) or radiosurgery compare to surgical resection for treatment of patients with hypothalamic hamartomas (HH), in terms of seizure outcome; neuropsychological, neuropsychiatric, social, and quality-of-life outcomes; and serious adverse events?
P: Patients with hypothalamic hamartomas (HH) (Subgroups: adult, pediatric, infants <2 years)
I: a) Laser therapy/laser interstitial thermal therapy (LITT) or b) Radiosurgery
C: Surgical resection
O: Seizure outcome; all-cause mortality (including SUDEP); neuropsychological, neuropsychiatric, social, quality of life outcomes; and serious adverse events

Figure 1. PRISMA flow diagram.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table I: Summary of Recommendation Mesial Temporal Lobe Epilepsy	
A. Summary of Recommendations Related to Anterior Temporal Lobectomy vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
I-A-1. **Anterior temporal lobectomy vs. medical therapy in patients at low risk of cognitive decline**	**I-A-1:** The AES/CNS guideline panel recommends the use of anterior temporal lobectomy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy who are at low risk of cognitive decline. (**Strong** Recommendation, **Moderate** Certainty of Evidence)
I-A-2. **Anterior temporal lobectomy vs. medical therapy in all other patients**	**I-A-2: T**he AES/CNS panel suggests the use of anterior temporal lobectomy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy at greater than low risk for cognitive decline. (**Conditional** Recommendation, **Very Low** Certainty of Evidence) *Remarks for Recommendations I-A-1 and I-A-2:* – Risk assessment for cognitive decline can be done using known and validated approaches, including but not limited to neuropsychological testing, fMRI, intra-carotid testing with anesthetics and multivariable prediction models. – The evaluation of risk-benefit ratio should consider the extent and type of resection. – A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.

B. Summary of Recommendations Related to Selective Amygdalo-Hippocampectomy Vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
I-B. Selective amygdalo-hippocampectomy vs. medical therapy in patients with drug-resistant mesial temporal lobe epilepsy	The AES/CNS guideline panel suggests the use of selective amygdalo-hippocampectomy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy. *Remarks:* - *A prerequisite for this recommendation is that the facility is equipped to offer selective amygdalo-hippocampectomy and that healthcare professionals have the proper training to perform the procedure.* - *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* (**Conditional** recommendation, **Very Low** certainty of evidence)

C. Summary of Recommendations Related to Laser Interstitial Thermal Therapy (LITT) vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
I-C. Laser Interstitial Thermal Therapy (LITT) vs. medical therapy in patients with drug-resistant mesial temporal lobe epilepsy	The AES/CNS guideline panel suggests for the use of laser interstitial thermal therapy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy. *Remarks:* - *A prerequisite for this recommendation is that the facility is equipped to offer LITT and that healthcare professionals have the proper training to perform the procedure.* - *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* (**Conditional** recommendation, **Very Low** certainty of evidence)

D. Summary of Recommendations Related to Radiosurgery vs. Medical Therapy in Patients with Drug-Resistant Mesial Temporal Lobe Epilepsy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
I-D. Radiosurgery vs. medical therapy in patients with drug-resistant mesial temporal lobe epilepsy	The AES/CNS guideline panel suggests against the use of radiosurgery compared to medical therapy with drug-resistant mesial temporal lobe epilepsy. *Remarks:* - *Healthcare professionals should consider the other assessed surgical approaches in this guideline, including anterior temporal lobectomy, selective amygdalo-hippocampectomy, and laser interstitial thermal therapy (LITT) when making this decision with their patients (refer to related recommendations).* - *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* (**Conditional** recommendation, **Very Low** certainty of evidence)

Table II: Summary of Recommendation Drug-Resistant Neocortical Epilepsy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
II. Resective or ablative surgery vs. medical therapy in drug-resistant neocortical epilepsy	The AES/CNS guideline panel suggests the use of resective or ablative surgery compared to medical therapy in people aged 2 years and older with drug-resistant neocortical epilepsy. Remarks: – A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences (e.g., physicians should account and discuss with patients the outcome differences between lesional versus non lesional epilepsy). – The consideration of functional proximity or overlap of epileptogenic zone to the functional cortex should be considered in decision making. (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Table III: Summary of Recommendations Drug-Resistant Drop-Attack, Lennox-Gastaut Syndrome, or Epileptic Encephalopathy	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
III-A. Callosotomy vs. VNS in adult patients with drug-resistant drop-attack, Lennox-Gastaut, or epileptic encephalopathy	The AES/CNS guideline panel suggests the use of Callosotomy compared to VNS in adults with drug-resistant drop-attack, Lennox-Gastaut Syndrome, or epileptic encephalopathy. *Remarks:* – *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* – *VNS is also an acceptable option. It is slightly less effective but often a safer alternative. Patients may place higher value on safety than effectiveness.* – *There is not sufficient evidence what type of callosotomy (anterior, posterior or complete callosotomy) should be performed.* (**Conditional** Recommendation, **Very Low** Certainty of Evidence)
III-B. Callosotomy vs. VNS in pediatric patients with drug-resistant drop-attack, Lennox-Gastaut, or epileptic encephalopathy	The AES/CNS guideline panel suggests the use of Callosotomy compared to VNS in children with drug-resistant drop-attack, Lennox-Gastaut Syndrome, or epileptic encephalopathy. *Remarks:* – *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* – *VNS is also an acceptable option. It is slightly less effective in terms of seizure outcomes but often a safer alternative. Patients and caregivers may place higher value on safety than effectiveness.* – *There is not sufficient evidence what type of callosotomy (anterior, posterior or complete callosotomy) should be performed.* (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Table IV: Summary of Recommendations Hypothalamic Hamartomas	
Treatment Intervention and Comparator	**Recommendation (please see Summary of Evidence for detailed evidence review of each intervention)**
IV-A. Laser interstitial thermal therapy (LITT) vs. surgical resection in hypothalamic hamartomas	The AES/CNS guideline panel recommends for the use of LITT compared to surgical resection in people with hypothalamic hamartoma (paradigmatic situation due to potential for catastrophic harm) *Remarks:* – *Access needs to be at a level 4 epilepsy center that has access to LITT* – *In some rare cases, LITT may not be feasible based on the anatomy* (**Strong** Recommendation, **Very Low** Certainty of Evidence)
IV-B. Radiosurgery vs. surgical resection in hypothalamic hamartomas	The AES/CNS guideline panel suggests either the use of radiosurgery or surgical resection in people with hypothalamic hamartoma. *Remarks:* – *If LITT is not available, then we suggest radiosurgery. Decision-making between patient and clinician is important.* – *A conditional recommendation highlights the need to account for individual patient circumstances and mandates shared decision-making to ensure that clinical decisions align with each patient's values and preferences.* (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

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Supplemental Materials 2: Evidence Profiles for each Recommendation

Evidence Profile, PICO I-A: Anterior temporal lobectomy compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy

Recommendation I-A-1: The AES/CNS guideline panel recommend the use of anterior temporal lobectomy compared to medical therapy in people aged 12 or older with drug-resistant mesial temporal lobe epilepsy that are at low risk of cognitive decline **(STRONG recommendation based on MODERATE certainty evidence)**.

Recommendation I-A-2: In all other people aged 12 or older with drug-resistant mesial temporal lobe epilepsy, the panel suggests the use of anterior temporal lobectomy **(CONDITIONAL recommendation, very low certainty evidence)**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (free of all seizures, including auras) (follow-up: mean 1 years; assessed with: proportion of participants achieving seizure freedom, independent outcome adjudication of seizures recorded in participant diaries)												
1[1]	randomised trials	serious[a]	not serious	not serious	not serious[2,b]	none	15/40 (37.5%)	1/40 (2.5%)	**RR 15.00** (2.08 to 108.23)	**350 more per 1,000** (from 27 more to 1,000 more)	⨁⨁⨁◯ Moderate[2,a,b]	CRITICAL
Seizure Freedom (free of disabling seizures) (follow-up: mean 1 years; assessed with: proportion of participants achieving seizure freedom, independent outcome adjudication of seizures recorded in participant diaries)												
1[1]	randomised trials	serious[a]	not serious	not serious	not serious[2,b]	none	23/40 (57.5%)	3/40 (7.5%)	**RR 7.67** (2.50 to 23.51)	**500 more per 1,000** (from 112 more to 1,000 more)	⨁⨁⨁◯ Moderate[2,a,b]	CRITICAL
Seizure Freedom (seizure free) (follow-up: mean 1 years; assessed with: proportion of participants achieving seizure freedom, patient report)												
1[3]	non-randomised studies	very serious[c]	not serious	not serious	not serious[2]	none	399/568 (70.2%)	64/466 (13.7%)	**RR 5.10** (2.67 to 9.75)	**563 more per 1,000** (from 229 more to 1,000 more)	⨁⨁◯◯ Low[2,c]	CRITICAL
Seizure Freedom (free of disabling seizures) (follow-up: mean 2 years; assessed with: rate of ocurrence of seizure freedom, independent outcome adjudication of seizures recorded in participant diaries)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
1[4]	randomised trials	serious[d]	not serious	not serious	not serious[2,b]	none	11/15 (73.3%)	0.05/23 (0.2%) [e]	**RR 34.50** (2.18 to 545.02)	**73 more per 1,000** (from 3 more to 1,000 more)	⨁⨁⨁◯ Moderate[2,b,d]	CRITICAL
								2.5%[f]		**838 more per 1,000** (from 30 more to 1,000 more)		
								7.5%[g]		**1,000 more per 1,000** (from 89 more to 1,000 more)		
Seizure Freedom (seizure free) (follow-up: range 2 years to 5 years; assessed with: proportion of participants achieving seizure freedom, patient report)												
3[5,6,7]	non-randomised studies	very serious[h]	not serious	not serious	not serious[2]	none	318/443 (71.8%)	64/395 (16.2%)	**RR 4.58** (3.61 to 5.80)	**580 more per 1,000** (from 423 more to 778 more)	⨁⨁◯◯ Low[2,h]	CRITICAL
Seizure Freedom (seizure free) (follow-up: range 10 years to 17 years; assessed with: proportion of participants achieving seizure freedom, patient report)												
2[6,7]	non-randomised studies	very serious[i]	not serious	not serious	not serious[2]	none	187/245 (76.3%)	32/179 (17.9%)	**RR 4.36** (3.16 to 6.02)	**601 more per 1,000** (from 386 more to 897 more)	⨁⨁◯◯ Low[2,i]	CRITICAL
Permanent, Unexpected Neurological Deficits (decline in verbal memory that interfered with the patients' occupation) (follow-up: mean 1 years; assessed with: proportion of participants with unexpected neurological deficits, from medical records)												
1[1]	randomised trials	serious[a]	not serious	not serious	serious[2,j]	none	2/40 (5.0%)	0.5/40 (1.3%)	**RR 4.00** (0.19 to 85.99)	**38 more per 1,000** (from 10 fewer to 1,000 more)	⨁⨁◯◯ Low[2,a,j]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
Permanent, Unexpected Neurological Deficits (memory disturbances) (follow-up: mean 13 years; assessed with: proportion of participants experiencing unexpected neurological deficits, from medical records)												
1[6]	non-randomised studies	extremely serious[k]	not serious	not serious	serious[2,j]	none	In one study with 671 participants, 51.50% underwent standard/anterior temporal lobectomy. Memory disturbances in 2 participants. There is no information regarding neurological deficits for the participants in the medical therapy group.				⨁◯◯◯ Very low[2,j,k]	CRITICAL
All-cause Mortality (follow-up: mean 1 years; assessed with: proportion of participants who died of any cause, medical records)												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[2,l]	none	0/40 (0.0%)	1/40 (2.5%)	**RR 0.33** (0.01 to 7.95)	**17 fewer per 1,000** (from 25 fewer to 174 more)	⨁◯◯◯ Very low[2,a,l]	CRITICAL
All-cause Mortality (follow-up: mean 1 years; assessed with: proportion of participants who died of any cause, medical records)												
1[3]	non-randomised studies	extremely serious[m]	not serious	not serious	very serious[2,l]	none	1/125 (0.8%)	0.5/71 (0.7%)	**RR 1.71** (0.07 to 41.54)	**5 more per 1,000** (from 7 fewer to 285 more)	⨁◯◯◯ Very low[2,l,m]	CRITICAL
All-cause Mortality (follow-up: mean 13 years; assessed with: proportion of participants who died of any cause, medial records)												
1[6]	non-randomised studies	extremely serious[k]	not serious	not serious	very serious[2,l]	none	7/364 (1.9%)	9/439 (2.1%)	**RR 0.94** (0.35 to 2.49)	**1 fewer per 1,000** (from 13 fewer to 31 more)	⨁◯◯◯ Very low[2,k,l]	IMPORTANT
Medical or Surgical Complications (serious adverse events) (follow-up: mean 2 years; assessed with: proportion of participants experiencing a medical or surgical complication, medical records)												
1[4]	randomised trials	very serious[n]	not serious	not serious	very serious[2,l]	none	6/15 (40.0%)	7/23 (30.4%)	**RR 1.31** (0.55 to 3.15)	**94 more per 1,000** (from 137 fewer to 654 more)	⨁◯◯◯ Very low[2,l,n]	CRITICAL
Medical or Surgical Complications (serious adverse events) (follow-up: mean 13 years; assessed with: proportion of participants experiencing medical or surgical complications, medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
1[6]	non-randomised studies	extremely serious[k]	not serious	not serious	serious[2,j]	none	In one study with 671 participants, 51.50% underwent standard/anterior temporal lobectomy. Serious adverse events were reported in 15 participants. There is no information regarding medical complications (serious adverse events) for the participants in the medical therapy group.				⨁◯◯◯ Very low[2,j,k]	CRITICAL
Medical or Surgical Complications (brain infection) (follow-up: mean 13 years; assessed with: proportion of participants experiencing medical or surgical complications, medical records)												
1[6]	non-randomised studies	extremely serious[k]	not serious	not serious	serious[2,j]	none	In one study with 671 participants, 51.50% underwent standard/anterior temporal lobectomy. Meningitis was reported in 1 participant. There is no information regarding medical complications (brain infection) for the participants in the medical therapy group.				⨁◯◯◯ Very low[2,j,k]	IMPORTANT
Quality of Life (follow-up: mean 1 years; assessed with: Quality of Life in Epilepsy 89 (QOLIE-89), higher scores indicate better quality of life ; Scale from: 0 to 100)[8op]												
2[1,4]	randomised trials	serious[q]	not serious	not serious	not serious[2,r]	none	55	63	-	MD (change scores) **17.53 higher** (11.91 higher to 23.14 higher)	⨁⨁⨁◯ Moderate[2,q,r]	CRITICAL
Quality of Life (follow-up: mean 2 years; assessed with: Quality of Life in Epilepsy 89 (QOLIE-89), higher scores indicate better quality of life; Scale from: 0 to 100)[os]												
1[4]	randomised trials	serious[n]	not serious	not serious	not serious[2,r]	none	15	23	-	MD (change scores) **8.5 higher** (1 lower to 18.1 higher)	⨁⨁⨁◯ Moderate[2,n,r]	CRITICAL
Quality of Life (follow-up: mean 13 years; assessed with: Perceived Life Changes questionnaire; Scale from: 0 to 100)												
1[6]	non-randomised studies	extremely serious[k]	not serious	serious[t]	not serious[2]	none	269	157	-	MD **14.72 higher** (9.37 higher to 20.07 higher)	⨁◯◯◯ Very low[2,k,t]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: mean 1 years; assessed with: Rey Auditory Verbal Learning Test (RAVLT) delayed recall, higher scores indicate better verbal memory ; Scale from: 0 to 15)[uv]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
1[4]	randomised trials	very serious[d]	not serious	not serious	very serious[2,w]	none	14	23	-	MD (change scores) **0.8 lower** (2.9 lower to 1.2 higher)[x]	⨁◯◯◯ Very low[2,d,w]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: mean 2 years; assessed with: Rey Auditory Verbal Learning Test (RAVLT) delayed recall, higher scores indicate better verbal memory ; Scale from: 0 to 15)[uv]												
1[4]	randomised trials	very serious[d]	not serious	not serious	very serious[2,w]	none	14	23	-	MD (change scores) **1.3 lower** (3.8 lower to 1.1 higher)[x]	⨁◯◯◯ Very low[2,d,w]	CRITICAL
Neuropsychological Outcome (naming) (follow-up: mean 1 years; assessed with: Boston Naming Test (BNT), higher scores indicate better language (naming); Scale from: 0 to 60)[y]												
1[4]	randomised trials	very serious[d]	not serious	not serious	very serious[2,w]	none	14	23	-	MD (change score) **4 lower** (8.6 lower to 0.5 higher)[x]	⨁◯◯◯ Very low[2,d,w]	IMPORTANT
Neuropsychological Outcome (naming) (follow-up: mean 2 years; assessed with: Boston Naming Test (BNT), higher scores indicate better language (naming) ; Scale from: 0 to 60)[y]												
1[4]	randomised trials	very serious[d]	not serious	not serious	very serious[2,w]	none	14	23	-	MD (change score) **2.7 lower** (6.7 lower to 1.3 higher)[x]	⨁◯◯◯ Very low[2,d,w]	IMPORTANT
Neuropsychiatric Outcome (depression) (follow-up: mean 1 years; assessed with: depression scale of the Center for Epidemiological Studies (CES-D))[z]												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[2,l]	none	7/40 (17.5%)	8/40 (20.0%)	**RR 0.87** (0.35 to 2.18)	**26 fewer per 1,000** (from 130 fewer to 236 more)	⨁◯◯◯ Very low[2,a,l]	IMPORTANT
Neuropsychiatric Outcome (depression) (follow-up: mean 1 years; assessed with: Profile of Mood States (POMS), higher scores indicate worse mood problems; Scale from: -32 to 204)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
1[3]	non-randomised studies	extremely serious[m]	not serious	not serious	not serious[2]	none	125	71	-	MD **19 lower** (29.43 lower to 8.57 lower)	⨁◯◯◯ Very low[2,m]	IMPORTANT
Neuropsychiatric Outcome (depression) (follow-up: mean 13 years; assessed with: proportion of participants with depression, participant report of 'having depressing feelings')												
1[6]	non-randomised studies	extremely serious[k]	not serious	not serious	very serious[2,l]	none	40/269 (14.9%)	18/157 (11.5%)	**RR 1.30** (0.77 to 2.18)	**34 more per 1,000** (from 26 fewer to 135 more)	⨁◯◯◯ Very low[2,k,l]	IMPORTANT
Neuropsychiatric Outcome (psychosis) (follow-up: mean 1 years; assessed with: proportion of participants neuropsychiatric outcome, medical records, report of transient psychosis)												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[2,l]	none	1/40 (2.5%)	0.5/40 (1.3%)	**RR 3.00** (0.13 to 71.51)	**25 more per 1,000** (from 11 fewer to 881 more)	⨁◯◯◯ Very low[2,a,l]	IMPORTANT
Social Outcome (employment) (follow-up: mean 1 years; assessed with: proportion of participants obtaining employment, medical records)												
1[1]	randomised trials	serious[a]	not serious	not serious	very serious[2,l]	none	23/40 (57.5%)	15/40 (37.5%)	**RR 1.53** (0.95 to 2.48)	**199 more per 1,000** (from 19 fewer to 555 more)	⨁◯◯◯ Very low[2,a,l]	IMPORTANT
Social Outcome (employment) (follow-up: mean 2 years; assessed with: proportion of participants obtaining employment, medical records)												
1[4]	randomised trials	very serious[d]	not serious	not serious	serious[2,j]	none	In one study with 38 participants, 15/38 (39.47%) underwent standard/anterior temporal lobectomy. There were no treatment group differences with respect to employment status, hours per week worked or sick days reported.				⨁◯◯◯ Very low[2,d,j]	IMPORTANT
Social Outcome (employment or in full time school) (follow-up: range 2 years to 5 years; assessed with: proportion of participants obtaining employment or attending school full time, medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anterior temporal lobectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
2[3,7]	non-randomised studies	extremely serious[aa]	not serious	not serious	very serious[2,l]	none	117/182 (64.3%)	52/89 (58.4%)	**RR 1.23** (0.70 to 2.18)	**134 more per 1,000** (from 175 fewer to 689 more)	⨁◯◯◯ Very low[2,aa,l]	IMPORTANT
Social Outcome (employment) (follow-up: range 13 years to 17 years; assessed with: proportion of participants obtaining employment, medical records)												
2[6,7]	non-randomised studies	extremely serious[ab]	not serious	not serious	very serious[2,l]	none	264/311 (84.9%)	143/166 (86.1%)	**RR 1.07** (0.75 to 1.52)	**60 more per 1,000** (from 215 fewer to 448 more)	⨁◯◯◯ Very low[2,ab,l]	IMPORTANT
Social Outcome (driving) (follow-up: range 2 years to 5 years; assessed with: proportion of participants who are able to drive, medical records)												
2[3,7]	non-randomised studies	extremely serious[aa]	not serious	not serious	not serious[2]	none	113/182 (62.1%)	26/89 (29.2%)	**RR 2.06** (1.47 to 2.90)	**310 more per 1,000** (from 137 more to 555 more)	⨁◯◯◯ Very low[2,aa]	IMPORTANT
Social Outcome (driving) (follow-up: range 13 years to 17 years; assessed with: proportion of participants who are able to drive, medical records)												
2[6,7]	non-randomised studies	extremely serious[ab]	serious[ac]	not serious	very serious[2,l]	none	191/311 (61.4%)	91/166 (54.8%)	**RR 0.93** (0.52 to 1.68)	**38 fewer per 1,000** (from 263 fewer to 373 more)	⨁◯◯◯ Very low[2,ab,ac,l]	IMPORTANT
Other Outcomes - not measured[ad]												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Rated down one level because of some come concerns with the measurement of the outcome due to a lack of blinding to the intervention.
b. We did not rate down for imprecision because although the optimal information size (OIS=250 events) is not met and we do not consider the results to be implausible.
c. Rated down two levels because of serious risk of bias due to lack of adjustment for important confounders and concerns with measurement of the outcome due to being self-reported.
d. Rated down one level because of high risk of bias due to deviation from intended intervention (30.43% of the participants allocated to medical therapy received surgery) and missing outcome data (15.879% of imputed data).

