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Gamma knife treatment for refractory epilepsy in seizure focus localized by positron emission tomography/CT★

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Abstract
A total of 80 patients with refractory epilepsy were recruited from the Inner Mongolia Medical College Affiliated Hospital. The foci of 60% of the patients could be positioned using a combined positron emission tomography/CT imaging modality. Hyper- and hypometabolism foci were examined as part of this study. Patients who had abnormal metabolism in positron emission tomography/CT imaging were divided into intermittent-phase group and the seizure-phase group. The intermittent-phase group was further divided into a single-focus group and a multiple-foci group according to the number of seizure foci detected by imaging. Following gamma knife treatment, seizure frequency was significantly lower in the intermittent-phase group and the seizure-phase group. Wieser's classification reached Grade I or II in nearly 40% of patients. Seizure frequency was significantly lower following treatment, but Wieser's classification score was significantly higher in the seizure-phase group compared with the intermittent-phase group. Seizure frequency was significantly lower following treatment in the single-focus group, but Wieser's classification score was significantly higher in the single-focus group as compared with the multiple-foci group.

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Key Words
epilepsy; seizure; positron emission tomography/CT; gamma knife radiosurgery; metabolism; ^{18}F-fluorodeoxyglucose; neural regeneration

Research Highlights
(1) Combined positron emission tomography/CT proved effective in localizing seizure focus (foci) in patients diagnosed with refractory epilepsy.
(2) This imaging modality proved more accurate in localizing a single focus than multiple foci and in patients with hypermetabolism than in hypometabolism.

Abbreviations
EEG, electroencephalogram; PET, positron emission tomography; FDG, ^{18}F-fluorodeoxyglucose

INTRODUCTION

Refractory epilepsy refers to frequent seizures that occur at least four times per month and affect patients' daily lives. A hallmark of this chronic form of epilepsy is that it cannot be controlled within 2 years of initial treatment with appropriate first-line antiepileptic drugs within the effective drug-blood concentration range and with no serious drug side effects. Additionally, a diagnosis of refractory epilepsy requires that no progressive central nervous system disease or space-occupying lesion was found at baseline or within this 2-year treatment window.

Due to ineffective drug treatment, some patients require surgical intervention or radiation therapy; thus, localization of an epileptogenic focus is the goal of surgical or gamma knife treatment for refractory epilepsy[1]. At present, the deployment of an electroencephalogram (EEG) is the preferred method for localization of an epileptogenic focus[2]. Although the EEG is helpful to the electrophysiological diagnosis of epilepsy, most EEG findings are presented as extensive abnormal EEGs[3], and it is thus difficult to determine the range of foci involved as well as their exact location[4]. It is also difficult to distinguish which disease may be responsible for causing abnormal EEG results. MRI can be used to help clarify brain structure, but this imaging modality exhibits low sensitivity for localization of seizure foci[5].

New developments in radiation medicine have advanced the use of minimally invasive, highly precise gamma knife treatment for epilepsy[6]. However, despite such advances, the biggest challenge in radiosurgery continues to be localization of the epileptogenic focus[7]. The invention of positron emission tomography (PET) has improved the detection and the rate of localization of the seizure focus, thus providing a reliable basis for localization of the seizure focus in gamma knife treatment[8]. The aim of our study was to evaluate the effects of gamma knife treatment on epilepsy after localization of the seizure focus using PET/CT.

RESULTS

Quantitative analysis of subjects and baseline analysis

Of the 80 enrolled patients, a total of 72 patients with metabolic abnormalities (42 males and 30 females; mean age, 19 ± 18 years; mean disease duration, 6 ± 10 years) as observed by PET imaging were diagnosed with refractory epilepsy. Non-metabolic abnormality population of eight patients was diagnosed with refractory epilepsy of a different origin. The past history of the patients included 20 cases of birth trauma, 6 cases of asphyxia, 4 cases of intracranial hematoma, 10 cases of brain injury, 9 cases of infection, 4 cases of brain tumors, 6 cases of other diseases, and 21 cases of unknown origin. A total of 24 cases suffered from simple partial seizures, 16 cases affected complex partial seizures, and 40 cases experienced full tonic-clonic seizures. Patients who had abnormal metabolism as shown in PET/CT imaging were divided into the intermittent-phase group (n = 60, lower-than-normal brain metabolism) and the seizure-phase group (n = 12, higher-than-normal brain metabolism). The intermittent-phase group was further divided into a single-focus group (n = 32) and a multiple-foci group (n = 28) according to the number of seizure foci as determined by PET/CT. All follow-ups ranged from 6 to 28 months. The patients with clinical data are shown in Table 1.

