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Original Article

The application value of ^{18}F-FDG PET/CT imaging in the gamma knife radiotherapy of lung cancer patients with brain metastases

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Abstract: This study aims to assess the effect of ^{18}F-FDG PET/CT imaging on the short- and long-term prognoses of lung cancer patients with brain metastases after gamma knife radiotherapy. 104 lung cancer patients with brain metastases were divided into the PET/CT (n = 52) and control groups (n = 52). In the PET/CT group, ^{18}F-FDG PET/CT imaging combined with gamma knife treatment was performed. Tumor targets were outlined and the prescription doses were determined based on the PET/CT findings during the gamma knife radiotherapy. In the control group, gamma knife treatment alone was given. The effective rates, local control rates, average survival times, and survival rates were compared. The preoperative and postoperative KPS scores at three months significantly differed in both groups (P = 0.000, 0.032). The clinical efficacy at postoperative three months significantly differed between the two groups (Z = -2.048, P < 0.05). In the PET/CT group, the effective rate at postoperative three months was 61.35% (32/52), significantly higher than the 42.30% (22/52) in the control group (P = 0.032). The local control rate significantly differed in the two groups [90.38% (47/52) vs. 75.00% (39/52); P = 0.038]. The average survival times were 14.2 and 12.2 months in the PET/CT and control groups (both P > 0.05). The incidence rate of acute and chronic adverse events was 21.15% in the PET/CT group, significantly lower than the 42.30% in the control group (P = 0.020). The application of ^{18}F-FDG PET/CT enables a closer tumor target delineation to the tumor biological target volume and increases the localized radiation dose in the high metabolic area during gamma knife radiotherapy. ^{18}F-FDG PET/CT imaging combined with gamma knife treatment is more efficacious and safer compared to gamma knife treatment alone.

Keywords: PET/CT, brain metastasis, gamma knife radiotherapy, efficacy

Introduction

Approximately 20%-40% of patients with malignant tumors suffer from brain metastases over the course of their disease progression [1, 2]. Lung cancer is the most common primary tumor associated with brain metastases, and roughly half of all lung cancer patients are diagnosed with brain metastases [3]. If no intervention is given, the clinical prognoses of lung cancer patients with brain metastases will be extremely poor, with a 1-year survival rate of 10.4% [4] and a median survival time one of 1 month [2, 5].

With the imaging technology optimization and effective systemic treatment, the median survival time of lung cancer patients with brain metastases can be prolonged to 6-8 months, or even longer. At present, whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) are adopted as the first-line therapy for newly-diagnosed brain metastases. Compared with traditional radiotherapy, the main advantages of gamma knife radiotherapy include accurate localization, a large local target dose, reliability, safety, and a rapid therapeutic effect. The principle of gamma knife treatment is to place the tumor lesions in high-energy gamma rays in an attempt to cause irreversible damage to the DNA chains in the tumor cells, eventually leading to tumor cell death [6].

Target delineation is one of the key procedures throughout radiotherapy. Current studies have demonstrated that the application of PET imaging can improve the clinical efficacy in the treatment of tumors by at least 30% [7]. PET/CT imaging, a noninvasive functional imaging procedure, can accurately and objectively display the locations, sizes, and borders of brain metastases through the tissue metabolic activity, tissue oxygen content, cell proliferation, and other biological pathways in the various stages of the tumor cells at the molecular level.

In this clinical trial, ^{18}F-FDG PET/CT imaging combined with gamma knife treatment was employed to delineate the tumor targets, measure the local radiotherapy doses, calculate the local tumor control rates, and evaluate the clinical prognoses of lung cancer patients with brain metastases, and to subsequently compare them with their counterparts undergoing gamma knife radiotherapy alone, aiming to provide clinical evidence for the feasibility of the application of ^{18}F-FDG PET/CT imaging combined with gamma knife treatment during radiotherapy.

Materials and methods

Inclusion criteria

(1) The primary lesions were confirmed through pathology, and the brain metastases were diagnosed using enhanced MRI; (2) The brain metastases was measurable on the images; (3) The KPS score was greater than 60, the number of lesions was less than 5, the maximum diameter was shorter than 5 cm, and the expected survival time was longer than 3 months; (4) Patients who did not receive chemotherapy in the previous four weeks.