e. Baseline risk from Engel, 2012.
f. Baseline risk based on Wiebe, 2001 looking at seizure freedom: free of all seizures including auras.
g. Baseline risk from Wiebe, 2001 looking at seizure freedom: free of disabling seizures.
h. Rated down two levels because all three included studies are at serious risk of bias due to lack of adjustment for important confounders, missing outcome data, and concerns with measurement of the outcome.
i. Rated down two levels because the two included studies are at serious risk of bias due to lack of adjustment for important confounders, missing outcome data, and concerns with measurement of the outcome due to being self-reported.
j. Rated down one level for imprecision because the optimal information size (OIS=250 events) was not met.
k. Rated down three levels because of critical risk of bias due to lack of adjustment for important confounders and serious risk of bias due to missing outcome data (16.44% missing data).
l. Rated down two levels for imprecision because the confidence interval is crossing the line of no effect (null, RR = 1), suggesting the possibility of a harm and a benefit.
m. Rated down three levels because of critical risk of bias due to lack of adjustment for important confounders.
n. Rated down one levels because of high risk of bias due to deviation from intended intervention (30.43% of the participants allocated to medical therapy received surgery) and missing outcome data (15.879% of imputed data).
o. MID: minimally important difference.
p. One observational study with 199 participants (Gilliam 1999), reported that in 125/199 (62.81%) participants who underwent standard/anterior temporal lobectomy, reported higher scores in the Epilepsy Surgery Inventory (ESI)-55 at follow-up than those who received medical therapy. (The ESI-55 consists of the SF-3630 and 19 additional epilepsy- specific items. The scale's possible scores range from 0 to 100. Higher scores represent better quality of life.)
q. Rated down two levels because one of the two included studies has high risk of bias due to deviation from intended intervention (30.43% of the participants allocated to medical therapy received surgery) and missing outcome data (15.879% of imputed data).
r. We did not rate down for imprecision because although the optimal information size (OIS=250 participants) is not met and we do not consider the results to be implausible.
s. One study with 84 participants (Jayalakshmi 2023), reported that in 61/84 (72.62%) participants that underwent standard/anterior temporal lobectomy their quality of life (QOLI 2-items) at 5 year follow-up was significantly better than those who received medical therapy. (The first (QOLI) was rated on a scale of 1 to 10 (10 was the highest rating); the second item (QOLII) rated from 1 to 5 (1 was the highest rating).)
t. We considered perceived life changes a surrogate for the outcome of quality of life. There is not enough information to assume there is high correlation between them.
u. 60% of participants in each group had left side of ictal onset. AMTL resection consisted of en bloc resection of the anterior 3.5 to 4 cm (in the dominant and nondominant hemispheres, respectively) of the lateral temporal lobe, sparing the superior temporal gyrus, followed by removal of the mesial structures including en bloc resection of the hippocampus and resection of parahippocampal gyrus and part of the amygdala.
v. The Rey Auditory Verbal Learning Test (RAVLT) evaluates verbal memory in patients ≥16 years of age. The test is designed as a list-learning paradigm in which the patient hears a list of 15 nouns and is asked to recall as many words from the list as possible. After five repetitions of free-recall, a second "interference" list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible. After the interference trial, the participant is immediately asked to recall the words from List A, which she or he heard five times previously. After a 20 min delay, the participant is asked to again recall the words from List A. After this "delayed recall" task, a list of 50 words is presented containing all of the words from Lists A and B, in addition to 20 phonemically and/or semantically similar words. Higher scores indicate better verbal memory.
w. Rated down two levels for imprecision because the confidence interval is crossing the line of no effect (null, MD = 0), suggesting the possibility of a harm and a benefit.
x. MD (change score) was calculated with the difference in adjusted mean change. Mean change was adjusted for age, gender, side of ictal onset, and the baseline value of the outcome variable using repeated measures analysis of covariance model.
y. The Boston Naming Test (BNT) is a brief language test that requires an examinee to name 60 line drawings of objects that are increasingly difficult to identify. If an examinee is unable to freely recall the name of an item, they are prompted with a phonemic cue after 20 seconds. The test is discontinued after 8 consecutive item failures.
z. Depression scale of the Center for Epidemiological Studies (CES-D; range of scores, 0 to 60.)
aa. Rated down three levels because the two included studies have critical risk of bias due to lack of adjustment for important confounders and concerns with measurement of the outcome.
bb. ab. Rated down three levels for risk of bias because the two included studies have critical risk of bias due to lack of adjustment for important confounders, missing outcome data, and concerns with measurement of the outcome.
cc. ac. Rated down one level for inconsistency because statistically, there is substantial heterogeneity with I2=75%. Additionally, point estimates of the two included studies have opposite direction and there is little overlap of the confidence intervals.
dd. ad. Outcomes not measured: SUDEP, medical or surgical complications (intracerebral hemorrhage with neurological deficits), neuropsychological outcomes (receptive language, verbal fluency, IQ), neuropsychiatric outcomes (personality changes, anxiety).

References

1. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345(5):311-8. doi: 10.1056/NEJM200108023450501.
2. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, Traversy G, Akl EA, Mayer M, Schünemann HJ, Guyatt GH. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022 Oct;150:216-224. doi: 10.1016/j.jclinepi.2022.07.014.

3. Gilliam F, Kuzniecky R, Meador K, Martin R, Sawrie S, Viikinsalo M, Morawetz R, Faught E. Patient-oriented outcome assessment after temporal lobectomy for refractory epilepsy. Neurology. 1999;53(4):687-94. doi: 10.1212/wnl.53.4.687.
4. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, Sperling MR, Gardiner I, Erba G, Fried I, Jacobs M, Vinters HV, Mintzer S, Kieburtz K; Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307(9):922-30. doi: 10.1001/jama.2012.220.
5. Kumlien E, Doss RC, Gates JR. Treatment outcome in patients with mesial temporal sclerosis. Seizure. 2002;11(7):413-7. doi: 10.1053/seiz.2001.0614.
6. Jayalakshmi S, Vasireddy S, Sireesha J, Vooturi S, Patil A, Sirisha S, Vadapalli R, Chandrasekhar YBVK, Panigrahi M. Long-term seizure freedom, resolution of epilepsy and perceived life changes in drug resistant temporal lobe epilepsy with hippocampal sclerosis: comparison of surgical versus medical management. Neurosurgery. 2023;92(6):1249-1258. doi: 10.1227/neu.0000000000002358.
7. Jones JE, Blocher JB, Jackson DC. Life outcomes of anterior temporal lobectomy: serial long-term follow-up evaluations. Neurosurgery. 2013 Dec;73(6):1018-25. doi: 10.1227/NEU.0000000000000145.
8. Wiebe, S, Matijevic, S, Eliasziw, M, Derry, P A. Clinically important change in quality of life in epilepsy.Journal of neurology, neurosurgery, and psychiatry; 2002.