Table 1 Clinical data in each group

Item	Intermittent-phase group		Seizure-phase group
	Single-focus	Multiple-foci	
n	32	28	12
Sex (*n*, male/female)	18/14	15/13	9/3
Age (mean ± SD, year)	21±16	19±13	18±17
Weight (mean ± SD, kg)	45±35	38±27	38±37
Height (mean ± SD, m)	1.2±0.5	1.4±0.4	1.1±0.7
Onset age (year)	5–37	7–32	1–35
Course of disease (year)	4–15	2–26	1–15
Formal treatment	Drug therapy	Drug therapy	Drug therapy
Number of seizures per year (mean ± SD)	4.3±1.6	4.2±1.8	4.6±1.6
Past history (*n*)			
Birth trauma	12	3	5
Asphyxia	4	1	1
Intracranial hematoma	1	1	2
Brain injury	6	3	1
Infection	6	2	1
Brain tumor	2	0	2
Other diseases	1	5	0
Unexplained origin	0	13	0

^{18}F-fluorodeoxyglucose (FDG) PET imaging of epilepsy patients

Of the 72 patients with metabolic abnormalities, 60 cases showed a hypometabolism focus and 12 cases had multiple hypermetabolism foci. Representative images are shown in Figure 1. ^{18}F-FDG PET/CT showed that hypometabolism foci were mainly located in the temporal lobe (48 cases), parietal lobe (12 cases), frontal lobe (9 cases), occipital lobe (6 cases), and the basal ganglia of the thalamus (5 cases). Of these 60 cases, 36 patients had a single focus and 24 patients had multiple foci. These foci were localized during the seizure stage using ^{18}F-FDG PET/CT imaging, a method that has a localization rate of 60% (36 cases in the intermittent-phase group had a single focus; 12 cases in the seizure-phase group had a hypermetabolism focus).

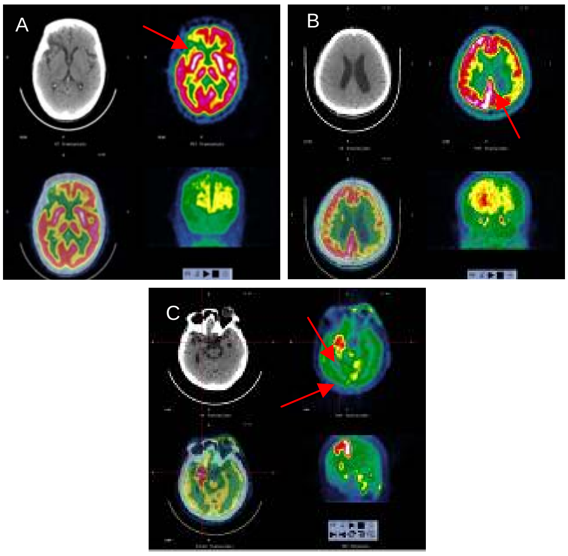

Figure 1 ^{18}F-fluorodeoxyglucose positron emission tomography (PET) imaging.

(A–C) Top left images, axial CT; top right images, axial PET; bottom left images, overlap of axial CT and axial PET; bottom right images, three-dimensional PET. Arrows show epileptogenic foci. Red color represents hypermetabolism region (compared with cerebral metabolism in the same layer; from high to low: red > yellow > green > blue).

(A) Hypometabolism focus of frontal parietal lobe; (B) hypometabolism focus of parietal lobe; (C) hypermetabolism focus of temporal lobe.

Comparison of ^{18}F-FDG PET and EEG results

The detection rate of seizure foci using PET was 90% (72/80). The detection rate of seizure foci using EEG was 70% (56/80), including 28 cases of diffuse slow wave; 16 cases of local slow wave and 12 cases of spike wave, sharp wave, or spike slow wave-like epilepsy waves.

Seizure changes before and after gamma knife treatment

The frequency of seizures in the intermittent- and seizure-phase groups was significantly lower following gamma knife treatment and decreased over time. Seizure frequency in the seizure-phase group at 6, 12, and 24 months post-treatment was significantly lower than that of the intermittent-phase group, indicating that PET localized a hypermetabolism focus more accurately than it did hypometabolism foci. The seizure frequency in the single-focus group at 6, 12, and 24 months post-treatment was significantly lower than that in the multiple-foci group, indicating that PET more accurately localized a single focus than it did multiple foci (Table 2).

Table 2 Comparison of seizure frequency (*n*/month) before and after gamma knife treatment

Group	*n*	Before treatment	After treatment (month)		
			6	12	24
Intermittent phase					
Single-focus	32	4.3±1.6	3.6±1.6	3.4±1.9	2.5±1.0
Multiple-foci	28	4.2±1.8	2.8±1.4	3.2±1.8	1.1±0.8
Seizure phase	12	4.6±1.6	1.9±1.7	2.6±1.7	1.0±0.1

Data are expressed as mean ± SD.

