

# Chapter 9

## Surgical Treatment for Epilepsy

### CQ 9-1

## Which kinds of epilepsies (syndromes) are indications for surgical treatment?

### Summary

The following five epilepsies (syndromes) can be treated with surgery: (1) mesial temporal lobe epilepsy, (2) partial epilepsy with responsible organic lesions detected, (3) partial epilepsy without detectable organic lesions, (4) partial epilepsy due to extensive lesions within one hemisphere, and (5) intractable epilepsy with atonic seizures.

### Comment

We consider that patients with epilepsy are candidates for surgical treatment when the epileptogenic zone can be determined by examinations, and resection of the epileptogenic zone is expected to result in no or acceptable sequelae. The above five epilepsy syndromes are treatable by surgery (surgically remediable syndromes)<sup>1)</sup>. (1) Mesial temporal lobe epilepsy (MTLE), especially MTLE with hippocampal sclerosis (HS) (MTLE-HS), is considered to be the best indication for surgical treatment as an independent syndrome, and significant seizure control is predicted<sup>2-4)</sup>. (2) For partial epilepsy, when a lesion is detected by diagnostic imaging and is resectable, we consider surgical treatment. Thermocoagulation surgery is effective for gelastic seizures induced by hypothalamic hamartoma<sup>5)</sup>. (3) Even when no lesion is depicted on MRI, surgical treatment may be indicated if the epileptogenic zone can be detected by EEG and functional neuroimaging. (4) Partial epilepsy caused by extensive lesions in unilateral hemisphere is included as a candidate for surgical treatment. Since the arrest or regression of psychomotor development is often induced in patients who have intractable epilepsy with infancy or early childhood onset, early surgical treatment is recommended<sup>6)</sup>. (5) Corpus callosotomy is effective for atonic seizures.

### ■ References

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## Is temporal lobe resection effective for drug-resistant temporal lobe epilepsy?

### Summary

The effectiveness and safety of temporal lobe resection have been established for drug-resistant temporal lobe epilepsy, and it is a treatment that should be considered for complex partial seizures that impede daily living. This treatment is particularly effective when localized temporal lobe lesions are depicted on MRI.

### Comment

The results of surgical treatment for temporal lobe epilepsy have been accumulated from major epilepsy centers around the world since the 1990's<sup>1)</sup>. In 2001, the superiority of surgical treatment to drug treatment was demonstrated by a randomized controlled trial (RCT)<sup>2)</sup>. In 2003, the American Academy of Neurology together with the American Epilepsy Society and the American Association of Neurological Surgeons published guidelines stating that "Patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center"<sup>3)</sup>.

The rate of freedom from seizures that impede daily living in patients who underwent surgery was 60–80% if MRI detected localized temporal lesions related to seizures, and the rate was approximately 50% if MRI detected no lesions<sup>4)</sup>. Apart from hippocampal sclerosis, localized lesions responsible for epilepsy include benign tumors such as ganglioglioma, dysembryoplastic neuroepithelial tumor and diffuse astrocytoma; cavernous malformations; and cerebral cortical dysplasia.

Postoperative complications such as speech disturbance, memory impairment, hemiparesis, and visual field defect may occur, but the incidence is low<sup>5)</sup>. Memory impairment after medial temporal lobe resection may involve various degrees of verbal memory loss if there is no hippocampal atrophy on the language dominant side, but in patients with hippocampal atrophy and below average preoperative memory, there is no change in verbal memory after surgery<sup>3)</sup>.

Temporal lobe resection has been shown to be highly effective and safe in patients with drug-resistant temporal lobe epilepsy, and is an established therapy. However, it takes more than 10 years on average from diagnosis to surgery. To address this issue, epileptologists in the United States performed a randomized controlled trial (RCT) and recommended that when two trials with appropriate antiepileptic drugs failed, surgery should be conducted at an early stage without waiting for years<sup>6)</sup>.