Evidence Profile, PICO I-B: Selective amygdalo-hippocampectomy compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy

The AES/CNS guideline panel suggests the use of selective amygdalo-hippocampectomy compared to medical therapy in people with drug-resistant mesial temporal lobe epilepsy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	selective amygdalo-hippocampectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (seizure free) (follow-up: mean 2 years; assessed with: rate of occurrence of seizure freedom, medical records)[a]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[2,c]	none	9/11 (81.8%)	0.5/8 (6.3%)	**RR 14.25** (0.95 to 214.03)	**828 more per 1,000** (from 3 fewer to 1,000 more)	⨁◯◯◯ Very low[2,b,c]	CRITICAL
								1.0%		**133 more per 1,000** (from 1 fewer to 1,000 more)		
								2.5%[3,d]		**331 more per 1,000** (from 1 fewer to 1,000 more)		
Quality of Life (follow-up: mean 2 years; assessed with: Quality of Life in Epilepsy Inventory (QOLIE-10), higher scores indicate worse quality of life ; Scale from: 10 to 50)[e]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[2,f]	none	6	6	-	MD **10.5 lower** (21.61 lower to 0.61 higher)	⨁◯◯◯ Very low[2,b,f]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: mean 2 years; assessed with: Verbaler Lernund Merkfähigkeitstest (VLMT), z scores, higher scores indicate better verbal memory; Scale from: 0 to 100)[g,h]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[i]	none	11	8	-	MD **16.02 lower** (30.96 lower to 1.08 lower)	⨁◯◯◯ Very low[b,i]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	selective amygdalo-hippocampectomy	medical therapy	Relative (95% CI)	Absolute (95% CI)		
Neuropsychological Outcome (Intelligence Quotient (IQ)) (follow-up: mean 2 years; assessed with: Hamburg-Wechsler Intelligence Test for Adults – Revision (HAWIE-R), z-scores normal values = 100 ± 15, higher scores high represent better IQ ; Scale from: 0 to 100)												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	very serious[2,j]	none	11	8	-	MD **3.36 lower** (15.5 lower to 8.78 higher)	⨁◯◯◯ Very low[2,b,j]	IMPORTANT
Neuropsychiatric Outcome (depression) (follow-up: mean 2 years; assessed with: Beck Depression Inventory (BDI), higher scores indicate worse depressive symptoms; Scale from: 0 to 63)[k]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[2,f]	none	11	8	-	MD **11.2 lower** (22.46 lower to 0.06 higher)	⨁◯◯◯ Very low[2,b,f]	CRITICAL
Social Outcome (employment) (follow-up: mean 2 years; assessed with: proportion of participants obtaining employment, medical records)												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	very serious[j]	none	7/11 (63.6%)	4/8 (50.0%)	**RR 1.27** (0.56 to 2.90)	**135 more per 1,000** (from 220 fewer to 950 more)	⨁◯◯◯ Very low[b,j]	CRITICAL
Other Outcomes - not measured[l]												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Seizure freedom defined as the absence of seizures that caused impairment of consciousness.
b. Rated down three levels because of critical risk of bias due to lack of adjustment for important confounders, deviation from the intervention (co-interventions are not similar between groups), and concerns with measurement of the outcome.
c. Rated down one level for imprecision because although the confidence interval does not cross the line of no effect, the optimal information size (OIS=250 events) is not met and we do not consider the results to be implausible.
d. 2.5% baseline risk taken from Wiebe 2001, control arm (medical therapy).
e. A Quality of Life in Epilepsy Inventory (QOLIE-10) a score greater than 32 indicates a subjectively impaired quality of life.
f. Rated down one level for imprecision because the confidence interval slightly crosses the line of no effect (null)
g. The VLMT is a German adaptation of The Rey Auditory Verbal Learning Test (RAVLT), which evaluates verbal memory in patients ≥16 years of age. The test is designed as a list-learning paradigm in which the patient hears a list of 15 nouns and is asked to recall as many words from the list as possible. After five repetitions of free-recall, a second "interference" list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible. After the interference trial, the participant is immediately asked to recall the words from List A, which she or he heard five times previously.

After a 20 min delay, the participant is asked to again recall the words from List A. After this “delayed recall” task, a list of 50 words is presented containing all of the words from Lists A and B, in addition to 20 phonemically and/or semantically similar words.

h. Raw scores were transformed into standard scores (mean = 100, SD = 10), summed, and divided by the number of added scores, reflecting the mean standard score.
i. Rated down one level for imprecision because the optimal size information (OIS=250) is not met.
j. Rated down two levels for imprecision because the confidence interval is very wide, crossing the line of no effect (null).
k. Beck Depression Inventory consists of 21 items scored 0-3. BDI was applied using a score of greater than 10 points as the cutoff indicating depressed mood.
l. Outcomes not measured: permanent, unexpected neurological deficits (excluding visual field deficits, expected with some surgical procedures), all-cause mortality, SUDEP, medical or surgical complications (brain infection, intracerebral hemorrhage with neurological deficits, serious adverse events), neuropsychological outcomes (receptive language, verbal fluency, naming), neuropsychiatric outcomes (personality changes, anxiety, psychosis), social outcomes (driving).

References

1. Vogt VL, Witt JA, Malter MP, Schoene-Bake JC, von Lehe M, Elger CE, Helmstaedter C. Neuropsychological outcome after epilepsy surgery in patients with bilateral Ammon's horn sclerosis. J Neurosurg. 2014;121(5):1247-56. doi: 10.3171/2014.7.JNS132037.
2. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, Traversy G, Akl EA, Mayer M, Schünemann HJ, Guyatt GH. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022 Oct;150:216-224. doi: 10.1016/j.jclinepi.2022.07.014.
3. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001 Aug 2;345(5):311-8. doi: 10.1056/NEJM200108023450501.

Evidence Profile, PICO I-C: Laser Interstitial Thermal Therapy (LITT) compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy

Recommendation I-C: The AES/CNS guideline panel suggests for the use of laser interstitial thermal therapy compared to medical therapy in people aged 12 years and older with drug-resistant mesial temporal lobe epilepsy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seizure Freedom (Engel I) (follow-up: mean 1 years; assessed with: proportion of participants achieving seizure freedom, medical records)									
3[1,2,3]	non-randomised studies	extremely serious[a]	not serious	not serious	not serious[4]	none	In three studies with 434 participants, 225/434 (51.85%) reported seizure freedom Engel I classification at 1 year follow-up after undergoing Laser Interstitial Thermal Therapy (LITT). [b]	⨁◯◯◯ Very low[4,a]	CRITICAL
Seizure Freedom (Engel I) (follow-up: median 4 years; assessed with: porportion of participants achieving seizure freedom, medical records)									
1[2]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In one study with 268 participants, 132/268 (49.25%) reported seizure freedom Engel 1 at a median follow-up of 4 years after undergoing Magnetic Resonance image-guided Laser Interstitial Thermal Therapy (MRgLITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
Seizure Freedom (International League Against Epilepsy (ILAE) I) (follow-up: 3 years; assessed with: proportion of participants achieving seizure freedom, medical records)									
1[5]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In one study with 33 participants, 22/33 (66.67%) reported seizure freedom ILAE I classification 3 years after undergoing Magnetic Resonance image-guided Laser Interstitial Thermal Therapy (MRgLITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
All-Cause Mortality (follow-up: median 3.75 years; assessed with: proportion of participants who died, medical records)									
2[2,3]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In two studies with 412 participants, 8/412 (1.94%) died at a median follow-up of 3.75 years after undergoing Laser Interstitial Thermal Therapy (LITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
Sudden Unexpected Death in Epilepsy (SUDEP) (follow-up: 1; assessed with: proportion of participants who presented SUDEP, medical records)									
1[2]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In one study with 277 participants, 1/277 (0.36%) presented SUDEP at 1 year after undergoing Magnetic Resonance image-guided Laser Interstitial Thermal Therapy (MRgLITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
Sudden Unexpected Death in Epilepsy (SUDEP) (follow-up: median 3.5 years; assessed with: proportion of participants who presented SUDEP, medical records)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1[3]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In one study with 135 participants, 4/135 (2.96%) presented SUDEP at a median follow-up of 3.5 years after undergoing Laser Interstitial Thermal Therapy (LITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
Medical or Surgical Complications (symptomatic intracranial hemorrhage) (follow-up: median 4 years; assessed with: proportion of participants who experienced a symptomatic intracranial hemorrhage, medical records)									
1[2]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[4,d]	none	In one study with 277 participants, 1/277 (0.36%) presented a symptomatic intracranial hemorrhage at a median follow-up of 4 years after undergoing a Magnetic Resonance image-guided Laser Interstitial Thermal Therapy (MRgLITT).	⨁◯◯◯ Very low[4,c,d]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: 1 years; assessed with: Rey Auditory Verbal Learning Test (RAVLT) delayed recall, higher scores indicate better verbal memory)									
1[1]	non-randomised studies	extremely serious[a]	not serious	not serious	very serious[4,e]	none	One study with 40 participants, reported a mean change from baseline of 0.91 (95% CI, -0.32 to 2.14) in verbal memory at 1 year follow-up after undergoing Laser Interstitial Thermal Therapy (LITT).	⨁◯◯◯ Very low[4,a,e]	CRITICAL
Other Outcomes - not measured[f]									
-	-	-	-	-	-	-		-	

CI: confidence interval

Explanations

a. Rated down three levels because of risk of bias due to prognostic factor imbalances and moderate risk of bias due to concerns with measurement of the outcome in the three included studies.
b. LITT: laser interstitial thermal therapy
c. Rated down three levels because of risk of bias due to prognostic factor imbalance and moderate risk of bias due to concerns with measurement of the outcome in the single included study.
d. Rated down one level for imprecision because the optimal information size (OIS=250 events) is not met.
e. Rated down to levels for imprecision because the confidence interval crosses the line of no effect (null), which implies the possibility of a benefit and a harm.
f. Outcomes not measured: permanent, unexpected neurological deficits (excluding visual field deficits, expected with some surgical procedures), medical or surgical complications (brain infection, serious adverse events), quality of life, neuropsychological outcomes (receptive language, verbal fluency, naming, IQ), neuropsychiatric outcomes (personality changes, depression, anxiety, psychosis), social outcomes (employment, driving).

References

1. Drane DL, Willie JT, Pedersen NP, Qiu D, Voets NL, Millis SR, Soares BP, Saindane AM, Hu R, Kim MS, Hewitt KC, Hakimian S, Grabowski T, Ojemann JG, Loring DW, Meador KJ, Faught E, Miller JW, Gross RE. Superior verbal memory outcome after stereotactic laser amygdalohippocampotomy. Front Neurol. 2021;12:779495. doi:10.3389/fneur.2021.779495
2. Youngerman BE, Banu MA, Khan F, McKhann GM, Schevon CA, Jagid JR, Cajigas I, Theodotou CB, Ko A, Buckley R, Ojemann JG, Miller JW, Laxton AW, Couture DE, Popli GS, Buch VP, Halpern CH, Le S, Sharan AD, Sperling MR, Mehta AD, Englot DJ, Neimat JS, Konrad PE, Sheth SA, Neal EG, Vale FL, Holloway KL, Air EL, Schwalb JM, D'Haese PF, Wu C. Long-term outcomes of mesial temporal laser interstitial thermal therapy for drug-resistant epilepsy and subsequent surgery for seizure recurrence: a multi-centre cohort study. J Neurol Neurosurg Psychiatry. 2023;94(11):879-886. doi: 10.1136/jnnp-2022-330979.
3. Esmaeili B, Hakimian S, Ko AL, Hauptman JS, Ojemann JG, Miller JW, Tobochnik S. Epilepsy-related mortality after laser interstitial thermal therapy in patients with drug-resistant epilepsy. Neurology. 2023;101(13):e1359-e1363. doi: 10.1212/WNL.0000000000207405.

4. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, Traversy G, Akl EA, Mayer M, Schünemann HJ, Guyatt GH. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022 Oct;150:216-224. doi: 10.1016/j.jclinepi.2022.07.014.
5. Mo J, Guo Z, Wang X, Zhang J, Hu W, Shao X, Sang L, Zheng Z, Zhang C, Zhang K. Magnetic resonance-guided laser interstitial thermal therapy vs. open surgery for drug-resistant mesial temporal lobe epilepsy: a propensity score matched retrospective cohort study. Int J Surg. 2024;110(1):306-314. doi: 10.1097/JS9.0000000000000811.

Evidence Profile, PICO I-D: Radiosurgery compared to medical therapy in patients with drug-resistant mesial temporal lobe epilepsy

Recommendation I-D: The AES/CNS guideline panel suggests against the use of radiosurgery compared to medical therapy in people aged 12 years or older with drug-resistant mesial temporal lobe epilepsy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seizure Freedom (Engel Ib classification) (follow-up: mean 1 years; assessed with: proportion of participants achieving seizure freedom, independent outcome adjudication of seizures recorded in participant diaries)									
1[1]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[2,b]	none	In one study with 31 participants, 4/31 (13%) reported seizure freedom (Engel Ib classification) one year after undergoing radiosurgery.	⊕◯◯◯ Very low[2,a,b]	CRITICAL
Seizure Freedom (Engel Ib classification) (follow-up: mean 3 years; assessed with: proportion of participants achieving seizure freedom, independent outcome adjudication of seizures recorded in participant diaries)									
1[1]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[2,b]	none	In one study with 31 participants, 23/31 (74.19%) reported seizure freedom (Engel Ib classification) three years after undergoing radiosurgery.	⊕◯◯◯ Very low[2,a,b]	CRITICAL
Permanent, unexpected neurological deficits (follow-up: mean 3 years; assessed with: proportion of participants experiencing an unexpected neurological deficit, medical records)									
1[1]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[2,b]	none	In one study with 31 participants, no permanent, unexpected neurological deficits were reported three years after undergoing radiosurgery.	⊕◯◯◯ Very low[2,a,b]	CRITICAL
Medical or Surgical Complications (serious adverse events) (follow-up: mean 3 years; assessed with: proportion of participants experiencing a serious adverse event, medical records)									
1[1]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[2,b]	none	In one study with 31 participants undergoing radiosurgery, 5/31 (16.13%) reported serious adverse events 3 years after undergoing radiosurgery.	⊕◯◯◯ Very low[2,a,b]	CRITICAL
Quality of Life (MID=10) (follow-up: mean 1 years; assessed with: Quality of Life in Epilepsy 89 (QOLIE-89), higher scores indicate better quality of life)[c]									
1[1]	non-randomised studies	extremely serious[d]	not serious	not serious	serious[2,e]	none	In one study with 23 participants included in analysis, there was an increase in quality of life one year after radiosurgery [mean change (95% CI) 0.57 (-0.05, 7.19)].	⊕◯◯◯ Very low[2,d,e]	CRITICAL
Quality of Life (MID=10) (follow-up: mean 3 years; assessed with: Quality of Life in Epilepsy 89 (QOLIE-89), higher scores indicate better quality of life)[c]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1[1]	non-randomised studies	extremely serious[d]	not serious	not serious	serious[2,e]	none	In one study with 23 participants included in analysis, there was an increase in quality of life three years after radiosurgery [mean change (95% CI) 7.61 (-0.30, 15.47)].	⊕◯◯◯ Very low[2,d,e]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: mean 1 years; assessed with: California Verbal Learning Test (CVLT), higher scores indicate better verbal memory)									
1[1]	non-randomised studies	extremely serious[f]	not serious	not serious	very serious[2,g]	none	In one study with 14 participants included in analysis, there was an increase in verbal memory one year after radiosurgery [mean change (95% CI) 0.6 (-1.32, 2.53)].	⊕◯◯◯ Very low[2,f,g]	CRITICAL
Neuropsychological Outcome (verbal memory) (follow-up: mean 3 years; assessed with: California Verbal Learning Test (CVLT), higher scores indicate better verbal memory)									
1[1]	non-randomised studies	extremely serious[f]	not serious	not serious	very serious[2,g]	none	In one study with 14 participants included in analysis, there was a decrease in verbal memory three years after radiosurgery [mean change (95% CI) -0.38 (-2.00, 1.23)].	⊕◯◯◯ Very low[2,f,g]	CRITICAL
Other Outcomes - not measured[h]									
-	-	-	-	-	-	-		-	

CI: confidence interval

Explanations

a. Rated down three levels because of prognostic factor imbalances and critical risk of bias due to concerns with measurement of the outcome.
b. Rated down one level for imprecision because the optimal information size (OIS=250 events) was not met.
c. MID: minimally important difference.
d. Rated down three levels because of prognostic factor imbalances and critical risk of bias due to concerns with measurement of the outcome and missing outcome data (i.e., 74% provided outcome data).
e. Rated down one level for imprecision because although the confidence interval does not cross the MID, the optimal size information (OIS=250 participants) is not met.
f. Rated down three levels because of prognostic factor imbalances and critical risk of bias due to concerns with measurement of the outcome and missing outcome data (i.e., 45.16% provided outcome data).
g. Rated down two levels for imprecision because the confidence interval crosses the line of no effect (null), which implies the possibility of a harm and a benefit.
h. Outcomes not measured: all-cause mortality, SUDEP, medical or surgical complications (brain infection, intracerebral hemorrhage with neurological deficits), neuropsychological outcomes (receptive language, verbal fluency, naming, IQ), neuropsychiatric outcomes (personality changes, depression, anxiety, psychosis), social outcomes (employment, driving).