Clinical follow-up of patients according to Wieser's classification

Nearly 40% of patients were cured of their epileptic symptoms following gamma knife treatment. The efficiency of the seizure-phase group was significantly better than that of the intermittent-phase group (Z = 2.202, P = 0.028, by chi-square test). The efficacy of the single-focus group was slightly higher than that of the multiple-foci group (Z = 2.389, P = 0.017, by chi-square test; Table 3).

Table 3 Clinical follow-up evaluation [*n* (%)] of patients in each group

Wieser's classification	Intermittent-phase group		Seizure-phase group (*n* = 12)	Total (*n* = 72)
	Single-focus (*n* = 32)	Multiple-foci (*n* = 28)		
Grades I–II	11(34)	8(29)	8(67)	27(38)
Grades II–IV	15(47)	10(36)	4(33)	29(40)
Grades V–VI	6(19)	10(36)	0	16(22)

Treatment complications

No patients suffered from neurological deficit, disability, or death during the follow-up period.

DISCUSSION

As demonstrated here, PET/CT is capable of providing imaging and quantitative analysis to increase the detection rate of seizure foci from metabolism, blood flow, biochemical function, oxygen consumption, protein synthesis, chemical transmitters, and neural receptors[9]. As early as the 1980s, Engel *et al* [10] located the epileptogenic focus using ^{18}F-FDG PET and found that the seizure focus exhibits hypometabolism during intermittent periods and undergoes hypermetabolism during the seizure period[11]. Since then, numerous studies have shown that during the intermittent period of epileptic seizure, local cerebral blood flow and regional cerebral glucose utilization in the seizure focus decreased significantly[12-13]. PET has high accuracy and specificity for localization of an epileptogenic focus during a seizure period, and PET/CT is more accurate than PET alone in the localization of the seizure focus[14].

In this study, 80 epilepsy patients underwent PET/CT brain imaging. The detection rate of epilepsy using ^{18}F-FDG PET imaging was 90% (72/80), which corresponds closely to the reported detection rate of 80–90%[15-16].

Existing surgical treatments typically damage brain tissue or destroy the complete brain structure[17]; such surgical interventions are risky and lead to anxiety for patients and their families alike, especially if the detected foci are numerous, very deep, or in an important functional region of the brain[18]. Radiation therapy such as gamma knife treatment is gradually gaining popularity as a surgical treatment of epilepsy[19]. At present, the exact mechanisms at work in radiation treatment of epilepsy are unknown[20]. The gamma knife offers characteristic and accurate three-dimensional positioning, with high-energy rays converging on targets, steep attenuation of radiation, and no damage to surrounding tissue[21]. By using varied collimator diameters and several isocentric techniques, gamma knife can be used in the effective, non-invasive, safe, and simple treatment of several brain diseases including epilepsy[22-23].

Previously published research has found that the majority of low-glucose metabolism regions detected by PET were consistent with an epileptogenic focus[24]. This was verified by depth electrodes and a pathological examination, but for multiple seizure foci, false positives may occur in PET[25-26]. Additionally, multiple seizure foci are difficult to treat. Our research has demonstrated that gamma knife treatment for refractory epilepsy after PET/CT localization is highly efficient and that the hypermetabolism foci results were better than the results found in the intermittent-phase group and that the single-focus group localization was better than that associated with multiple foci[27]. There were similar reports in surgery, such as research done by Koutroumanidis *et al* [28], who found that a better effect could be achieved if a unilateral hypometabolism area revealed by PET was selected as a surgery target. For bilateral hypometabolism foci, the effect was poor. However, in some cases, after removal of the more strongly affected side using a gamma knife, the number of seizures will be reduced despite a non-perfect unilateral focus[29].

For the treatment of multiple seizure foci, we relied on domestic results[30] and found that 31.6% of patients were unaffected and 26.3% of patients experienced a positive effect when both the seizure focus and the suspicious epileptogenic focus were treated. Our results were lower than the 14.3% ineffective rate as well as the 48.6% of “excellent effect” cases reported by other researchers. We expect that this discrepancy may be correlated with our study’s small sample size[31-32].

Radiosurgery has no obvious side effects for epilepsy treatment[33] due to this therapy’s low radiation dose. The localization of an epileptogenic focus by PET/CT was accurate; once localized, such foci can be treated effectively with a low radiation dose and a reduction of brain tissue damage[34].

SUBJECTS AND METHODS

Design

A neuroimaging-based non-randomized concurrent-control study.

Time and setting

The study was performed at the Affiliated Hospital of Inner Mongolia Medical College, China from April 2007 to December 2010.

Subjects

Epilepsy patients were screened and treatments were administered at Department of Neurology and the Gamma Knife Center, the Affiliated Hospital of Inner Mongolia Medical College, China between April 2007 and December 2010.