Comparison between surgical and medical treatments involves an inherent limitation of the low level of evidence. The evaluation bias always occurs because blinding of medical and surgical treatments is impossible (see Systematic Review Digest on page 148). If surgical treatment is believed to be clearly effective, randomization becomes an ethical concern. Furthermore, we often have further difficulty in accomplishing a clinical trial since subject recruitment is challenging. This is shown by the fact that the randomized trial of Engel et al.<sup>6)</sup> was terminated prematurely. No comparative trials have been reported, probably because long-term comparative studies are especially difficult to complete. In a case series report, the rate of seizure recurrence after surgery was several percent per year, and the seizure-free rate was approximately 50% after 10 years<sup>7)</sup>.

Regarding the surgical methods, in addition to the classical standard anterior temporal lobe resection, various approaches to the medial temporal lobe have been proposed. Anterior temporal lobectomy is superior to selective amygdalohippocampectomy in seizure outcome<sup>8), 9)</sup>. The superiority of selective resection for postoperative cognitive function has not been shown so far. For patients with high risk of postoperative memory impairment, new therapies such as multiple hippocampus transection, laser ablation and hippocampal electrical stimulation therapy have been proposed, and evaluation of these methods is awaited.

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- 2) Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001; 345(5): 311-318.
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## What are the indications for chronic intracranial EEG (long-term intracranial EEG) in presurgical evaluation?

### Summary

There is no clear criterion for the indication of chronic intracranial EEG as a presurgical evaluation for epilepsy surgery. The current consensus is described below, but it may be changed by the advances and widespread use of other presurgical examinations.

### Comment

Although there is no clear criterion for the indication of chronic intracranial EEG, this examination has been regarded as a gold standard for determining the epileptogenic zone and the extent of resection area since over 50 years ago<sup>1)</sup>.

The consensus to date for the indications includes: (1) patients with partial epilepsy diagnosed by seizure symptoms and other noninvasive examinations (including positron emission tomography and magnetoencephalography) even without any localized lesion detected by MRI; (2) patients with localized lesions demonstrated by MRI, which are inconsistent with the epileptogenic zones localized by other noninvasive examinations, or in whom multiple epileptogenic zones are suggested by noninvasive examinations; (3) regardless of the presence or absence of localized lesions on MRI, patients with epileptogenic lesions near the functional area, in whom high-resolution focus localization and brain function mapping are required<sup>1, 2)</sup>.

Chronic subdural EEG recording is often omitted when noninvasive examination results are consistent with anatomical findings in patients with mesial temporal lobe epilepsy associated with unilateral hippocampal sclerosis or partial epilepsy with localized neocortical lesions. Also, this examination is often omitted in a standard extensive resection (including callosotomy) (especially in children). Furthermore, this examination is usually not done before corpus callosotomy for generalized seizures.

There are two types of intracranial electrodes: subdural electrodes that are placed on the brain surface and depth electrodes placed inside the brain. In the former case, electrodes are placed by craniotomy; and in the latter, electrodes are stereotactically implanted. We have no conclusion about their superiority, and both are used when necessary<sup>3)</sup>.

Even though the required recording period has not been established, the recording is done for usually 1–4 weeks in many institutions. While it usually takes more than two weeks to perform an adequate examination, the incidence of wound infection or intracranial infection increases as the placement period increases. Complications of chronic intracranial EEG recording include infection, cerebrospinal fluid leak, and focal neurologic symptoms. The incidence rate is 8.3% (7.7% cured within 3 months, 0.6% prolonged)<sup>4)</sup>.

In EEG analyses, in addition to conventional visual inspection, new analytical methods are available using signal processing for a broader frequency range. For functional brain mapping, in addition to the classical electrical stimulation method, new method is available to identify the high-frequency oscillations during a task. However, the superiority of these new analytical methods has not been established<sup>5, 6)</sup>.

### ■ References

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## How to determine the timing of considering surgical treatment?