References

1. Barbaro NM, Quigg M, Ward MM, Chang EF, Broshek DK, Langfitt JT, Yan G, Laxer KD, Cole AJ, Sneed PK, Hess CP, Yu W, Tripathi M, Heck CN, Miller JW, Garcia PA, McEvoy A, Fountain NB, Salanova V, Knowlton RC, Bagić A, Henry T, Kapoor S, McKhann G, Palade AE, Reuber M, Tecoma E. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. Epilepsia. 2018;59(6):1198-1207. doi:10.1111/epi.14045.
2. Zeng L, Brignardello-Petersen R, Hultcrantz M, Mustafa RA, Murad MH, Iorio A, Traversy G, Akl EA, Mayer M, Schünemann HJ, Guyatt GH. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022 Oct;150:216-224. doi: 10.1016/j.jclinepi.2022.07.014.

Evidence Profile, PICO II: Resective surgery compared to medical therapy in patients with drug-resistant neocortical epilepsy

Recommendation II: The AES/CNS guideline panel suggests the use of resective or ablative surgery compared to medical therapy in people aged 2 years and older with drug-resistant neocortical epilepsy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seizure Freedom (Engel Ia) - Mostly Paediatrics (follow-up: 1 years; assessed with: proportion of participants who achieved seizure freedom Engel Ia classification, medical records)									
2[1,2]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[b]	none	In two studies with 446 participants, with about 80% pediatric population, at 1 year follow-up, 255 (57.17%) had achieved seizure freedom Engel Ia classification after undergoing resective surgery.	⊕◯◯◯ Very low[a,b]	CRITICAL
Seizure Freedom (Engel I)- Adults (follow-up: 1 years; assessed with: proportion of participants who achieved seizure freedom Engel I classification, medical records)									
1[3]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 110 adult participants, at 1 year follow-up, 72 (65.4%) achieved seizure freedom Engel I after undergoing resective surgery.	⊕◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (Engel Ia)- Mostly Paediatrics - Medium Term Follow-up (follow-up: 2 years; assessed with: proportion of participants who achieved seizure freedom Engel Ia; medical records)									
1[1]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 105 participants (87% belong to pediatric population), at 2 year follow-up, 59 (56.19%) had achieved seizure freedom Engel I classification after undergoing resective surgery.	⊕◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (Engel I) Mixed and Paediatric - Medium Term Follow-up (follow-up: 2 years; assessed with: proportion of participants who achieved seizure freedom Engel I; medical records)									
2[4,5]	non-randomised studies	extremely serious[a]	not serious	not serious	not serious	none	• Pediatric and adult population (Jayalakshmi 2019) One study included 188 participants (around 50% adults and 50% children) and reported that 124 (66%) achieved seizure freedom Engel I classification after undergoing resective surgery, at 2 year follow-up. • Pediatric population (Yardi 2020) One study included 788 participants of which 574 are pediatrics (73%). This study reported that 544 (69%) achieved seizure freedom Engel I classification after undergoing resective surgery, at 2 year follow-up.	⊕◯◯◯ Very low[a]	CRITICAL
Seizure Freedom at Long Term Follow-up (Engel 1a)- Paediatric and Adult (follow-up: mean 6 years; assessed with: proportion of participants who achieved seizure freedom Engel Ia classification, medical records)[d]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
5[1,2,6,7,8]	non-randomised studies	extremely serious[e]	not serious	not serious	not serious	none	• Pediatric population (Xue 2016, Bulacio 2022, Burgeois 1999, Ramirez-Molina 2017) Four studies with 591 participants providing outcome data (>80% under 18 years), reported that 304 (51.44%) achieved seizure freedom Engel Ia after undergoing resective surgery. • Adult population (Ramirez-Molina 2017, Lazow 2012) Two studies with 124 participants providing outcome data reported that 61 (49.19%) achieved seizure freedom Engel Ia after undergoing resective surgery. [f]	⨁◯◯◯ Very low[e]	CRITICAL
Seizure Freedom at Long Term Follow-up (Engel I)- Mixed and Paediatric (follow-up: mean 7 years; assessed with: proportion of participants who achieved seizure freedom Engel I; medical records)									
2[6,7]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[b]	none	Two studies with 164 participants, reported that 118 (71.95%) achieved seizure freedom Engel I at the longest follow-up after undergoing resective surgery. One of the included studies, Ramirez 2017, reported no difference in the proportion of participants achieving seizure freedom (Engel I classification) between children <6 years of age (32/40, 80%) and adults >20 years of age (53/66, 80%).	⨁◯◯◯ Very low[a,b]	CRITICAL
Permanent, Unexpected Neurological Deficits- Adults and Paediatrics (follow-up: mean 6.3 years; assessed with: proportion of participants experiencing a permanent unexpected neurological deficit, medical records)									
2[6,8]	non-randomised studies	extremely serious[a]	not serious	not serious	serious[b]	none	**Paediatrics:** In two included studies with 211 participants, permanent unexpected neurological deficits were reported in 7 out of 211 (3.32%) among those <18 years of age**Adults:** Ramirez reported that 1 out of 66 (1.52) had permanent unexpected neurological deficits , after undergoing resective surgery. Ramirez: permanent complications (including motor involvement and visual deficit due to ischemic complications) Burgeois: Permanent deficit after sustaining either a surgery-related injury to the surrounding brain or after resection of a structural lesion from the motor cortex	⨁◯◯◯ Very low[a,b]	CRITICAL
All-Cause Mortality- Mixed and Paediatrics (follow-up: mean 3.5 years; assessed with: proportion of participants who died of any cause, medical records)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[5,8]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In two studies with 359 participants, at a mean follow-up of 3.5 years, none of the participants had died after undergoing resective surgery.Burgeous 1999: 171 participants, 100% were pediatrics Jayalakshmi 2019: 188 participants (Mixed) [g]	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (brain infection)- Paediatrics (follow-up: mean 5 years; assessed with: proportion of participants who experienced a brain infection, medical records)									
1[8]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 171 participants, at a mean follow-up of 5 years, a brain infection was reported in 1 (0.58%) after undergoing resective surgery. [h]	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications- Paediatrics (intracranial hemorrhage) - Medium Term Follow-up- Paediatrics (follow-up: mean 5 years; assessed with: proportion of participants who experienced an intracranial hemorrhage, medical records)									
1[8]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 171 participants, at a mean follow-up of 5 years, none of the participants had presented an intracranial hemorrhage after undergoing resective surgery. [h]	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications- Mixed (adverse event) - Long term Follow-up (follow-up: 6.6 years; assessed with: proportion of participants experiencing an adverse event, medical records)									
1[7]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 58 participants, at 6.6 years follow-up, 3 (5.17%) participants reported a surgical complications. Two participants had cerebrospinal fluid leaks and one had an infection.	⨁◯◯◯ Very low[b,c]	CRITICAL
Quality of Life (MID=10)- Adults (follow-up: 1 years; assessed with: Quality of Life in Epilepsy (QOLIE), participant reported; lower scores indicate better quality of life)									
1[3]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[i]	none	In one study with 110 participants, quality of life at 1 year follow up after reported a mean change (SD) -10.8 (3.97). [k]	⨁◯◯◯ Very low[i,j]	CRITICAL
Neuropshychological Outcomes (cognition)- Paediatrics (Medium term follow up) (follow-up: mean 5 years; assessed with: proportion of participants who showed cognitive status improvement, measured with different instruments, participant reported)[l]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1[8]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[b]	none	In one study with 171 participants, at baseline, 89 (52%) reported normal cognitive function and 82 (47.99%) 'less-than normal'. At a mean follow-up of 5 years after resective srugery, 43/171 (25%) reported and improvement in congnitive status, while 5/171 (2.92%) worsened after undergoing resective surgery. [h]	⨁◯◯◯ Very low[b,i]	CRITICAL
Neuropsychological Outcomes (cognition) Adults Long term followup (follow-up: median 9 years; assessed with: proportion of participants who improved, remained unchanged, or worsened compared to baseline; measured with a standard neuropsychological test battery; participant reported)[m]									
1[6]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[b]	none	In one study with 66 adult participants >20 years of age, at a median of 9 years follow-up after resective surgery, 27 (40.9%) reported cognitive improvement after surgery; 4 (6.06%) worsened, and 23 (34.84%) had no change.	⨁◯◯◯ Very low[b,i]	
Neuropsychological Outcomes (cognition)- Paediatrics (follow-up: median 5 years; assessed with: proportion of participants who improved, remained unchanged, or worsened compared to baseline; measured with a neuropsychological test battery tailored to the age of participants; parent reported)[n]									
1[6]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[b]	none	In one study with 40 participants <6 years of age, at a median follow-up of 5 years after resective surgery, 15 participants (37.5%) reported cognitive improvement, 5 (12.5%) had no change, and none worsened.	⨁◯◯◯ Very low[b,i]	
Neuropsychiatric Outcomes- Paediatrics (behavior) (follow-up: median 5 years; assessed with: proportion of participants who improved in their behavior and psychosocial development, participant reported)[o]									
1[8]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[b]	none	In one study with 171 participants, at a median follow-up of 5 years after resective surgery, 53 (31%) reported behavioral improvement. [h]	⨁◯◯◯ Very low[b,i]	
Social Outcomes (employment)- Mixed (follow-up: 6.6 years; assessed with: proportion of participants who obtained employment, medical records)									
1[7]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	In one study with 56 participants, at 6.6 years follow-up after resective surgery, 35 (62.5%) reported employment, compared to 34 (60.71%) before resective surgery.	⨁◯◯◯ Very low[b,c]	
Social Outcomes (school performance)- Paediatrics (follow-up: median 5 years; assessed with: proportion of participants who achieved 'normal schooling')[p]									
1[8]	non-randomised studies	extremely serious[i]	not serious	not serious	serious[b]	none	In one study with 125 paticipants included in analysis, at a median follow-up of 5 years after undergoing resective surgery, 95 (76%) reported normal schooling, compared to 83 (66.4%) before surgery.	⨁◯◯◯ Very low[b,i]	

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Other Outcomes - not measured[q]									
-	-	-	-	-	-	-		-	

CI: confidence interval

Explanations

a. Rated down three levels because or risk of bias due to prognostic factor imbalance (lack of a comparison group) in the two included studies.
b. Rated down one level for imprecision because the Optima Information Size (OIS) is not met (OIS=250 events), which introduces risk of random error.
c. Rated down three levels because or risk of bias due to prognostic factor imbalance (lack of a comparison group) in the single included study.
d. Long term follow-up: >5 years.
e. Rated down three levels because or risk of bias due to prognostic factor imbalance (lack of a comparison group) in the five included studies.
f. One of the included studies reported that 30 out of 40 (75%) children <6 years of age, and 47 out of 66 (71.21%) adults >20 years of age, achieved seizure freedom Engel Ia classification.
g. There was no difference in the proportion of participants who died between participants <18 years of age (n=171) and those >18 years of age (n=188).
h. This study included participants <18 years of age only.
i. Rated down three levels because or risk of bias due to prognostic factor imbalance (lack of a comparison group) and critical risk of bias due to concerns with measurement of the outcome in the single included study.
j. Rated down one level for imprecision because the Optimal Information Size (OIS) is not met (OIS=250 participants), which introduces risk of random error.
k. The total QOLIE-10 scores range between 5 and 50, where high scores indicate a poor quality of life.
l. "Intelligence quotients (IQs) determined by the Wechsler test were divided into “normal” (either verbal or performance IQ more than 90), “slightly retarded” (scores between 90 and 70), “moderately retarded” (scores between 70 and 50), or “severely retarded” (scores less than 50). Those children with a normal IQ were subdivided according to the presence or absence of learning disabilities such as memory deficit, limited attention span, poor speed factor, and problem-solving ability. "
m. Participants underwent a standard neuropsychological test battery assessing language, reading skills, verbal memory, visuospatial memory, visual constructive functions, visual explorations, attention and executive functions, visual perception, abstract reasoning, and depressive symptoms.
n. Parents underwent Vineland Adaptive Behavioral Scale (VABS). The Preschool Neuropsychological Test was assessed as well. They also used the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-3), the revised Griffiths Mental Development Scales that was made for children between 2 and 8 years, and the Beck Depression Inventory.
o. "Data on behavior and psychosocial development were divided into four groups: normal behavior, minor psychological impairment (inhibition, anxiety), hyperactivity, and psychosis." No further description of measurement instruments is provided.
p. School performance was divided into the following groups: younger than 6 years of age (preschool age); normal schooling; moderate difficulties with a school delay of less than 2 years; severe difficulties with a delay of over 2 years; and no possibility of schooling. Moderate, severe, and no possibility of schooling were grouped under "less-than normal schooling' for analysis.
q. Other outcomes not measured: SUDEP, neuropsychological outcomes (verbal memory, receptive language, verbal fluency, naming, IQ), neuropsychiatric outcomes (personality changes, anxiety psychosis), social outcomes (driving).

References

1. Xue H, Cai L, Dong S, Li Y. Clinical characteristics and post-surgical outcomes of focal cortical dysplasia subtypes. J Clin Neurosci. 2016;23:68-72. doi: 10.1016/j.jocn.2015.04.022.
2. Bulacio JC, Bena J, Suwanpakdee P, Nair D, Gupta A, Alexopoulos A, Bingaman W, Najm I. Determinants of seizure outcome after resective surgery following stereoelectroencephalography. J Neurosurg. 2021 Oct 22;136(6):1638-1646. doi: 10.3171/2021.6.JNS204413.
3. Sun Y, Wang X, Che N, Qin H, Liu S, Wu X, Wei M, Cheng H, Yin J. Clinical characteristics and epilepsy outcomes following surgery caused by focal cortical dysplasia (type IIa) in 110 adult epileptic patients. Exp Ther Med. 2017;13(5):2225-2234. doi: 10.3892/etm.2017.4315.
4. Yardi R, Morita-Sherman ME, Fitzgerald Z, Punia V, Bena J, Morrison S, Najm I, Bingaman W, Jehi L. Long-term outcomes of reoperations in epilepsy surgery. Epilepsia. 2020;61(3):465-478. doi: 10.1111/epi.16452.
5. Jayalakshmi S, Nanda SK, Vooturi S, Vadapalli R, Sudhakar P, Madigubba S, Panigrahi M. Focal cortical dysplasia and refractory epilepsy: role of multimodality imaging and outcome of surgery. AJNR Am J Neuroradiol. 2019;40(5):892-898. doi: 10.3174/ajnr.A6041.

