CHAPTER SEVEN

# Surgical treatment of low-grade brain tumors associated with epilepsy

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## Abstract

*Objective:* To explore the strategy of surgical treatment of low-grade brain tumors associated with epilepsy.

*Methods:* Clinical data of 158 patients with low-grade brain tumors were collected from January 2011 to December 2017 in Guangdong Sanjiu brain hospital. All patients received Preoperative evaluation. Lesion site: 18 cases were located in multiple cerebral lobes, 10 cases were in the functional zones, 130 cases were in the non-functional zones (including 74 cases were in the medial of temporal lobe). The surgical strategy included

*International Review of Neurobiology*, Volume 151
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2020.03.021

subtotal resection, gross-total resection and enlarged resection. Postoperative effects were evaluated by Engel classification.

*Results:* A total of 158 patients underwent surgical treatment, among these patients, only 1 patient underwent intracranial electrode implantation. Surgical methods: 34 cases of subtotal resection, 3 cases of gross-total resection, 119 cases of enlarged resection (including Anterior temporal lobectomy in 74 cases) and 2 case of Selective hippocampal amygdalectomy. The final pathology suggested that there are 74 cases of ganglionglioma, 25 cases of dysembryoplastic neuroepithelial tumors, 9 cases of pilocytic astrocytoma, 16 cases of oligodendroglioma, 10 cases of pleomorphic xanthoastrocytoma, 4 case of diffuse astrocytoma, 9 cases of unclassified astrocytoma, 11 case of oligoastrocytoma. The follow-up time was between 1 and 7 years, with an average of $3.44 \pm 1.77$ years. Postoperative recovery: 147 patients had an Engel Class I outcome, 10 patients were in Engel Class II, 1 patient was in Class IV.

*Conclusion:* The strategy of surgical treatment of low-grade brain tumors associated with epilepsy should pay more attention to the preoperative assessment of the epileptogenic zone. The tumor is not exactly the same as the epileptogenic zone, and the strategy of surgical treatment depends on the tumor feature as well as whether it was located in temporal lobe or involved in functional areas.

## 1. Introduction

Although many types of tumor can cause a seizure, neuroglial tumors, and gliomas are the most common ones. Dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas (GGs), low-grade glial tumors, glioblastomas, metastases, leptomeningeal tumors and primary CNS lymphomas are associated with seizures in varying rates (van Breemen, Wilms, & Vecht, 2007).A seizure is the most common presenting symptom, however, patients may also begin to develop seizures later in the course of the disease (Kerkhof & Vecht, 2013). These epilepsy are often refractory to medical treatment (Nowell, Miserocchi, & Mcevoy, 2015), if not controlled well, it will seriously affect the quality of life, lead to cognitive deficit, and may even lead to disability. Currently, most studies show that unless the epilepsy is completely cured, patients will still be unable to live independently (Guerrini, Rosati, Giordano, et al., 2013; Radhakrishnan, Abraham, Vilanilam, et al., 2016; Ranger & Diosy, 2015). So when we design the treatment strategy for patients with low grade brain tumors, the possible treatment goals in the management of tumor-related epilepsy are summarized as follows: (1) Establish the histological diagnosis. (2) Improve seizure

control/achieve seizure freedom. (3) Improve survival. (4) Improve quality of life. Care of these patients is complex, and requires a multidisciplinary team approach (Giulioni, Marucci, Pelliccia, et al., 2017a). However, the extent of surgical resection of tumors is still controversial (Englot, Han, Berger, et al., 2012). We summarize data of patients with low-grade brain tumors accompanied by epilepsy, who underwent surgical treatment in epilepsy center of Guangdong sanjiu Brain Hospital from January 2011 to December 2017. The clinical characteristics and pathological results were analyzed, and the surgical strategies for these diseases were further explored.

## 2. Methods

### 2.1 Patients data

A retrospective study enrolled 158 consecutive patients with epilepsy who underwent surgery for histopathologically confirmed low grade brain tumors between January 2011 and December 2017. There were 97 males and 61 females. The age of onset ranged from 4 to 62 years, with an average age of $25.17 \pm 14.65$ years. The course of disease ranged from 0.5 to 612 months, with an average of $(84.86 \pm 97.08)$ months. Location of lesion: 18 cases of multilobe, 10 cases of functional area and 130 cases of non-functional area (74 cases of medial temporal lobe). All cases were examined 1.5–3 T brain magnetic resonance imaging (MRI).