### Summary

When seizures have continued even after two or more regimens of appropriately selected antiepileptic drugs given as monotherapy or combination therapy, classify such epilepsy with uncontrolled seizures for a certain period as drug-resistant epilepsy, and consider surgical treatment. The “certain period” of persistent seizures is considered to be one year or longer (or a period at least three times the pre-treatment interval between seizures). Earlier surgery should be considered in children.

### Comment

The ILAE<sup>1)</sup> defines drug-resistant epilepsy as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom for an adequate period”. An adequate period without seizures may be considered as at least one year (or a minimum of three times the pre-treatment inter-seizure interval) without seizure recurrence. For adults, surgical treatment should be considered promptly when epilepsy is judged to be drug resistant. For childhood, early surgery is desirable considering functional and survival outcomes. The ILAE Commission on Neurosurgery<sup>2)</sup> also recommends early surgery. The goal of surgical treatment is not only to eliminate seizures but also to improve quality of life. Intellectual impairment and psychiatric disorder are not exclusion criteria for surgical indication. In children, it is known that psychomotor development improves when seizures are controlled after surgical treatment (treatable epileptic encephalopathy)<sup>3)</sup>.

### ■ References

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## Is surgical treatment effective even for drug-resistant epilepsies in children?

### Summary

The surgical treatment is widely used for children with drug-resistant epilepsy and is recommended as a treatment by international experts despite no high-grade evidence supporting its efficacy. Epilepsy syndromes in children are diverse, and poorly controlled epileptic seizures may affect cognitive and behavioral developments. Therefore, presurgical evaluation should be performed at an appropriate timing in a specialized hospital or center.

### Comment

The outcome of surgical treatment for drug-resistant epilepsy in children is better than that in adults, especially when a lesion is confirmed pathologically or by MRI<sup>1)</sup>. However, there is no high-grade evidence for it, and the ILAE recommends the treatment based on expert consensus<sup>2)</sup>.

The conspicuous features of epilepsy surgery in children include a high proportion of multilobar resection and hemispherectomy (including callosotomy), and cerebral cortical dysplasia as a common etiology. Surgical resection of localized cortical dysplasia results in a high rate of seizure-free outcome<sup>3, 4)</sup>.

Children are affected by diverse epilepsy syndromes, and poor control of epileptic seizures has a risk of worsening cognitive and behavioral developments. Therefore, presurgical evaluation should be performed at an appropriate timing in a specialized hospital or center<sup>3)</sup>. Good seizure control by surgery sometimes improves developmental outcomes, especially in the case of infants treated with hemispherectomy<sup>4)</sup>.

In children with severe epilepsy showing localized lesions or hemispheric lesions, good outcome may be obtained even when EEG demonstrates extensive bilateral epileptic abnormalities.

### ■ References

- 1) Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, et al. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res.* 2010; 89(2-3): 310-318.
- 2) Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia.* 2006; 47(6): 952-959.
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## What is the risk of psychiatric symptoms after epilepsy surgery?

### Summary

- (1) The risk of psychiatric symptoms after epilepsy surgery is high in patients with a past history or a family history of psychiatric symptoms (including anxiety, depression, and psychosis) before epilepsy surgery, and in those in whom seizures persist after surgery.
- (2) Explain to patients before surgery the possibility of psychiatric symptoms after epilepsy surgery.
- (3) For early detection and early treatment of psychiatric symptoms, we should follow the patients carefully for approximately 6 months to 1 year.

### Comment

It is desirable that all patients treated with epilepsy surgery should receive psychiatric evaluation before surgery<sup>1)</sup>. A past history of psychiatric disease is not a contraindication for surgery under the condition that psychiatric intervention is given. The frequency of de novo postsurgical psychiatric symptoms such as anxiety, depression and psychosis, including mild conditions such as adaptation disorder, is 1.1–18.2%<sup>2)</sup>. Presurgical psychiatric complications frequently exacerbate or recur up to one year after surgery. Regular close psychiatric follow-up after surgery leads to good outcome.