6. Ramírez-Molina JL, Di Giacomo R, Mariani V, Deleo F, Cardinale F, Uscátegui-Daccarett AM, Lorenzana P, Tassi L. Surgical outcomes in two different age groups with Focal Cortical Dysplasia type II: Any real difference? Epilepsy Behav. 2017;70(Pt A):45-49. doi: 10.1016/j.yebeh.2017.02.031.
7. Lazow SP, Thadani VM, Gilbert KL, Morse RP, Bujarski KA, Kulandaivel K, Roth RM, Scott RC, Roberts DW, Jobst BC. Outcome of frontal lobe epilepsy surgery. Epilepsia. 2012;53(10):1746-55. doi: 10.1111/j.1528-1167.2012.03582.x.
8. Bourgeois M, Sainte-Rose C, Lellouch-Tubiana A, Malucci C, Brunelle F, Maixner W, Cinalli G, Pierre-Kahn A, Renier D, Zerah M, Hirsch JF, Goutières F, Aicardi J. Surgery of epilepsy associated with focal lesions in childhood. J Neurosurg. 1999;90(5):833-42. doi: 10.3171/jns.1999.90.5.0833.

Evidence Profile, PICO III-A: Callosotomy compared to VNS in adult patients with drug-resistant drop-attack, Lennox-Gastaut Syndrome, or epileptic encephalopathy

Recommendation III-A: The AES/CNS guideline panel suggests the use of Callosotomy compared to VNS in adults with drug-resistant drop-attack, Lennox-Gastaut syndrome, or epileptic encephalopathy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (Rathore Class I - IV) - short term follow-up (follow-up: 1 years; assessed with: proportion of participants achieving seizure freedom Class I - IV); medical records)[a]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	13/24 (54.2%)	0/0	**proportion 0.54** (0.35 to 0.73)	**540 more per 1,000** (from 350 more to 730 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (drop-attack freedom, Rathore Class II) - short term follow-up (follow-up: 1 years; assessed with: proportion of participants achieving seizure freedom; medical records)												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	4/24 (16.7%)	0/0	**proportion 0.17** (0.06 to 0.37)	**170 more per 1,000** (from 60 more to 370 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
All Seizure Freedom - medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants achieving complete seizure freedom; medical records)												
2[2,3]	non-randomised studies	extremely serious[b]	serious[d]	not serious	serious[c]	none	6/68 (8.8%)	0/0	**proportion 0.02** (0.00 to 0.07)	**20 more per 1,000** (from 0 fewer to 70 more)	⨁◯◯◯ Very low[b,c,d]	CRITICAL
Seizure Freedom (>90% reduction sezure frequency) (follow-up: mean 5.5 years; assessed with: proportion of participants who achieved >90% reduction in seizure frequency; medical records)												
2[4,5]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	15/48 (31.3%)	0/0	**proportion 0.30** (0.15 to 0.52)	**300 more per 1,000** (from 150 more to 520 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (drop-attack freedom) - medium term follow-up (follow-up: 3 years; assessed with: proportion of participants achieving drop- attack freedom; medical records)												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	45/52 (86.5%)	0/0	**proportion 0.81** (0.68 to 0.89)	**810 more per 1,000** (from 680 more to 890 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
All Seizure Freedom - long term follow-up (follow-up: mean 10.35 years; assessed with: proportion of participants achieving complete seizure freedom; medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
2[6,7]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	8/46 (17.4%)		**proportion 0.17** (0.04 to 0.51)	**170 more per 1,000** (from 0 more to 1 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (drop-attack freedom) - long term follow-up (follow-up: mean 9.88 years; assessed with: proportion of participants achieving drop-attack freedom; medical records)												
2[7,8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	28/62 (45.2%)		**proportion 0.45** (0.33 to 0.58)	**450 more per 1,000** (from 330 more to 580 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure Freedom (drop-attack reduction or freedom) (follow-up: mean 10.35 years; assessed with: proportion of participants achieving drop-attack reduction or freedom; medical records)												
2[6,7]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	13/89 (14.6%)		**proportion 0.57** (0.09 to 0.95)	**570 more per 1,000** (from 90 more to 950 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, Unexpected Neurological Deficit - medium term follow-up (follow-up: mean 2.97 years; assessed with: proportion of participantes experiencing the outcomes, includes chronic disconnection syndrome, problematic neurological deficits, cognitive deficit aggravated; medical records)												
3[1,3,4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	3/96 (3.1%)		**proportion 0.03** (0.00 to 0.12)	**30 more per 1,000** (from 120 fewer to 0 fewer)	⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, Unexpected Neurological Deficit - long term follow-up (follow-up: mean 6.7 years; assessed with: proportion of participants experiencing the outcomes, includes left sided hemiparesis; medical records)												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	1/20 (5.0%)		**proportion 0.05** (0.01 to 0.28)	**50 more per 1,000** (from 10 more to 280 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
All Cause Mortality - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants who died; medical records)												
2[2,4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	1/34 (2.9%)		**proportion 0.02** (0.01 to 0.11)	**20 more per 1,000** (from 10 more to 110 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
All Cause Mortality - long term follow-up (follow-up: mean 6.7 years; assessed with: proportion of participants who died; medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 20 participants, after undergoing callosotomy, none of them had died at 6.7 years follow-up.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (brain infection) medium term follow-up (follow-up: mean 3.2 years; assessed with: proportion of participants who had a brain infection post-surgery; medical records)												
1[2]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	1/52 (1.9%)		**proportion 0.07** (0.01 to 0.35)	**70 more per 1,000** (from 10 more to 350 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (intracranial hemorrhage) short-term follow-up (follow-up: 1 years; assessed with: proportion of participants who experienced an intracranial hemorrhage; medical records)												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 24 participants, none of them reported having an intracranieal hemorrhage after callosotomy.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (intracranial hemorrhage) - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants who experienced an intracranial hemorrhage; medical records)												
2[2,3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	2/67 (3.0%)		**proportion 0.04** (0.01 to 0.13)	**40 more per 1,000** (from 10 more to 130 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (serious adverse events) - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants experiencing a serious adverse event; medical records)[e]												
3[2,3,4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	18/87 (20.7%)		**proportion 0.13** (0.03 to 0.42)	**130 more per 1,000** (from 30 more to 420 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or Surgical Complications (serious adverse events) - long term follow-up (follow-up: mean 8.8 years; assessed with: proportion of participants experiencing a serious adverse event; medical records)[f]												
3[6,7,8]	non-randomised studies	extremely serious[b]	serious[g]	not serious	serious[c]	none	11/82 (13.4%)		**proportion 0.10** (0.00 to 0.37)	**100 more per 1,000** (from 0 fewer to 370 more)	⨁◯◯◯ Very low[b,c,g]	CRITICAL
Quality of Life (improvement in quality of life/overall daily function) - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants with improvement; caregiver reported)												
2[3,4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	19/42 (45.2%)		**proportion 0.45** (0.31 to 0.60)	**450 more per 1,000** (from 310 more to 600 more)	⨁◯◯◯ Very low[b,c]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
Quality of Life (improvement in quality of life/overall daily function) - long term follow-up (follow-up: mean 9.9 years; assessed with: proportion of participants with improvement; caregiver reported))												
2[7,8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	34/62 (54.8%)		**proportion 0.56** (0.32 to 0.78)	**560 more per 1,000** (from 320 more to 780 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological Outcomes (verbal fluency) - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants with speech function improvement; parent/caregiver reported)												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	11/52 (21.2%)		**proportion 0.21** (0.12 to 0.34)	**210 more per 1,000** (from 120 more to 340 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological Outcomes (verbal fluency) - long term follow-up (follow-up: mean 14 years; assessed with: standardized instruments, no further details)												
1[7]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	One study with 26 participants reported that language functions appeared to be unaltered after surgery compared to presurgical results. Three patients, all of them submitted to complete CC, showed reduced verbal fluency and speech initiative during conversation, which was confirmed by caregivers.				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological Outcome (IQ) - medium term follow-up (follow-up: mean 3.3 years; assessed with: Performance and verbal intelligence quotients (PIQ and VIQ) were measured using the Wechsler Adult Intelligence Scale or the Wechsler Intelligence Scale for Children)												
1[2]	non-randomised studies	extremely serious[b]	not serious	not serious	not serious	none	In one study with 15 participants, no patient experienced a change in IQ score greater than 7 points after callosotomy,				⨁◯◯◯ Very low[b]	CRITICAL
Neuropsychological Outcome (IQ) - long term follow-up (follow-up: mean 7 years; assessed with: Wechsler Adult Intelligence Scale; medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
2[5,6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	Sakas 1996: • Twelve patients underwent pre- and postoperative psychological tests. • There was improvement in concentration. • The mean full scale VIQ and PIQ for the patients tested pre-operatively was 92, 96, and 88. The mean postoperative figures were 95, 97, and 93. • IQ mean change = 3 • VIQ mean change = 1 • PIQ mean change = 5 Marino 1990: • 28 patients underwent callosotomy and reported Improvement in attention disturbance and in motor tasks via WAIS in 10 patients.				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychiatric Outcomes (personality changes) - medium term follow-up (follow-up: mean 3.3 years; assessed with: improvement in hyperactivity; parent/caregiver reported)												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 52 participants, hiperactivity improved in 14 (27%), remained unchanged in 0, declined in 1 (2%), and 37 (71%) had no problem or no function.				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychiatric Outcomes (personality changes) - long term follow-up (follow-up: mean 9.9 years; assessed with: improvement in behaviour/aggressiveness)												
2[7,8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	24/62 (38.7%)		**proportion 0.39** (0.28 to 0.51)	**390 more per 1,000** (from 280 more to 511 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Social Outcomes (work/school) - medium term follow-up (follow-up: median 3.6 years; assessed with: proportion of participants experiencing the outcome)												
1[4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 20 participants, employment and schooling changes wre reported as follows: • of 4 participants living a simple situation of autonomy at home, 1 participant transitione to a work situation in a specialized structure, and 1 to a part-time work situation. • of 15 participants living in permanent medical-social assistance, 1 transitioned to adapted life at home, 3 to a specialized school, and 1 to normal schooling. • 1 participant with normal scolarity did not change.				⨁◯◯◯ Very low[b,c]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
Social Outcomes (employment) - long term follow-up (follow-up: mean 6.7 years; assessed with: proportion of participants experiencing the outcome)												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 20 participants, pre-operatively, no patient had either regular employment or was taking up training. Postoperatively, 7 patients became able to undertake full employment, 9 patients were taking up training, and 4 patients remained unable to take up employment or training.				⨁◯◯◯ Very low[b,c]	CRITICAL

CI: confidence interval

Explanations

a. Rathore class: Class 1, free of all types of seizures; Class 2, seizure without impairment of consciousness and drop attacks; Class 3, seizures with impairment of consciousness, but no drop attacks or generalized tonic-clonic seizures; Class 4, ≥90 % reduction in drop attacks; Class 5, ≥50 % but <90 % reduction of drop attacks; Class 6, <50 % reduction in drop attacks; Class 7, no appreciable change in seizure frequency/severity; Class 8, worse seizures. Classes 1–4 were defined as a favorable seizure outcome, while classes 5–8 were considered a poor seizure outcome.
b. Rated down three levels for critical risk of bias due to a lack of a comparison group and risk of prognostic imbalance.
c. Rated down one level for imprecision because the Optimal Information Size is not met (OIS = 250); which introduces risk of random error.
d. Rated down one level for inconsistency. There is considerable statistical heterogeneity (I2 = 96%) that we could not explain.
e. Includes: marked disconnection syndrome, transient akinetic state, transient hemiparesis, balance disorders related to apraxia.
f. Includes: left sided hemiparesis, akinesis, disconnection syndrome, venous air embolism, operative complications.
g. Rated down one level for inconsistency, as there is considerable statistical heterogeneity (I2 = 89%) that we could not explain.

References

1. Kagawa K, Hashizume A, Katagiri M, Seyama G, Okamura A, Kawano R, Iida K. Comparison of seizure outcomes and ADL recovery period after total or anterior corpus callosotomy in adolescent and young adults with drop attacks and severe mental retardation. Epilepsy Res. 2021;176:106706. doi: 10.1016/j.eplepsyres.2021.106706.
2. Mamelak AN, Barbaro NM, Walker JA, Laxer KD. Corpus callosotomy: a quantitative study of the extent of resection, seizure control, and neuropsychological outcome. J Neurosurg. 1993;79(5):688-95. doi: 10.3171/jns.1993.79.5.0688.
3. Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia. 2001 ;42(1):67-71. doi: 10.1046/j.1528-1157.2001.081422.x.
4. Rougier A, Claverie B, Marchal C, Pedespan JM, Loiseau P. Social outcome of 20 anterior callosotomies for drug-resistant epilepsy. Neurochirurgie. 1995;41(6):413-8.
5. Marino R Jr, Radvany J, Huck FR, De Camargo CH, Gronich G. Selective electroencephalograph-guided microsurgical callosotomy for refractory generalized epilepsy. Surg Neurol. 1990;34(4):219-28. doi: 10.1016/0090-3019(90)90132-9.
6. Sakas DE, Phillips J. Anterior callosotomy in the management of intractable epileptic seizures: significance of the extent of resection. Acta Neurochir (Wien). 1996;138(6):700-7. doi: 10.1007/BF01411475.
7. Passamonti C, Zamponi N, Foschi N, Trignani R, Luzi M, Cesaroni E, Provinciali L, Scerrati M. Long-term seizure and behavioral outcomes after corpus callosotomy. Epilepsy Behav. 2014;41:23-9. doi: 10.1016/j.yebeh.2014.08.130.
8. Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L, Saute R, Salles C, Hoefel JR, Soder RB, da Costa JC, Hemb M, Theys T, Palmini A. Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity. Neurology. 2016;87(19):1968-1974. doi: 10.1212/WNL.0000000000003307.