### 2.2 Preoperative investigations

History acquisition was completed by two senior surgeons independently, then, they complemented each other. Video-EEG was performed before operation. For patients with frequent seizures (more than once a month), detailed analysis of ictal semiology and long video-EEG monitoring is essential. Other examination included Motor or language functional MRI (fMRI) and T2 flair sequence, neuropsychological assessment and $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$ FDG-PET). The objective of preoperative assessment is to determine the correlation between tumors and Epileptogenic zone. When Electro-clinical-anatomical appearance is inconsistent, invasive examinations, including intracranial electrode implantation, should be considered.

### 2.3 Epileptogenic zone (EZ) and surgery

Identify the possible location of epileptogenic zone based on preoperative investigations. Under intraoperative cortical electroencephalogram monitoring and according to the discharges of cortex around the lesions during the operation, three surgical methods including subtotal resection, gross total resection and enlarged resection of tumors were adopted. The enlarged excision included resection of tumors and peripheral discharge cortex. If it located in functional area, it can be resected under wake-up anesthesia or cortical electric stimulation with the patient's cooperation. Judgment of extent of surgical resection based on 24 h Postoperative MRI Examination.

### 2.4 Follow-up

Postoperative seizure outcome was assessed based on Engel's classification (Engel, Van Ness, Rasmussen, & Ojemann, 1993).

## 3. Results

1. *Surgical results*: 34 cases accepted Subtotal resection, 3 cases accepted gross resection, enlarged resection were in 119 cases (including anterior temporal lobectomy in 74 cases), and selective hippocampal amygdala resection in 2 cases. Early motor disturbance occurred in 3 cases, mild hemiplegia in 1 case and visual field defect in 2 cases.
2. *Pathologic examination of results*: All cases were histologically diagnosed according to the World Health Organization (WHO) classification of tumors of the central nervous system (Louis, Perry, Reifenberger, et al., 2016) and the more recent classifications for FCD (Blumcke, Thom, Aronica, et al., 2011) and hippocampal sclerosis (HS) (Blumcke, Thom, Aronica, et al., 2013). There were 74 cases of ganglioma, including 32 cases with FCD, 6 cases with hippocampal sclerosis and 1 case with heterotopic gray matter; 25 cases with embryonic dysplasia neuroepithelial tumors, including 9 cases with FCD, 2 cases with hippocampal sclerosis and 1 case with heterotopic gray matter; 9 cases with pilocytic astrocytoma, including 1 case with FCD; 16 cases with oligodendroglioma, including 2 cases with FCD; 9 cases with polymorphic yellow astrocytoma. There were 4 cases of diffuse astrocytoma, including 1 case with FCD, 9 cases with

unclassified astrocytoma, 11 cases with oligodendroid-astrocytoma, 3 cases with FCD and 1 case with glioma of vascular center.

3. *Follow-up results and prognosis*: The follow-up time was 1–7 years, with an average of (3.44 + 1.77) years. There were 119 cases of enlarged resection, 116 cases of Engel grade I, 2 cases of Grade II and 1 case of Grade III. Among the patients who underwent subtotal resection, 34 had Engel grade I in 28 cases and Engel grade II in 6 cases. Three cases underwent gross total resection, 2 cases were Engel grade I and 1 case was Engel grade II. Selective hippocampal amygdala resection was performed in 2 cases, Engel grade I in 1 case and Engel grade IV in 1 case.

## 4. Discussion

How to design the surgical excision boundary of low-grade epileptic tumors? At present, there is no consensus yet.

### 4.1 Relationship between the extent of tumor resection and prognosis?

Numerous studies have confirmed that total resection of tumors is a good prognostic factor for well-controlled seizures after surgery (Giulioni, Marucci, Pelliccia, et al., 2017b). Englot et al. (2012) collected data of 1181 low-grade epileptic tumors located in temporal lobe from 41 studies. It was found that only 42.7% of epilepsy patients had seizures free after subtotal resection, while the total resection is 78.6%. If the total resection of tumor combined with selective excision of epileptogenic structures, such as hippocampectomy, neocortex excision, or hippocampus plus neocortex excision, the rate of seizure free increased to 86.0%–87.0%. Therefore, total resection of tumors should be emphasized. It is worth noting that resection should be avoided under a single modality image as far as possible, which may ignore part of the lesion. The field of tumors should be observed under multimodal imaging, and various pathological components should be adequately removed, such as calcified lesions on CT, enhanced lesions on T1 and enhanced lesions on T2 Flair sequences. Sometimes after tumor surgery, little residue does not necessarily lead to poor seizure control. In the study of our Hospital, 7 patients underwent subtotal resection of tumors, including 4 patients involving basal ganglia through medial temporal lobe and 3 patients involving central and deep pyramidal tracts. All the 7 patients had small

residual tumors in basal ganglia or deep white matter, but no seizures occurred after operation.