Inclusion criteria

(1) All diagnoses were consistent with epilepsy and epileptic syndrome classifications made in 1989 by the International League Against Epilepsy[35]. (2) Clinically diagnosed patients with epilepsy whose age ranged from

1 to 37 years and whose seizure frequency was greater than or equal to twice a year (including patients who did not take antiepileptic drugs and those patients whose use of antiepileptic drugs failed to satisfactorily control seizures). (3) Patient condition was confirmed by EEG. (4) All patients received two or more antiepileptic drugs as formal treatment (*i.e*., phenobarbitone, sodium valproate, carbamazepine, topiramate), but these medications reduced seizure frequency to less than 50%. (5) Patients or their legal guardians who agreed with the relevant examination and treatment and provided written informed consent.

Exclusion criteria

(1) Epilepsy combined with diseases or dysfunction of other major organs (*e.g*., heart, lung, liver, kidney dysfunction); disorders of the blood; or malignant tumor(s). (2) Patients who had severe disorders of consciousness, mental retardation, and/or mental disorders. (3) Pregnant or lactating women. (4) Patients who were not able to tolerate and cooperate with clinical examinations and who could not effectively adhere to and manage their treatment or who were considered by the researchers to be otherwise unsuitable for study participation. (5) Patients who were already enrolled in other related clinical observation trials.

Methods

PET/CT imaging

A MINItrace cyclotron (GE Healthcare, United StatesConnecticut) and the imaging agent ^{18}F-FDG (produced chemical synthesis with 95% radiochemical purity) were used. After the patients were fasted for 6 hours, 111–185 MBq ^{18}F-FDG was injected into the cubital vein during the seizure or intermittent stage. Patients wore ear plugs, and their vision was blocked *via* conventional methods. Following 30 minutes of quiet rest, a Discover ST imager (GE Healthcare) was used for brain PET/CT three-dimensional-tomography. Cross-sectional, coronal, and sagittal images were reconstructed using a computer-aided art iterative algorithm.

Evaluation of cerebral metabolism

Image readout by a double-blind method was performed by two experienced PET/CT diagnosis experts. Visual and semi-quantitative analyses were performed. The abnormality standard for visual analysis was two or more consecutive frames that had local or diffuse higher or lower radioactivity at both the cross-section and the coronary section of the region of interest (ROI). Simultaneously, the left and right sides were required to show an apparent asymmetrical shape. Hypometabolism foci had low distributions of radioactivity, while hypermetabolism foci had high distributions of radioactivity. The asymmetry index was used as a quantitative analysis indicator. An asymmetry index of greater than 15% was generally considered abnormal, and the seizure focus could be identified[36].

$$AI = \frac{\text{ROI on lesion side} - \text{ROI on normal side}}{\text{ROI on lesion side} + \text{ROI on normal side}} \times 200\%$$

Radiosurgery treatment

An OUR-XGD gamma knife (Shenzhen Oreworld International Science and Technology Development, Shenzhen, Guangdong Province, China) was used for treatment. First, a sereotactic headstock was installed, and fixed PET images were fused by software. A gamma knife program system and the treatment's target volume were determined according to the epileptogenic and suspect epileptogenic zones from PET/CT imaging, and were then selected *via* the delineation of the target treatment dose using Treatment Planning System software (Shenzhen Oreworld International Science and Technology Development). A 45–55% isodose curve was used to surround the epileptogenic focus, and a peripheral dose of 9–13 Gy was administered according to focus size, location, and structure of the surrounding area[37]. The most effective treatment was noted after repeated simulation display and evaluation.

Efficacy analysis

Follow-up was performed at 6, 12, and 24 months post-treatment *via* outpatient review and telephone inquiry. The effectiveness of the treatment was determined according to Wieser's classification of surgical treatment for epilepsy (International League Against Epilepsy, September 2000)[38], in which: (1) Grade I is classified by having no seizures or related signs. (2) Grade II patients may have signs of seizures but no actual seizures. (3) Grade III patients have between one and three seizures each year. (4) Grade IV patients have more than four seizures per year, but the number of seizures decreases by 50% after treatment. (5) Grade V patients have seizures that decrease to less than 50% after treatment. (6) Grade VI patients have seizures that increase in number following treatment.

Based on these criteria, Grades I–II denoted that patients were cured of their refractory epilepsy, grades III–IV denoted an effective treatment, and grades V–VI denoted an ineffective treatment.

Statistical analysis

Data were analyzed using SPSS 13.0 software (SPSS, Chicago, IL, USA). The localization difference of foci by ^{18}F-FDG PET and EEG was compared using the chi-square test. A value of $P < 0.05$ was considered statistically significant. Rank-sum test with a $P < 0.05$ was considered to be a significant difference in comparison of treatment efficacy.

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Conflicts of interest: None declared.

Ethical approval: The study was approved by the Ethics Committee of Affiliated Hospital of Inner Mongolia Medical College, China.

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