Evidence Profile, PICO III-B: Callosotomy compared to VNS in pediatric patients with drug-resistant drop-attack, Lennox-Gastaut syndrome, or epileptic encephalopathy

Recommendation III-B: The AES/CNS guideline panel suggests the use of Callosotomy compared to VNS in adults and children with drug-resistant drop-attack, Lennox-Gastaut syndrome, or epileptic encephalopathy. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
All Seizure Freedom - medium term follow-up (follow-up: mean 2.5 years; assessed with: proportion of participants achieving complete seizure freedom; medical records)												
3[1,2,3]	non-randomised studies	very serious[a]	not serious	not serious	serious[b]	none	15/67 (22.4%)	3/36 (8.3%)	**OR 2.18** (0.58 to 8.27)	**82 more per 1,000** (from 33 fewer to 346 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
Seizure Freedom (drop-attack freedom) - medium term follow-up (follow-up: 2 years; assessed with: proportion of participants who achieved drop-attack freedom)												
1[1]	non-randomised studies	very serious[c]	not serious	not serious	serious[b]	none	4/13 (30.8%)	0/4 (0.0%)	**OR 4.26** (0.19 to 97.49)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low[b,c]	CRITICAL
								0.5%		**16 more per 1,000** (from 4 fewer to 324 more)		
								8.3%		**195 more per 1,000** (from 66 fewer to 815 more)		
All Seizure Freedom - long term follow-up (follow-up: mean 5.8 years; assessed with: proportion of participants achieving complete seizure freedom; medical records)												
1[4]	non-randomised studies	very serious[c]	not serious	not serious	very serious[d]	none	1/17 (5.9%)	1/14 (7.1%)	**OR 0.81** (0.05 to 14.28)	**13 fewer per 1,000** (from 68 fewer to 452 more)	⨁◯◯◯ Very low[c,d]	CRITICAL
All Seizure Freedom - short term follow-up (follow-up: 1 years; assessed with: proportion of participants achieving complete seizure freedom; medical records)												
3[5,6,7]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	14/102 (13.7%)	0/0	**proportion 0.14** (0.08 to 0.22)	**140 more per 1,000** (from 80 more to 220 more)	⨁◯◯◯ Very low[e,f]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
Seizure Freedom (>90% reduction in seizure frequency) - short term follow-up (follow-up: mean 1.5 years; assessed with: proportion of participants achieving >90% reduction in seizure frequency; medical records)												
1[8]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	10/16 (62.5%)	0/0	**proportion 0.62** (0.38 to 0.82)	**620 more per 1,000** (from 820 fewer to 380 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Seizure Freedom (drop-attack freedom) - short term follow-up (follow-up: mean 1.5 years; assessed with: proportion of participants who achieved >90% reduction in seizure frequency; medical records)												
1[8]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	16/16 (100.0%)	0/0	**proportion 1.0** (0.9 to 1.0)	**1,000 more per 1,000** (from 900 more to 1,000 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
All Seizure Freedom - medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants who achieved complete seizure freedom; medical records)												
6[6,7,9,10,11,12]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	26/177 (14.7%)	0/0	**proportion 0.19** (0.13 to 0.26)	**190 more per 1,000** (from 130 more to 260 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Seizure Freedom (>90% reduction in seizure frequency) (follow-up: mean 5 years; assessed with: proportion of participants who achieved >90% reduction in seizure frequency; medical records)												
1[13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	25/34 (73.5%)	0/0	**proportion 0.74** (0.56 to 0.86)	**740 more per 1,000** (from 560 more to 860 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Seizure Freedom (drop-attack freedom) (follow-up: mean 3 years; assessed with: proportion of participants achieving drop-attack freedom; medical records)												
3[9,10,11]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	38/63 (60.3%)	0/0	**proportion 0.57** (0.35 to 0.76)	**570 more per 1,000** (from 350 more to 760 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
All Seizure Freedom - long term follow-up (follow-up: mean 6 years; assessed with: proportion of participants who achieved complete seizure freedom; medical records)												
1[14]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	5/41 (12.2%)	0/0	**proportion 0.12** (0.05 to 0.26)	**120 more per 1,000** (from 50 more to 260 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Seizure Freedom (>90% reduction in seizure frequency) (follow-up: mean 6 years; assessed with: proportion of participants who achieved >90% reduction in seizure frequency; medical records)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
1[15,16]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	9/45 (20.0%)	0/0	**proportion 0.17** (0.04 to 0.51)	**170 more per 1,000** (from 40 more to 510 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Seizure Freedom (drop-attack freedom) (follow-up: mean 5.5 years; assessed with: proportion of participants achieving seizure freedom; medical records)												
2[14,15]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	37/60 (61.7%)	0/0	**proportion 0.62** (0.42 to 0.78)	**620 more per 1,000** (from 420 more to 780 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Permanent, Unexpected Neurological Deficits (follow-up: 2 years; assessed with: proportion of participants experiencing the outcome; medical records)												
1[1]	non-randomised studies	extremely serious[c]	not serious	not serious	very serious[d]	none	0/14 (0.0%)	0/10 (0.0%) 1.0%[d]	**OR 0.72** (0.01 to 39.52)	**0 fewer per 1,000** (from 0 fewer to 0 fewer) **3 fewer per 1,000** (from 10 fewer to 275 more)	⨁◯◯◯ Very low[c,d]	CRITICAL
Permanent, Unexpected Neurological Deficits - medium term follow-up (follow-up: mean 3.3 years; assessed with: proportion of participants who experienced the outcome; medical records)												
6[6,7,9,10,11,13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	5/183 (2.7%)	0/0	**proportion 0.00** (0.00 to 0.04)	**0 fewer per 1,000** (from 0 fewer to 40 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Permanent, Unexpected Neurological Deficits - long term follow-up (follow-up: mean 5.5 years; assessed with: proportion of participants who experienced the outcome; medical records)												
2[14,15]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	0/70 (0.0%)	0/0	**proportion 0.00** (0.00 to 0.01)	**0 fewer per 1,000** (from 0 fewer to 10 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
All Cause Mortality - medium term follow-up (follow-up: 2 years; assessed with: proportion of participants who died; medical records)												
1[3]	non-randomised studies	extremely serious[c]	not serious	not serious	very serious[d]	none	0/24 (0.0%)	0/20 (0.0%)	**OR 0.84** (0.02 to 44.05)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low[c,d]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
								1.0%		**2 fewer per 1,000** (from 10 fewer to 298 more)		
All Cause Mortality - medium term follow-up (follow-up: mean 4.4 years; assessed with: proportion of participants who died; medical records)												
3[7,10,13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	0/74 (0.0%)	0/0	**proportion 0.00** (0.00 to 0.01)	**0 fewer per 1,000** (from 0 fewer to 10 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
All Cause Mortality - short term (follow-up: 1.5 years; assessed with: proportion of participants who died; medical records)												
1[8]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	0/16 (0.0%)	0/0	**proportion 0.00** (0.00 to 0.06)	**0 fewer per 1,000** (from 0 fewer to 60 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or surgical complications (brain infection) - short term follow-up (follow-up: 1.5 years; assessed with: proportion of participants experiencing brain infection; medical records)												
1[8]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	1/16 (6.3%)	0/0	**proportion 0.06** (0.01 to 0.34)	**60 more per 1,000** (from 10 more to 340 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or Surgical Complications (brain infection) - medium term follow-up (follow-up: 4.7 years; assessed with: proportion of participants experiencing brain infection; medical records)												
1[10]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	1/17 (5.9%)	0/0	**proportion 0.06** (0.01 to 0.32)	**60 more per 1,000** (from 10 fewer to 320 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or Surgical Complications (intracranial hemorrhage) - medium term follow-up (follow-up: mean 3.5 years; assessed with: proportion of participants experiencing an intracranial hemorrhage; medical records)												
1[13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	1/34 (2.9%)	0/0	**proportion 0.03** (0.00 to 0.18)	**30 more per 1,000** (from 0 fewer to 180 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or Surgical Complications (serious adverse events) - medium term follow-up (follow-up: 2 years; assessed with: proportion of participants experiencing serious adverse events)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
1[1]	non-randomised studies	extremely serious[c]	not serious	not serious	very serious[g]	none	3/14 (21.4%)	1/10 (10.0%)	**OR 2.45** (0.22 to 27.84)	**114 more per 1,000** (from 76 fewer to 656 more)	⨁◯◯◯ Very low[c,g]	CRITICAL
Medical or Surgical Complications (serious adverse events) - medium term follow-up (follow-up: mean 3.2 years; assessed with: proportion of participants experiencing serious adverse events; medical records)												
7[6,7,9,10,11,12,13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	38/211 (18.0%)	0/0	**proportion 0.18** (0.09 to 0.32)	**180 more per 1,000** (from 90 more to 320 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or Surgical Complications (serious adverse events) - short term follow-up (follow-up: mean 1 years; assessed with: proportion of participants experiencing serious adverse events; medical records)												
2[5,8]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	3/36 (8.3%)	0/0	**proportion 0.09** (0.03 to 0.25)	**90 more per 1,000** (from 30 more to 250 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Medical or Surgical Complications (serious adverse events) - long term follow-up (follow-up: mean 6 years; assessed with: proportion of participants with serious adverse events; medical records)												
3[14,15,16]	non-randomised studies	extremely serious[e]	serious[h]	not serious	serious[f]	none	25/86 (29.1%)	0/0	**proportion 0.17** (0.01 to 0.87)	**170 more per 1,000** (from 10 more to 870 more)	⨁◯◯◯ Very low[e,f,h]	CRITICAL
Quality of Life (improvement in quality of life and attention) - medium term follow-up (follow-up: 2 years; assessed with: proportion of participants with improvement in quality of life; medical records)[i]												
1[3]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[b]	none	20/24 (83.3%)	17/20 (85.0%)	**OR 0.88** (0.17 to 4.51)	**17 fewer per 1,000** (from 359 fewer to 112 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Quality of Life (improvement in quality of life/overall daily function) - medium term (follow-up: mean 3.8 years; assessed with: proportion of participants with improvement; medical records)												
4[6,7,9,17]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	90/155 (58.1%)	0/0	**proportion 0.58** (0.50 to 0.66)	**580 more per 1,000** (from 500 more to 650 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Quality of Life (improvement in quality of life/overall daily function) - long term (follow-up: mean 6.3 years; assessed with: proportion of participants with improvement)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Callosotomy	VNS	Relative (95% CI)	Absolute (95% CI)		
2[15,16]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	26/45 (57.8%)	0/0	**proportion 0.58** (0.43 to 0.71)	**580 more per 1,000** (from 430 more to 710 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Neuropsychological Outcomes (developmental status) - short term follow-up (follow-up: 1 years; assessed with: proportion of participants with improved developmental status compared to baseline; based on the results of interviews and a simple questionnaire)												
1[5]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	2/20 (10.0%)	0/0	**proportion 0.10** (0.03 to 0.32)	**100 more per 1,000** (from 30 more to 320 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Neuropsychological Outcomes (IQ) - medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants with improvement in IQ scales compared to baseline)												
2[6,10]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	28/76 (36.8%)	0/0	**proportion 0.35** (0.21 to 0.53)	**350 more per 1,000** (from 210 more to 530 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Neuropsychiatric Outcomes (behaviour) - short term follow-up (follow-up: 1 years; assessed with: Child behavior check list score (CBCL), scores ≥64 indicated significant clinical behavioral problems; parent/caregiver reported; Scale from: 0 to 100)												
1[8]	non-randomised studies	extremely serious[e]	not serious	not serious		none	16	0	-	**0** (0 to 0)	-[e]	CRITICAL
Neuropsychiatric Outcomes (behaviour improvement) (follow-up: mean 3 years; assessed with: proportion of participants with improved behaviour; as reported by parents/caregivers)												
3[10,11,13]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	41/65 (63.1%)	0/0	**proportion 0.63** (0.50 to 0.74)	**630 more per 1,000** (from 500 more to 740 more)	⨁◯◯◯ Very low[e,f]	CRITICAL
Social Outcomes (starting education) (follow-up: mean 7.3 years; assessed with: proportion of participants who started special education classes; medical records)												
1[16]	non-randomised studies	extremely serious[e]	not serious	not serious	serious[f]	none	8/16 (50.0%)	0/0	**proportion 0.50** (0.27 to 0.73)	**500 more per 1,000** (from 250 more to 730 more)	⨁◯◯◯ Very low[e,f]	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Rated down two levels because of lack of adjustment for important confounders in the three included comparative observational studies.
b. Rated down one level for imprecision because the the confidence interval is very wide and crosses the line of no effect (null), suggesting the possibility of a benefit and a harm.
c. Rated down two levels for risk of bias due to lack of adjustment of important confounders in the single included study.
d. Rated down two levels for imprecision because the confidence interval is extremely wide, crossing the line of no effect (null), which suggests the possibility of an important harm and important benefit.
e. Rated down three levels for risk of bias due to lack of a comparator group and critical risk of confounding from prognostic imbalances.

f. Rated down one level for imprecision because the optimal information size (OIS=250) is not met, which introduces risk of random error.
g. Rated down to levels for imprecision because the confidence interval is very wide and crosses the line of no effect (null), suggesting the possibility of important harm and important benefit.
h. Rated down for inconsistency one level. There is considerable statistical heterogeneity (I2=93%) that cannot be explained.
i. The quality of life information was gathered using QOLIE-31, and the attention-level evaluation was based on the attention-related part of the SNAP-IV questionnaire12 (18 items), to which an extra question regarding verbal fluency was added.

References

1. You SJ, Kang HC, Ko TS, Kim HD, Yum MS, Hwang YS, Lee JK, Kim DS, Park SK. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. Brain Dev. 2008;30(3):195-9. Doi: 10.1016/j.braindev.2007.07.013.
2. Otsuki T, Kim HD, Luan G, Inoue Y, Baba H, Oguni H, Hong SC, Kameyama S, Kobayashi K, Hirose S, Yamamoto H, Hamano S, Sugai K; FACE Study Group. Surgical versus medical treatment for children with epileptic encephalopathy in infancy and early childhood: Results of an international multicenter cohort study in Far-East Asia (the FACE study). Brain Dev. 2016;38(5):449-60. Doi: 10.1016/j.braindev.2015.11.004.
3. Cukiert A, Cukiert CM, Burattini JA, Lima AM, Forster CR, Baise C, Argentoni-Baldochi M. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. Seizure. 2013;22(5):396-400. Doi: 10.1016/j.seizure.2013.02.009.
4. Kim HJ, Kim HD, Lee JS, Heo K, Kim DS, Kang HC. Long-term prognosis of patients with Lennox—Gastaut syndrome in recent decades. Epilepsy Res. 2015;110:10-9. Doi: 10.1016/j.eplepsyres.2014.11.004.
5. Na JH, Kim HD, Lee YM. Effective application of corpus callosotomy in pediatric intractable epilepsy patients with mitochondrial dysfunction. Ther Adv Neurol Disord. 2022; 21;15:17562864221092551. Doi: 10.1177/17562864221092551.
6. Liang S, Li A, Jiang H, Meng X, Zhao M, Zhang J, Sun Y. Anterior corpus callosotomy in patients with intractable generalized epilepsy and mental retardation. Stereotact Funct Neurosurg. 2010;88(4):246-52. Doi: 10.1159/000315462.
7. Liang S, Zhang S, Hu X, Zhang Z, Fu X, Jiang H, Xiaoman Y. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. Eur J Paediatr Neurol. 2014 ;18(6):670-6. Doi: 10.1016/j.ejpn.2014.05.004.
8. Chandra SP, Kurwale NS, Chibber SS, Banerji J, Dwivedi R, Garg A, Bal C, Tripathi M, Sarkar C, Tripathi M. Endoscopic-Assisted (Through a Mini Craniotomy) Corpus callosotomy combined with anterior, hippocampal, and posterior commissurotomy in Lennox-Gastaut Syndrome: a pilot study to establish its safety and efficacy. Neurosurgery. 2016;78(5):743-51. Doi: 10.1227/NEU.0000000000001060.
9. Shim KW, Lee YM, Kim HD, Lee JS, Choi JU, Kim DS. Changing the paradigm of 1-stage total callosotomy for the treatment of pediatric generalized epilepsy. J Neurosurg Pediatr. 2008;2(1):29-36. Doi: 10.3171/PED/2008/2/7/029.
10. Rathore C, Abraham M, Rao RM, George A, Sankara Sarma P, Radhakrishnan K. Outcome after corpus callosotomy in children with injurious drop attacks and severe mental retardation. Brain Dev. 2007;29(9):577-85. Doi: 10.1016/j.braindev.2007.03.008.
11. Iwasaki M, Uematsu M, Nakayama T, Hino-Fukuyo N, Sato Y, Kobayashi T, Haginoya K, Osawa S, Jin K, Nakasato N, Tominaga T. Parental satisfaction and seizure outcome after corpus callosotomy in patients with infantile or early childhood onset epilepsy. Seizure. 2013;22(4):303-5. Doi: 10.1016/j.seizure.2013.01.005.
12. Carmant L, Holmes GL, Lombroso CT. Outcome following corpus callosotomy. J Epilepsy. 1998;11(4):224-228. https://doi.org/10.1016/S0896-6974(98)00022-X
13. Cendes F, Ragazzo PC, da Costa V, Martins LF. Corpus callosotomy in treatment of medically resistant epilepsy: preliminary results in a pediatric population. Epilepsia. 1993;34(5):910-7. Doi: 10.1111/j.1528-1157.1993.tb02111.x.
14. Ukishiro K, Osawa SI, Iwasaki M, Kakisaka Y, Jin K, Uematsu M, Yamamoto T, Tominaga T, Nakasato N. Age-related recovery of daily living activity after 1-stage complete corpus callosotomy: a retrospective analysis of 41 cases. Neurosurgery. 2022;90(5):547-551. Doi: 10.1227/neu.0000000000001871.
15. Yang PF, Lin Q, Mei Z, Chen ZQ, Zhang HJ, Pei JS, Tian J, Jia YZ, Zhong ZH. Outcome after anterior callosal section that spares the splenium in pediatric patients with drop attacks. Epilepsy Behav. 2014;36:47-52. Doi: 10.1016/j.yebeh.2014.04.019.
16. Turanli G, Yalnizoğlu D, Genç-Açikgöz D, Akalan N, Topçu M. Outcome and long term follow-up after corpus callosotomy in childhood onset intractable epilepsy. Childs Nerv Syst. 2006;22(10):1322-7. Doi: 10.1007/s00381-006-0045-3.
17. Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia. 2001 ;42(1):67-71. doi: 10.1046/j.1528-1157.2001.081422.x.