The reasons may be as follows: Firstly, There is likely to be a difference in causing the possibility of epilepsy. The residual part of the tumors located in the deep white matter or basal ganglia does not cause epilepsy, but the tumors in the cortex or near cortex which are more likely to cause epilepsy have been completely removed, so the prognosis is still good; secondly, after subtotal resection, the local occupying or compressing effect of the original tumors has been relieved and the stimulation to the surrounding cortex was reduced. Therefore, subtotal resection in order to protect the function of tumors is allowed in involving deep functional structures.

## 4.2 Is gross total tumor resection enough?

At present, many neurosurgeons in our country attach great importance to the total removal of tumors, but neglect the treatment of "epileptogenic areas." The common misconception is that epilepsy is caused by tumors, so long as epilepsy can be controlled by excision of tumors, however, Epileptic zone sometimes is not the same as tumors in epilepsy surgery. Sometimes the epileptogenic area is beyond the scope of the tumor because of dural pathology. As shown in the meta-analysis above, combined with extended resection of the epileptogenic structure can further improve the surgical effect (Hamer & Knake, 2008).

How to expand the resection scope of Epileptogenic structure? An empirical approach is to enlarge the 1–2 cm cortex around the tumor to control seizures better. However, some intracranial electrode studies have shown that the distant cortex beyond 1.5 cm of the tumor boundary can also with in the onset of seizures (Mittal, Barkmeier, Hua, et al., 2016).

Generally speaking, the extent of resection should be based on preoperative assessment data such as history, imaging, preoperative electroencephalogram, PET, intraoperative cortical electroencephalogram, education level of patients and the demands of brain function. For example, if low-grade tumors located in the neocortex of temporal lobe, should medial temporal lobe structures such as hippocampus and amygdala be removed? if the patient has a long history (more than 1 year), drug-resistant, anatomical-electro-clinical symptoms were consistent with typical medial temporal lobe epilepsy, and MRI also showed high signal in medial temporal lobe, we

inclined to wider resection (such as anterior temporal lobe resection includes amygdala and hippocampectomy). Conversely, more conservative resection of the periphery tumors and preservation of the medial temporal lobe structure can be considered. The pathology of tumors, such as embryonic dysplasia neuroepithelioma tumors (DNET), there are different ways to deal with it (Chassoux, Landré, Mellerio, et al., 2013). If DNET shows simple type on the image, only by removed the tumors can achieve good seizure control. If DNET is complex or non-specific form, it needs to be further combined with epileptogenic cortex excision on the basis of tumor excision. Patients' self-condition and family background are also considered as one of the factors: if the patients' self-condition as well as family economic condition is good, and the willingness of maintaining advanced brain functions such as memory is strongly, it may be the best choice for SEEG to assess whether functional areas are involved in. However, if there are obvious memory impairment or neurological deficit before operation, surgical removal of temporal lobe is unlikely to cause new neurological deficits. If the family is in low-income group, economic conditions can afford to only once operation, we can consider active anterior temporal lobectomy, and try to solve the problem of tumors and epilepsy in one step in order to avoid reoperation.

Interestingly, the tumor could also modify synchronization within cerebral networks, with randomization in neural dynamics, causing seizure onset (Amaral, Diazguilera, Moreira, et al., 2004; Bartolomei, Bosma, Klein, et al., 2010; Bartolomei, Chauvel, & Wendling, 2005; Bartolomei, Wendling, Régis, et al., 2004; Stam & Reijneveld, 2007) it is hypothesized that a brain tumor interferes with widespread functional circuits rather than with only the site of the lesion itself (Herman, 2002). For patients with intractable epilepsy generated by a paralimbic (fronto)-temporo-insular Grade II glioma, even if it does not invade the hippocampus, hippocampal resection allowed a complete control of seizure, Conversely, if only completed maximal resection of the tumor involving the insula and anterior temporal lobe, all the patients still have seizures after surgery (Ghareeb & Duffau, 2012). Especially, in our experience, when it located in the parietal or occipital lobes, the treatment strategy is more complicated, involving with ventral and dorsal pathways. For example, we encountered a case of patients with ganglioma located in the occipital lobe, who still had seizures after gross resection and peripheral tumor discharge cortex. Postoperative

electroencephalogram showed significantly temporal lobe discharges. However, due to the high technical requirements of iEEG, long period of diagnosis and treatment, and high economic costs, few experts consider to implanted intracranial electrodes for low-grade tumors regularly.