Risk factors for psychiatric symptoms such as anxiety, depression, and psychosis after epilepsy surgery are residual seizures after surgery and presence of a family history or past history of psychiatric condition before surgery. In surgically treated patients with temporal lobe epilepsy, the rate of de novo depression after surgery is 4–18%, occurring 3–12 months after surgery and lasting for 1 to 11 months. The rate of de novo anxiety disorder occurring after surgery is 3–26%, showing a peak in the first month after surgery. The rate of de novo psychiatric disorders developing after surgery is 1.1%, and the occurrence of psychiatric disorders is not related to the postsurgical seizure control or laterality of the resected hemisphere<sup>3)</sup>.

In patients with favorable seizure outcome (seizure-free) after surgery, the outcome of psychiatric symptoms is also favorable, but in rare cases adaptation disorder may occur. A hypothesis of “burden of normality” has been proposed to explain this phenomenon. It may be a kind of reaction of cured epilepsy patients to their new situation, that they should take on various social obligations that have been neglected while they were affected by epilepsy<sup>4)</sup>.

Treatment is basically the same as the usual treatment for psychiatric symptoms. In patients who did not receive any explanation about the risk of postsurgical psychiatric symptoms before surgery, the patients and families often react to or resist the involvement of psychiatrists after surgery. Therefore, participation of a psychiatrist in the treatment team before surgery is desirable.

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### ■ Search formula and secondary reference sources

Search formula

epilepsy [majr] AND mental disorders [majr] AND therapy [sh] Filters: Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Publication

PubMed = 86

# Should temporal lobe resection be added to drug therapy in drug-resistant temporal lobe epilepsy?

## Recommendation

We recommend temporal lobectomy in addition to drug therapies in patients with drug-resistant epilepsy (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note:** In the GRADE system, when the evidence level is “very low”, in principle it is not possible to grade “strong recommendation”. Since temporal lobe resection is highly effective with a low incidence of adverse effects, almost all the panelists supported “strong recommendation”, but due to the constraint of the GRADE system, the final grading was “weak recommendation”.

## 1. Background, priority of the problem

For drug-resistant epilepsy, adding further new drugs has limited effect. The temporal lobe resection is expected to achieve seizure-free condition despite its invasiveness.

## 2. Comment

### Evidence summary

There were 2 randomized controlled trials (RCTs) (total 118 patients) on the effectiveness of temporal lobe resection versus medical therapy for drug-resistant epilepsy<sup>1, 2</sup>. With regard seizure outcome, the relative risk was 20.57 (95% confidence interval 4.24–99.85) and the number needed to treat (NNT: indicating the number of persons needed to treat to achieve the outcome for one person) was 4, showing superiority of temporal lobe resection. Neither of the two RCTs mentioned decrease of antiepileptic drugs after surgery. Death rate did not differ between two groups.

The relative risk of surgical complications was 12.33 (95% confidence interval 1.67–90.89), and was higher in the temporal lobe resection group. Death, memory impairment, and psychiatric symptoms were not significantly different between the two groups. Quality of life (QOL) improvement was superior in the temporal lobe resection group.

## 3. Panel meeting

### 3-1. What is the overall quality of evidence across outcomes?

Since it was not possible to mask the intervention, the risk of bias was high overall in the collected studies. Bias for death was considered not serious, while that for the other outcomes was considered serious and was downgraded one rank. Inconsistency and non-directness of the results were without question and considered not serious. For imprecision, confidence intervals crossed the clinical decision threshold in many items, and was downgraded one or two ranks. Publication bias could not be judged because of the small number of studies. Consequently, the level of evidence for the outcomes was as follows: “low” for seizure freedom, death, surgical complications, and quality of life improvement; and “very low” for memory impairment and psychiatric symptoms. The overall level of evidence was “D (very low)”.