Evidence Profile, PICO IV-A: Laser Interstitial Thermal Therapy compared to Surgical Resection in patients with hypothalamic hamartoma

Recommendation IV-A: The AES/CNS guideline panel suggests/recommends for the use of LITT compared to surgical resection in people with hypothalamic hamartoma (paradigmatic situation due to potential for catastrophic harm) (**Strong** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Seizure freedom (Engel I) - pediatric population, short term follow-up (follow-up: mean 1.2 years; assessed with: proportion of participants achieving seizure freedom, medical records)[a]									
3[1,2,3]	non-randomised studies	extremely serious[b]	not serious	serious[c]	serious[d]	none	In three studies 156 participants, 112 (71.79%) were classified as Engel at 1.2 years after undergoing MRgLITT.	⨁◯◯◯ Very low[b,c,d]	CRITICAL
Seizure Freedom (ILAE 1) - mix population, short term follow-up (follow-up: mean 1.4 years; assessed with: proportion of participants achieving seizure freedom, medical records)[a]									
1[4]	non-randomised studies	extremely serious[b]	not serious	serious[e]	serious[d]	none	In one study with 18 participants, 11 (61.1%) were classified as Engel I at 1.4 years after undergoing LITT.	⨁◯◯◯ Very low[b,d,e]	CRITICAL
Seizure freedom (free of gelastic seizures) - mix population, short term follow-up (follow-up: mean 1 years; assessed with: proportion of participants achieving freedom of gelastic seizures, medical records)[a]									
1[5]	non-randomised studies	extremely serious[b]	not serious	not serious[f]	serious[d]	none	In one study with 71 participants, 66 (93%) were classified as Engle I at 1 year after undergoing MRgLITT.	⨁◯◯◯ Very low[b,d,f]	CRITICAL
Permanent, unexpected neurological deficit - pediatric population, short term follow-up (follow-up: mean 1.2 years; assessed with: proportion of participants experiencing the event, medical records)[a]									
2[1,2]	non-randomised studies	extremely serious[b]	not serious	serious[g]	serious[d]	none	In two studies with 105 included participants, there were 2 patients with permanent neurological deficits, which includes memory dysfunction and persistent memory disturbance. (2%)	⨁◯◯◯ Very low[b,d,g]	CRITICAL
Permanent, unexpected neurological deficit - mix population, short term follow-up (follow-up: mean 1.4 years; assessed with: proportion of participants experiencing the event, medical records)[a]									
1[4]	non-randomised studies	extremely serious[b]	not serious	serious[h]	serious[d]	none	In one study with 18 participants, 4 of them experienced a permanent neurological deficit (no further description). (22%)	⨁◯◯◯ Very low[b,d,h]	CRITICAL
All cause mortality - pediatric population, short term follow-up (follow-up: mean 1 years; assessed with: proportion of participants who died, medical records)[a]									
2[2,3]	non-randomised studies	extremely serious[b]	not serious	serious[i]	serious[d]	none	In two studies with 109 participants, 0 deaths were reported at 1 year follow-up. (0%)	⨁◯◯◯ Very low[b,d,i]	CRITICAL
Medical or surgical complications; adverse and serious adverse events - pediatric population, short term follow-up (follow-up: mean 1.2 years; assessed with: proportion of participants experiencing the event, medical records)[a]									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
5[1,2,3,4,5]	non-randomised studies	extremely serious[b]	not serious	serious[i]	serious[d]	none	**Weight gain (Yao 2022,)** One study with 47 participants reported weight gain in 2 (4.25%) of them. **Endocrine outcome - TSH and cortisol disturbances, endocrinological side effects (Yao 2022, Boerwinkle 2018)** In two studies with 98 participants, 2 (2.04%) of them reported endocrinological disturbances. **Disturbance of sodium metabolism (Gadgil 2020)** In one study with 58 participants, 4 (6.9%) of them reported sodium metabolism disturbances. **Respiratory failure (Gadgil 2020)** In one study with 58 participants, 1 (1.72%) of them had respiratory failure. **Neurological and psychiatric side effects (Boerwinkle 2018)** In one study with 51 participants, there were no (0%)neurological or neuropsychiatric side effects.	⨁◯◯◯ Very low[b,d,j]	CRITICAL
Medical or surgical complications; adverse and serious adverse events - mix population, short term follow-up (follow-up: mean 1.2 years; assessed with: proportion of participants experiencing an event, medical records)[a]									
2[4,5]	non-randomised studies	extremely serious[b]	not serious	serious[k]	serious[d]	none	**Newly diagnosed hypothyroidism (Xu 2018)** In one study wtih 18 participants, one (5.6%) reported hypothyroidism of new diagnosis. **New subjective short-term memory issues, weight gain, or increased appetite (Xu 2018)** In one study with 18 participants none (0%)of the participants reported any of these events. **Worsened diabetes insipidus (Curry 2018)** In one study with 71 participants, one (1.41%) of them reported worsening of diabetes insipidus.	⨁◯◯◯ Very low[b,d,k]	CRITICAL
Other outcomes - not measured[l]									
-	-	-	-	-	-	-		-	

CI: confidence interval

Explanations

a. Short term follow-up : ≥1 year- <2 years.
b. Rated down three level because of critical risk of bias due to concerns about prognostic imbalance arising from the lack of a comparison group.
c. Rated down one level for indirectness because all three included studies enrolled participants with a history of prior epilepsy surgery, ranging from 13% to 33% of participants.
d. Rated down one level for imprecision because the optimal information size is not met (OIS = 300 events).
e. Rated down one level for indirectness because the single included study enrolled participants with a previous surgical procedure (33%).
f. Rated down one level for indirectness because 25% of the participants included in the single study had a previous surgical intervention.
g. Rated down one level for indirectness because 23% of the total included participants had a previous surgical procedure.
h. Rated down one level for indirectness because 6/16 (33%) participants had a previous surgical procedure (5/18 had undergone surgery, 2/18 had undergone radiosurgery).
i. Rated down one level for indirectness because 15/109 (14%) of the in included participants had a previous surgical procedure.

j. Rated down one level for indirectness because two of the five included studies (Yao 2022 and Gadgil 2020) enrolled patients with a previous surgical procedure (15.38% of all participants reporting this outcome).
k. Rated down one level for indirectness because 25% of the total included participants in the two studies had a previous surgical procedure.
l. Other outcomes not measured: SUDEP, medical or surgical complication (brain infection, intracranial hemorrhage with neurological deficits), neuropsychological outcomes (verbal memory, receptive language, verbal fluency, naming, IQ,), neuropsychiatric outcomes (personality changes, depression, anxiety, psychosis), social outcomes (employment, driving).

References

1. Yao Y, Wang X, Hu W, Zhang C, Sang L, Zheng Z, Mo J, Liu C, Qiu J, Shao X, Zhang J, Zhang K. Magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: surgical approach and treatment outcomes. *J Clin Med*. 2022;11(21):6579. doi: 10.3390/jcm11216579.
2. Gadgil N, Lam S, Pan IW, LoPresti M, Wagner K, Ali I, Wilfong A, Curry DJ. Staged magnetic resonance-guided laser interstitial thermal therapy for hypothalamic hamartoma: analysis of ablation volumes and morphological considerations. *Neurosurgery*. 2020;86(6):808-816. doi: 10.1093/neuros/nyz378.
3. Boerwinkle VL, Foldes ST, Torrisi SJ, Temkit H, Gaillard WD, Kerrigan JF, Desai VR, Raskin JS, Vedantam A, Jarrar R, Williams K, Lam S, Ranjan M, Broderson JS, Adelson D, Wilfong AA, Curry DJ. Subcentimeter epilepsy surgery targets by resting state functional magnetic resonance imaging can improve outcomes in hypothalamic hamartoma. *Epilepsia.* 2018;59(12):2284-2295. doi: 10.1111/epi.14583.
4. Xu DS, Chen T, Hlubek RJ, Bristol RE, Smith KA, Ponce FA, Kerrigan JF, Nakaji P. Magnetic Resonance imaging-guided laser interstitial thermal therapy for the treatment of hypothalamic hamartomas: a retrospective review. *Neurosurgery*. 2018;83(6):1183-1192. doi: 10.1093/neuros/nyx604.
5. Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. *Epilepsy Res*. 2018;142:131-134. doi: 10.1016/j.eplepsyres.2018.03.013.

Evidence Profile, PICO IV-B: Radiosurgery compared to Surgical Resection in patients with hypothalamic hamartoma