## 4.3 Indication for intracranial electrode implantation

In preoperative evaluation, intracranial electroencephalogram (iEEG) should be used when scalp electroencephalogram cannot accurately identify epileptogenic zone or the results of anatomy-electro-clinical are inconsistent, or the epileptogenic zones are closely related to the important functional areas. Intracranial electrode electroencephalogram (EEG), including subdural electroencephalogram (Subdural EEG) and stereo-electroencephalogram (Stereo-EEG), the implantation of a subdural grid carries substantial risks of infection and hemorrhage, and commits the patient to undergoing two surgical procedures (Radhakrishnan et al., 2016). Perhaps most importantly, extraoperative mapping only samples cortex and provides no information on the underlying white matter tracts, Stereo-EEG can accurately locate the onset of epilepsy and the mode of epileptic discharge conduction, which is helpful to understand the pathophysiological mechanism of epilepsy caused by tumors (Mittal et al., 2016; Sweet, Hdeib, Sloan, et al., 2013).

## 4.4 Significance of intraoperative electrophysiological monitoring

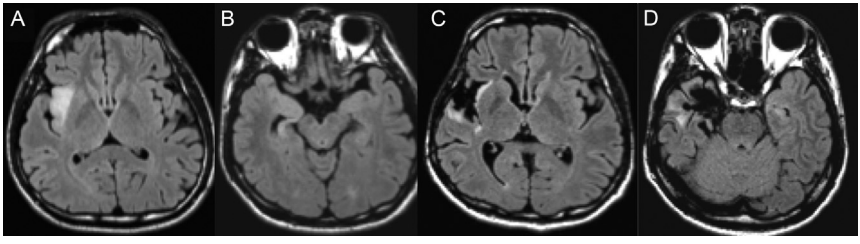
Intraoperative cortical electroencephalogram (ECoG) reflects the intermittent discharge of the brain. However, intraoperative EEG may be affected by anesthesia drugs. Because of short intraoperative monitoring time, the collected EEG signals are limited to the exposed brain tissue, and mainly in the cerebral surface cortex. It is difficult to detect the whole epileptic network. Therefore, the detection of epileptic discharge by ECoG has limitations in both time and space. At present, the significance of guidance and prognosis of ECoG for epilepsy surgery are still controversial. Most experts believe that although ECoG cannot be used as a "gold standard," but its application can significantly improve the outcome of seizure control (Fallah, Weil, Sur, et al., 2015; Mikuni, Ikeda, Takahashi, et al., 2006; Wray, McDaniel, Saneto, et al., 2012; Yao, Zheng, Wang, et al., 2018).