Exclusion criteria

(1) Patients with severe, uncontrolled medical complications; (2) Patients who had been treated for brain metastases; (3) Patients whose liver and kidney function, blood routine, or ECG showed abnormalities were excluded from this investigation. Written informed consents were obtained from all the participants. The study procedures were approved by the ethics committee of the Affiliated Hospital of Inner Mongolia Medical University (WZ2019027).

Data acquisition

The clinical data of the 104 cases of lung cancer patients with brain metastases treated with gamma knife radiotherapy from January 2012 to December 2015 were retrospectively analyzed in this study. All the patients were randomly assigned into the PET/CT group (n = 52) or the control group (n = 52). The patients in the PET/CT group were treated with gamma knife radiotherapy within 2 weeks after their ^{18}F-FDG PET/CT scan, and the patients in the control group were treated with gamma knife radiotherapy alone.

Therapeutic method

First, all the patients were placed in the Leksell stereotactic positioning head frame under local anesthesia, and they underwent a location enhancement scan of T1 weighted axial with 3.0T MRI (GE), with a thickness of 3 mm seamless scanning. The treatment was based on the OUR-XGD gamma knife treatment planning system (Shenzhen Australian Fertility Corporation, China). The planning target volume (PTV) was delineated based on the tumor morphology, which was displayed on the enhanced localization MRI in the control group. To be closer to the biological target volume of the tumor, the ^{18}F-FDG PET/CT images were fused with the MRI images, and the PTV was delineated based on the high metabolic zone shown on the PET/CT images in the PET/CT group. According to the tumor size, the pathological characteristics, the peri-tumoral edema, and the patient's functional status, a 40%-60% isodose curve was utilized to pack the PTV with a peripheral dose of 12-20 Gy and a central dose of 20-33 Gy. According to each patient's physical conditions, mannitol, dexamethasone, or other intracranial pressure treatment were administered after the gamma knife treatment.

Efficacy evaluation criteria during follow-up

All the patients were followed up every three months until the patient's death or until the conclusion of this study. The brain metastases after the gamma knife treatment were evaluated based on the WHO solid tumor efficacy evaluation criteria into CR (complete remission), PR (partial remission), SD (stable disease), or PD (progression disease), respectively. Effective rate of tumor = (CR + PR)/sum × 100%, local control rate of tumor = (CR + PR + SD)/sum × 100%. Survival time is defined as from the diagnosis of the brain metastases to death or to the last follow-up date. The median

Table 1. Clinical characteristics of the patients in the two groups

Clinical characteristics	Age	Preoperative KPS score	Peripheral dose
PET/CT group	60.50±10.85	74.42±9.16	15.51±1.35
Control group	59.25±9.16	72.50±8.13	14.46±1.34
T value	0.635	1.132	3.981
P value	0.527	0.260	< 0.001

survival period is defined as the survival time corresponding to the cumulative survival rate of 0.5, indicating that only 50% of the individuals can survive during this period.

Statistical analysis

All the data analyses were performed using SPSS 19.0 statistical software (SPSS Inc., Chicago, IL). The survival times and rates were statistically analyzed and calculated using the Kaplan-Meier method and by plotting the cumulative survival rates. The baseline data of all the patients in the two groups were statistically compared using independent samples *t*-tests or *chi*-square tests. A *P* value of less than 0.05 was considered statistically significant.

Results

Baseline data

The baseline data of all the patients in the two groups were statistically compared using independent samples *t*-tests or *chi*-square tests. The ages, genders, pathological types, maximum diameters and locations of the brain metastases, RPA grades, or the preoperative KPS scores did not significantly differ between the two groups (all $P > 0.05$). The PET/CT imaging altered the target delineation and peripheral dose settings in some patients treated with gamma knife radiosurgery. Hence, the peripheral dose in the PET/CT group was calculated as 15.51±1.35, significantly higher compared to the peripheral dose of 14.46±1.34 in the control group ($P < 0.001$), as demonstrated in **Tables 1**, **2**.

Preoperative and postoperative KPS scores

As illustrated in **Table 3**, the preoperative KPS score in the PET/CT group was 74.42±9.16, which did not significantly differ from the KPS score of 72.50±8.13 in the control group (t = 1.132, P = 0.260). The KPS scores at postoperative 3 and 12 months did not significantly differ between the two groups (t = 1.476, P = 0.144; t = 0.560, P = 0.578). However, the KPS score at postoperative 6 months was 78.84±16.51, remarkably higher when compared with the KPS score of 70.79±19.64 in the control group (t = 2.003, P = 0.049).