\* For surgical therapy, since blinding of the control group is difficult, the level of evidence is generally low.

### 3-2. How is the balance between benefits and harms?

Temporal lobe resection can be expected to control seizures. As a result, antiepileptic drugs are possibly reduced although it is not shown in RCT. The incidence of serious adverse effects was low. Therefore, the risk of temporal lobe resection is considered to be smaller as compared to its benefit.

### 3-3. What about patients’ values and preference?

Some patients may feel resistance in to receive invasive surgical therapy, but the beneficial effect of seizure-free produced by the surgery outweighs the resistance to the invasive procedure. There is perhaps no significant uncertainty or variability in value among the patients.



### **3-4. What is the balance between net benefit and cost or resources?**

The medical insurance fee scale for epilepsy surgery using a microscope (including temporal lobe resection) is 131,630 points (as of January 11, 2018). The surgery is conducted under general anesthesia and requires neurosurgeons.

However, through reducing antiepileptic drugs, decreasing hospitalization duration accompanying reduced seizures, and enabling more active social activities, epilepsy surgery is expected to lead to saving in the long term. For this reason, the cost can be considered negligible.

### **3-5. Recommendation grading**

During the discussions at the panel meeting, temporal lobe resection was expected to eliminate seizures, and overall the cost of the surgery could be considered negligible. Even taking the adverse effects into account, the surgery was supported by panelists.

At the panel meeting, many panelists supported a recommendation grade of “strong recommendation”. However, in the GRADE system, when the evidence level is “very low”, in general we are not able to grade “strong recommendation”. For this reason, the final grading was “weak recommendation”.

## **4. Descriptions in other related guidelines**

In Japan, the Japan Epilepsy Society published the “Guideline on indications for epilepsy surgery”<sup>3)</sup> in 2008, and “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy”<sup>4)</sup> in 2010.

The “Guideline on indications for epilepsy surgery” recommends surgical treatment for mesial temporal lobe epilepsy at a suitable timing, stating that “since surgical results are superior in cases of mesial temporal lobe epilepsy with a localized organic lesion or with extensive lesions in unilateral hemisphere, consider surgical treatment from an early stage and do not miss the timing of surgery”. The “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy” also follows the above recommendation, stating that “patients should be selected in accordance with the guideline on indications for epilepsy surgery”.

In overseas countries, the Quality Standards Subcommittee of the American Academy of Neurology, the American Epilepsy Society, and the American Association of Neurological Surgeons published a guideline<sup>5)</sup> in 2003. The guideline states that “drug-resistant epilepsy should be considered for referral to an epilepsy surgery center” and that “patients who meet established criteria for an anteromesial temporal lobe resection and who accept the risks and benefits of this procedure should be offered surgical treatment”.

## **5. Treatment monitoring and evaluation**

Monitoring and evaluation during the perioperative period of treatment are generally performed by a neurosurgeon. After this period, although a neurosurgeon is not necessarily required to monitor and evaluate the patients, follow-up and support for the patients should be provided.

## **6. Possibility of future research**

Some memory-preserving or minimally invasive surgery may be developed in the future. In addition, we would like to know the surgical outcomes and adverse events over a longer follow-up period because the observation periods of the two RCTs were 1 year<sup>1)</sup> and 2 years<sup>2)</sup>.

## **7. RCT reports reviewed for this CQ**

Wiebe 2001<sup>1)</sup>, Engel 2012<sup>2)</sup>

## **8. List of appendices (to be shown later)**

Appendix CQ9-2-01. Flow diagram and literature search formula

Appendix CQ9-2-02. Risk of bias summary

Appendix CQ9-2-03. Risk of bias graph

Appendix CQ9-2-04. Forest plot

Appendix CQ9-2-05. Summary of findings (SoF) table

Appendix CQ9-2-06. Evidence-to-decision table

## ■ References

- 1) Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001; 345(5): 311-318.
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