Recommendation IV-B: The AES/CNS guideline panel suggests either the use of radiosurgery or surgical resection in people with hypothalamic hamartoma. (**Conditional** Recommendation, **Very Low** Certainty of Evidence).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
Seizure freedom (Engel I) - adult population, short follow-up time (follow-up: mean 1.2 years; assessed with: proportion of participants with seizure freedom, medical records)[a]												
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 26 participants, none of the participants experienced seziure freedom Engel I at 1 year after radiosurgery. [d]				⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure freedom (Engel I) - pediatric population, medium term follow-up (follow-up: mean 2.28 years; assessed with: proportion of participants with seizure freedom; medical records)[e]												
1[2]	non-randomised studies	extremely serious[f]	not serious	serious[g]	serious[c]	none	0/4 (0.0%)	4/10 (40.0%)	not estimable[h]	**400 fewer per 1,000** (from 790 fewer to 10 more)	⨁◯◯◯ Very low[c,f,g]	CRITICAL
Seizure freedom (Engel 1) - pediatric population, medium term follow-up (follow-up: mean 2.35 years; assessed with: proportion of participants with seizure freedom, medical records)[e]												
2[3,4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In two studies with 34 participants, 10 (29.41%) of them experienced seziure freedom Engel I at 2.35 years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure freedom (Engel I) - adult population, medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants with seizure freedom, medical records)[e]												
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[i]	serious[c]	none	2/4 (50.0%)	8/29 (27.6%)	**OR 2.62** (0.31 to 21.92)	**224 more per 1,000** (from 170 fewer to 617 more)	⨁◯◯◯ Very low[c,f,i]	CRITICAL
Seizure freedom (Engel I) - adult population, medium term follow-up (follow-up: mean 2 years; assessed with: proportion of participants with seizure freedom, medical records)[e]												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 24 participants, 11 of them experienced seizure freedom Engel 1 at 2 years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure freedom (complete seizure freedom) - mix population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants with seizure freedom, medical records)[e]												
1[7]	non-randomised studies	extremely serious[b]	not serious	not serious	not serious	none	In one study with 27 participants, 10 (37%) experienced complete seizure freedom at 3 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
Seizure freedom (Engel I) - mix population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants with seizure freedom, medical records)												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 48 participants, 15 (31.25%) experienced seizure freedom Engel 1 at 3 years after undergoing radiosurgery. [j]				⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure freedom (Engel I) - adult population, long term follow-up (follow-up: mean 9.8 years; assessed with: proportion of participants with seizure freedom, medical records)[k]												
1[9]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 10 participants, 3 (30%) experienced seizure freedom Engel I at 9.8 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Seizure freedom (Engel I) - mix population, long term follow-up (follow-up: mean 6 years; assessed with: proportion of participants with seizure freedom; medical records)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 48 participants, 19 (39.58%) of them experienced seizure freedom Engel I at 6 years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, unexpected neurological deficits - pediatric population, short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event, medical records)												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 participants, none (0%) experienced a permanent unexpected neurological deficit at 1.15 years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, unexpected neurological deficit - pediatric, medium term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event; medical records)												
1[4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 10 participants, none (0%) of them reported any permanent, unexpected neurological deficit 2.7 years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, unexpected neurological deficit - adult population, medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants experiencing the event, medical records)[e]												
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[i]	serious[c]	none	0/4 (0.0%)	1/32 (3.1%)	not estimable[i]	**30 fewer per 1,000** (from 300 fewer to 240 more)	⨁◯◯◯ Very low[c,f,i]	CRITICAL
Permanent, unexpected neurological deficit - mix population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants experiencing the event, medica records)[e]												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 24 particpants, none (0%) of them experienced a permanent, unexpected neurological deficit 3 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Permanent, unexpected neurological deficit - mix population, long term follow-up (follow-up: mean 7.8 years; assessed with: proportion of participants experiencing the event, medical records)[k]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
2[8,9]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	**Permanent side effects (no further description) (Regis 2017)** Of 48 participants included, none of them (0%) experienced a permanent, unexpected neurological deficit 6 years after undergoing radiosurgery. **Neurological complication (no further description) (Romanelli 2022)** Of 10 particpants included, none of them (0%) experienced a permanent, unexpected neurlogical deficit 9.8 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
All-cause mortality - pediatric population, short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants who died; medical records)[a]												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 participants, 0 deaths were rerported at 1 year after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
All-cause mortality - adult population; medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants who died; medical records)[e]												
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[l]	serious[c]	none	0/4 (0.0%)	4/36 (11.1%)	not estimable[m]	**110 fewer per 1,000** (from 390 fewer to 170 more)	⨁◯◯◯ Very low[c,f,i]	CRITICAL
All-cause mortality - mix population, medium term follow-up (follow-up: mean 3.5 years; assessed with: proportion of participants who died; medical records)[e]												
2[6,10]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In two studies with 63 participants, 2 (3.17%) died at 3.5 year follow-up after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
All-cause mortality - mix population, long term follow-up (follow-up: mean 5.9 years; assessed with: proportion of participants who died; medical records)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 48 participants, 0 deaths were reported at 5.9 years follow-up after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
SUDEP - mix population, long term follow-up (follow-up: mean 5.9 years; assessed with: proportion of participants with SUDEP; medical records)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 48 particpants, there were 0 events o SUDEP at 5.9 years follow-up after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (brain infection) - pediatric population; short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event; medical records)[a]												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 participants, 0 (0%) reported brain infection 1.15 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (brain infection) - adult population. medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants experiencing the event; medical records)[e]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[i]	serious[c]	none	0/4 (0.0%)	2/36 (5.6%)	not estimable[n]	**60 fewer per 1,000** (from 330 fewer to 220 more)	⨁◯◯◯ Very low[c,f,i]	CRITICAL
Medical or surgical complications (intracranial hemorrhage) - short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event; medical records)[a]												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 participants, 0 (0%) reported an intracranial hemorrhage at 1.15 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (intracranial hemorrhage) - medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants experiencing the event; medical records)[e]												
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[i]	serious[c]	none	0/4 (0.0%)	6/36 (16.7%)	not estimable[o]	**170 fewer per 1,000** (from 460 fewer to 120 fewer)	⨁◯◯◯ Very low[c,f,i]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - children population, short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event; medical records)[a]												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 particpants, 1 (6.67%) reported transient increases in the frequency of gelastic seizures and 3 (20%) reported weight gain at 1.15 years after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - children population, medium term follow-up (follow-up: mean 2.7 years; assessed with: proportion of participants experiencing the event; medical records)[e]												
1[4]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 19 participants, 0 (0%) reported endocrine, visual, neurological or hypothalamic disorders de novo after undergoing radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - adult population, medium term follow-up (follow-up: mean 4.8 years; assessed with: proportion of participants experiencing the event; medical records)[e]												
1[5]	non-randomised studies	extremely serious[f]	not serious	serious[i]	serious[c]	none	In one study with 40 participants, 4 underwent radiosurgery and 36 surgical resection: • 0/4 (0%) and 1/36 (2.78%) reported transient right hemiparesia (40 participants provided outcome data) [RD -0.03 (95% CI, -0.30 to 0.24)]. • 0/4 (0%) and 11/32 (34.38%) reported hormonal problems (decreased libido in 5 patients, sodium abnormalities in 4, and temperature regulation disturbances in 2 patients, one of whom also had thyroid dysfunction); 36 participants provided outcome data. [RD -0.34 (95% CI, -0.65 to -0.03)]. • 0/4 (0%) and 20/32 (62.5%) reported weight gain (36 participants provided outcome data) [RD -0.63 (95% CI, -0.94 to -0.31)].				⨁◯◯◯ Very low[c,f,i]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - adult population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants experiencing the event)[e]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
1[7]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 27 participants: • 3 (11.11%) reported transient poikilothermia • 0 (0%) reported no thyroxyne blood level lowering and no hypernatremia. • 0 (%) reported weight gain • 0 (0%) reported new visual acuity or visual field deficits				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - mix population, medium term follow-up (follow-up: mean 3.5 years; assessed with: proportion of participants experiencing the event; medical records)[e]												
2[6,10]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 39 participants (Tripathi 2024): • 1 (2.56%) reported poikilothermia • 2 (5.13%) reported GH and cortisol deficit In one study with 24 participants (Schulze-Bonhage 2008) • 4 (16.67%) reported weight again • 5 (20.83%) reported brain edema (MRI at 3 months post-radiosurgery)				⨁◯◯◯ Very low[b,c]	CRITICAL
Medical or surgical complications (adverse and serious adverse events) - mix population, long term follow-up (follow-up: mean 5.9 years; assessed with: proportion of participants experiencing the event; medical records)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	not serious	none	In one study with 48 participants: • 3 (6.25%) reported transient poikilothermia • 8 (16.67%) reported transient seizure increase • 0 (0%) reported endocrinologic side effects (especially no morbid obesity, no diabetes insipidus)				⨁◯◯◯ Very low[b]	CRITICAL
Quality of life - adult population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants who improved quality of life; parental and clinician report)[e]												
1[7]	non-randomised studies	extremely serious[b]	not serious	not serious	not serious	none	In one study with 27 participants, the study authors report the followin: "On the basis of parental reports and our own subjective observations, the children operated on except one (who was a failure for seizure control) exhibited marked improvements in behavior, school performance, and quality of life. The improvement was dramatic in nine of these patients."				⨁◯◯◯ Very low[b]	CRITICAL
Neuropsychological outcomes (verbal memory) - adult population, short term follow-up (follow-up: mean 1.15 years; assessed with: The Verbal Learning and Memory Test - VLMT trial 7; score with z-scores; higher scores mean better verbal memory)[a]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
1[1]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[p]	none	In one study with 26 participants, verbal memory was assessed with the Verbal Learning and Memory Test - VLMT trial 7. At short term follow-up, there was little to no difference, with a mean change from baseline -0.7 (95% CI -1.45 to 0.05).				⨁◯◯◯ Very low[b,p]	CRITICAL
Neuropsychological outcomes (IQ) - adult population, short term follow- up (follow-up: mean 1.15 years; assessed with: standardized z-scores; medical records)[aq]												
1[1]	non-randomised studies	extremely serious[c]	not serious	not serious	serious[c]	none	In one study with 26 participants, cognitive performance was reported as follows: - Comparison of standard scores (z-scores) prior to and after surgery showed no significant changes but showed a trend of decrease in visual learning as well as a trend of increase in selective attention test performance. - Categorical changes in ≥ 1 SD in cognitive performance: • In verbal learning and relative verbal memory loss, more patients showed decreased performance (42.3% and 50%, respectively) compared to selective attention (3.8%, N = 1). • In several cognitive test parameters (verbal delayed recall, verbal recognition, visual learning, selective attention, verbal short-term memory), more than half of the patients remained unchanged in their performance after stereotactic radiosurgery, and even improvements were observed.				⨁◯◯◯ Very low[c]	CRITICAL
Neuropsychological outcomes (verbal memory) - mix population, medium term follow-up (follow-up: mean 2 years; assessed with: standardized neuropsychological test battery comprising the domains of attention, verbal and visuospatial memory, visuoconstruction, visual planning, naming, and verbal phonemic fluency; medical records)[e]												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 17 participants, change in ≥1 SD after radiosurgery were reported as follows: • 5 (29.41%) declined, • 10 (58.82%) remained unchanged, and • 2 (11.76%) improved.				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological outcomes (verbal fluency) - mix population, medium term follow-up (follow-up: mean 2 years; assessed with: standardized neuropsychological test battery comprising the domains of attention, verbal and visuospatial memory, visuoconstruction, visual planning, naming, and verbal phonemic fluency; medical records)												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 18 participants providing outcome data, change in ≥1 SD after radiosurgery were reported as follows: • 1 (5.5%) declined, • 15 (83.33%) remained unchanged, • 2 (11.11%) improved				⨁◯◯◯ Very low[b,c]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
Neuropsychological outcome (naming) - mix population, medium term follow-up (follow-up: mean 2 years; assessed with: standardized neuropsychological test battery comprising the domains of attention, verbal and visuospatial memory, visuoconstruction, visual planning, naming, and verbal phonemic fluency; medical records)[e]												
1[6]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 16 participants providing outcome data, change in ≥ 1 SD after radiosurgery were reported as follows: • 1 (6.25%) declined, • 14 (87.5%) remained unchanged, • 1 (5.88%) improved				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological outcome (verbal memory) - mix population, long term follow-up (follow-up: mean 5.9 years; assessed with: Wechsler Memory Scale III - verbal delayed recall; standardized z-scores; medical records)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 39 participants, change in ≥ 1 SD after radiosurgery were reported as follows:0 86 14 • 0 (0%) declined • 34 (86%) remained unchanged • 5 (14%) improved				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychological outcome (receptive langage) - mix population, long term follow-up (follow-up: mean 3 years; assessed with: Wechsler intelligence scales - verbal comprehension index; higher scores indicate better verbal comprehension; standardized z-scores)[k]												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[p]	none	In one study with 39 participants, there was little to no improvement in receptive language, (IQv index) with a mean change score from baseline of 0.85 (95% CI, -3.84 to 5.54) at 3 years follow-up.				⨁◯◯◯ Very low[b,p]	CRITICAL
Neuropsychological outcome (IQ) - mix population, long term follow-up (follow-up: mean 3 years; assessed with: Wechsler Intelligence Scale; standardized z-scores; medical records)												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[p]	none	In one study with 39 participants, there was an improvement in cognition, with and IQ mean change score from baseline of 2.95 (95% CI, -0.33 to 6.23) at 3 years follow-up.				⨁◯◯◯ Very low[b,p]	CRITICAL
Neuropsychiatric outcomes (behavior changes) - pediatric population, short term follow-up (follow-up: mean 1.15 years; assessed with: proportion of participants experiencing the event; medical records)[a]												
1[3]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 15 participants (Schulze-Bonhage 2007), behaviour changes were reported as follows: "According to parent's report, 1 patient with Engel II outcome who also showed improved vigilance after treatment, was reported to be more difficult to handle and to react more often aggressively. No other newly emerging psychiatric problems were noted."				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychiatric outcome (personality changes) - mix population, medium term follow-up (follow-up: mean 3 years; assessed with: proportion of participants experiencing an increase in aggressive behavior; parental and clinician observations)[e]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiosurgery	Surgical Resection	Relative (95% CI)	Absolute (95% CI)		
1[7]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 27 participants, 16 (60%) reported an increase in aggressive behavior and 10 (37%) reported marked inhibition three years after radiosurgery.				⨁◯◯◯ Very low[b,c]	CRITICAL
Neuropsychiatric outcome (personality changes) - mix population, long term follow-up (follow-up: mean 5.9 years; assessed with: proportion of participants experiencing the event; medical records)												
1[8]	non-randomised studies	extremely serious[b]	not serious	not serious	serious[c]	none	In one study with 34 participants, 21 (61.76%) had severe heteroaggressive rage before radiosurgery. Among thise gorup, 10 (47.62%) were cured, 8 (38.1%) improved, 2 (9.5%) stable, and one (4.76%) continued to worsen at 5.9 years after undergoing radiosugery.				⨁◯◯◯ Very low[b,c]	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a. Short term follow-up: ≥1 year- <2 years.
b. Rated down three levels for risk of bias due to prognosis imbalance arising from a lack of a comparison group.
c. Rated down one level for imprecision because the optima information size is not met (OIS = 300 events).
d. "About one year after seed implantation, 4 out of 26 patients with HHs had one to three seizure days per year (± auras, class 3), and three of these patients showed more than 90% seizure reduction. Two of them had been completely seizure-free for the past 3 months, but formally, no patient could be classified as class 1 or 2 after one year as there was a running down of seizures during the course of the first months following interstitial radiosurgery."
e. Medium term follow-up: ≥ 2 years to ≤ 5 years.
f. Rated down three levels due to lack of adjustment for important confounders.
g. Of the 10 participants, 1 underwent surgical resection and 9 endoscopic disconnection.
h. We used risk difference for analysis RD (95% CI) = -0.40 (-0.79 , -0.01).
i. Rated down one level for indirectness because 40% of the included participants had undergone a previous surgical procedure.
j. One study, Tripathi 2024, included 39 participants and 18 (46.15%) reported having seizure freedom Engel II and Engel II.
k. Long term follow-up: > 5 years.
l. We used risk difference for analysis (RD). RD (95% CI) = -0.03 (-0.30 to 0.24).
m. We used risk difference (RD) for analysis. RD (95% CI) = -0.11 (-0.39 to 0.17).
n. We used risk difference (RD) for analysis. RD (95% CI) = -0.06 (-0.33 to 0.22).
o. We used risk difference (RD) for analysis. RD (95% CI) = -0.17 (-0.46 to 0.12).
p. Rated down one level for imprecision because the optimal information size is not met (OIS = 400 participants per group).
q. In order to test for general intelligence, the German adaptations of either the Wechsler Adult Intelligence Scale—Revised (N = 13), the Wechsler Intelligence Scale for Children (WISC-III, N = 2), the a German multiple choice vocabulary test (MWT-B, N = 8) were applied.

References

1. Wagner K, Buschmann F, Zentner J, Trippel M, Schulze-Bonhage A. Memory outcome one year after stereotactic interstitial radiosurgery in patients with epilepsy due to hypothalamic hamartomas. Epilepsy Behav. 2014;37:204-9. doi: 10.1016/j.yebeh.2014.06.031.
2. Shim KW, Chang JH, Park YG, Kim HD, Choi JU, Kim DS. Treatment modality for intractable epilepsy in hypothalamic hamartomatous lesions. Neurosurgery. 2008;62(4):847-56; discussion 856. doi: 10.1227/01.neu.0000318170.82719.7c.
3. Schulze-Bonhage A, Ostertag C. Treatment options for gelastic epilepsy due to hypothalamic hamartoma: interstitial radiosurgery. Semin Pediatr Neurol. 2007;14(2):80-7. doi: 10.1016/j.spen.2007.03.006.
4. Savateev AN, Golanov AV, Saushev DA, Osinov IK, Kostyuchenko VV, Dalechina AV, Melikian AG, Vlasov PA, Mazerkina NA, Makashova ES. Stereotaksicheskaya radiokhirurgiya pri epilepsii u patsientov s gamartomoi gipotalamusa [Stereotactic radiosurgery for epilepsy related to hypothalamic hamartoma]. Zh Vopr Neirokhir Im N N Burdenko. 2022;86(4):14-24. Russian. doi: 10.17116/neiro20228604114.
5. Drees C, Chapman K, Prenger E, Baxter L, Maganti R, Rekate H, Shetter A, Bobrowitz M, Kerrigan JF. Seizure outcome and complications following hypothalamic hamartoma treatment in adults: endoscopic, open, and Gamma Knife procedures. J Neurosurg. 2012;117(2):255-61. doi: 10.3171/2012.5.JNS112256.
6. Schulze-Bonhage A, Trippel M, Wagner K, Bast T, Deimling FV, Ebner A, Elger C, Mayer T, Keimer R, Steinhoff BJ, Spreer J, Fauser S, Ostertag C. Outcome and predictors of interstitial radiosurgery in the treatment of gelastic epilepsy. Neurology. 2008;71(4):277-82. doi: 10.1212/01.wnl.0000318279.92233.82.

7. Régis J, Scavarda D, Tamura M, Nagayi M, Villeneuve N, Bartolomei F, Brue T, Dafonseca D, Chauvel P. Epilepsy related to hypothalamic hamartomas: surgical management with special reference to gamma knife surgery. Childs Nerv Syst. 2006;22(8):881-95. doi: 10.1007/s00381-006-0139-y.
8. Régis J, Lagmari M, Carron R, Hayashi M, McGonigal A, Daquin G, Villeneuve N, Laguitton V, Bartolomei F, Chauvel P. Safety and efficacy of Gamma Knife radiosurgery in hypothalamic hamartomas with severe epilepsies: A prospective trial in 48 patients and review of the literature. Epilepsia. 2017;58 Suppl 2:60-71. doi: 10.1111/epi.13754.
9. Romanelli P, Tuniz F, Fabbro S, Beltramo G, Conti A. Image-guided LINAC radiosurgery in hypothalamic hamartomas. Front Neurol. 2022;13:909829. doi: 10.3389/fneur.2022.909829.
10. Tripathi M, Sheehan JP, Niranjan A, Ren L, Pikis S, Lunsford LD, Peker S, Samanci Y, Langlois AM, Mathieu D, Lee CC, Yang HC, Deng H, Rai A, Kumar N, Sahu JK, Sankhyan N, Deora H. Gamma knife radiosurgery for hypothalamic hamartoma: a multi-institutional retrospective study on safety, efficacy, and complication profile. Neurosurgery. 2025;96(2):426-437. doi: 10.1227/neu.0000000000003110.