### 4.5 Surgical strategy for functional area tumors

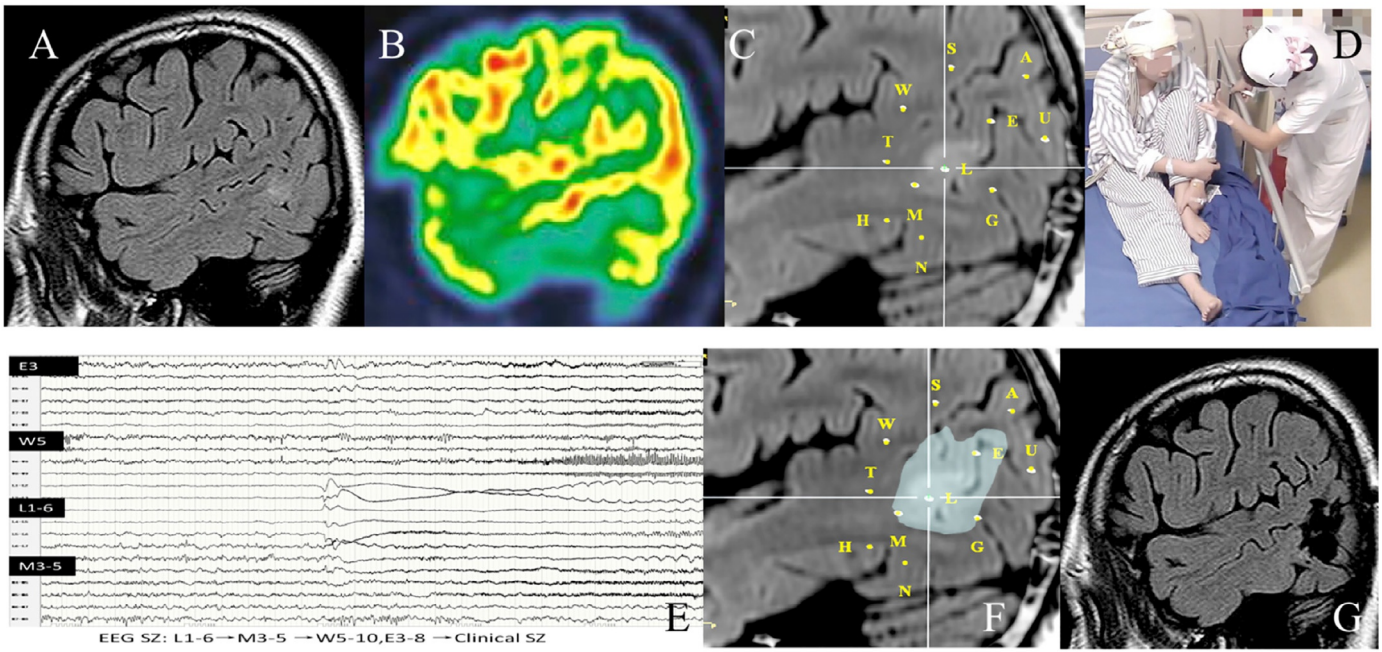
Functional protection is paramount. For patients with low-grade tumors, it is not advisable to sacrifice important functions (motor, language, etc.) for total removal of tumors. Tumor resection should be as complete as possible under the premise of preserving function. Tumor cells usually have no function, so if the margin of the lesion is clear, the tumor can be removed completely; if the margin is not clear, the maximum resection of the tumor can be carried out under cortical and subcortical stimulation nor intraoperative wake-up anesthesia. Age is not an absolute risk factor for wake-up anesthesia. It has been assessed that children with good mental development who can cooperate with simple language and exercise tasks can also perform in wake-up anesthesia. Among the cases in our hospital, 3 children underwent operation under intraoperative wake-up anesthesia. The youngest age was 10 years old.

## 5. Conclusion

Our data support for the operation of patients with low-grade epileptic tumors, it should be avoided to regard them as oncological operations only, we should be fully remove the tumors and epileptogenic structures to the greatest extent with modern epilepsy surgery concept.




Case-1: M, 29y, R hand. Seizure onset: 23y, semiology: GTCS. MRI shows that the lesion involves in the insula, amygdala, and hippocampus. Surgical strategy: Total insulectomy + amygdalactomy + hippocampectomy + partial superior temporal gyrus. Postoperative pathology: oligodendroid astrocytoma (WHO II). Seizure free: 5 years.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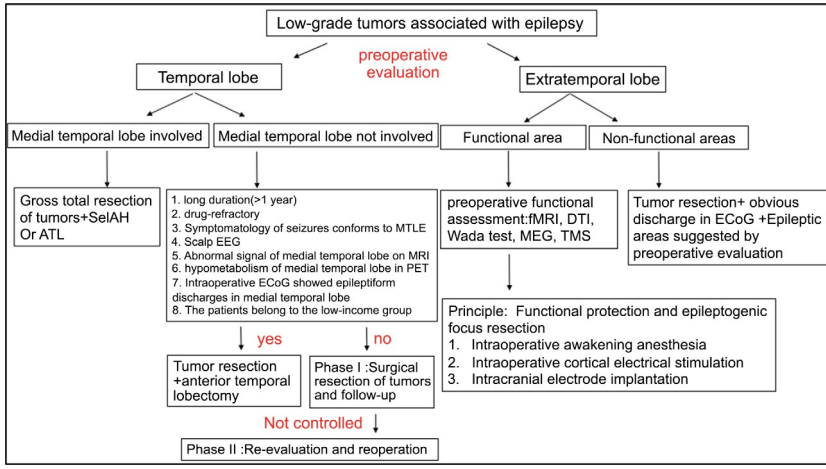
Case-2: Female, 14y, R hand. Seizure onset: 10y. (A)–(B) Lesions and hypometabolism in the left temporal lobe. (C) The plan of intracranial electrode implantation. (D) Semiology: Comprehensive aphasia → dialeptic. Intracranial electrode implantation was performed for two reasons: first of all, language function should be protected; secondly, boundary of epileptogenic zone should be determined. SEEG shows that the onset originates from the core of the lesion and spreads rapidly to the surrounding cortex. Surgical strategy: Extended resection of lesions under intraoperative wake-up anesthesia. Postoperative pathology: oligodendroid astrocytoma (WHO II). She was seizure free for 4 years.

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