Clinical efficacy after the gamma knife treatment

We evaluated the brain metastases by comparing the enhanced cranial MRIs of all the patients at 3 months after the gamma knife treatment in the two groups. The clinical efficacy of all the patients in the two groups was statistically compared, as illustrated in **Table 4**. At postoperative 3 months, the tumor recurrence rates in the PET/CT group and control group were 9.6% and 25.0%, and the difference was statistically significant (P = 0.038), and the rates were 27.27% and 47.72% at 6 months after the corresponding treatment, and this difference was also statistically significant (P = 0.048).

Survival times and rates

At the final follow-up, there were 11 surviving patients in the PET/CT group and 8 surviving patients in the control group. In the PET/CT group, 10 (24.4%) patients died of intracranial diseases, and in the control group 16 (36.4%) patients died of intracranial diseases. In addition, 31 (75.6%) and 28 (63.6%) patients died of extracranial diseases in the PET/CT and control groups (χ^2 = 1.433, P = 0.231). The percentages of the causes of death did not significantly differ between the two groups (**Figure 1**, **Table 5**).

Postoperative adverse reactions

No patient died after undergoing the gamma knife treatment. According to the RTOG evaluation criteria, an acute radiation response of the central nervous system (grades I-II) occurred in 9 patients in the PET/CT group and 17 patients in the control group. The symptoms were relieved by dehydration, intracranial pressure reduction and symptomatic treatment, respectively. No severe acute radiation reaction (≥ grade III) occurred. In the PET/CT group,

Table 2. Clinical characteristics of the patients in the two groups

Clinical characteristics	PET/CT group	Control group	X^2/*Z* value	*P* value
Gender				
Male	36	33		
Female	16	19	0.388	0.543
Pathology				
Adenocarcinoma	32	38		
Squamous cell carcinoma	12	8		
Small cell carcinoma	8	6	1.600	0.449
Number of brain metastases#				
1	21	12		
2~3	15	17		
4~5	16	23	-1.868	0.062
Maximum diameter of the brain metastasis (cm)#				
≤ 2	65	82		
2~3	57	64		
3~5	13	18	-0.161	0.872
Location of the brain metastasis				
Supratentorial	38	35		
Subtentorial	4	6		
Whole brain	10	11	0.571	0.752
RPA grade#				
Grade I	24	30		
Grade II	18	16		
Grade III	10	6	-1.305	0.192
Extracranial metastasis				
Yes	21	26		
No	31	26	0.971	0.325

#Nonparametric rank sum test.

Table 3. Comparison of the KPS scores in the two groups

Parameter	PET/CT group	Control group	*t* value	*P* value
Preoperative KPS	74.42±9.16	72.50±8.13	1.132	0.260
3 m KPS	84.17±13.18Δ	79.15±19.32Δ	1.476	0.144*
6 m KPS	78.84±16.51	70.79±19.64	2.003	0.049
1 y KPS	71.30±21.17	67.50±23.37	0.560	0.578

*Variance is not uniform, applying t-test; ΔCompared with preoperative KPS, $P < 0.05$.

Table 4. Comparison of the clinical efficacy in the two groups (n, %)

Parameter	PET/ CT group	Control group	X^2/Z value	*P* value
Quantity	52	52	-2.048	0.041
CR	12	9		
PR	20	13		
SD	15	17		
PD	5	13		
Effective rate	32 (61.53)	22 (42.30)	4.585	0.032
Local control rate	47 (90.38)	39 (75.00)	4.300	0.038

2 cases suffered from grades I-II adverse responses of the central nervous system, and 5 patients in the control group suffered similarly. No grade III or IV adverse events were observed in the two groups (**Table 6**).

Discussion

The Karnofsky performance status (KPS) is a quantitative indicator of patient health status and activity. Many studies have applied KPS as a prognostic marker, and it has been proven to be the optimal prognostic predictor [8]. Patients with a KPS score > 70 are generally expected to have longer survival [3, 9, 10]. In this study, the preoperative KPS scores of all the enrolled patients were higher th-

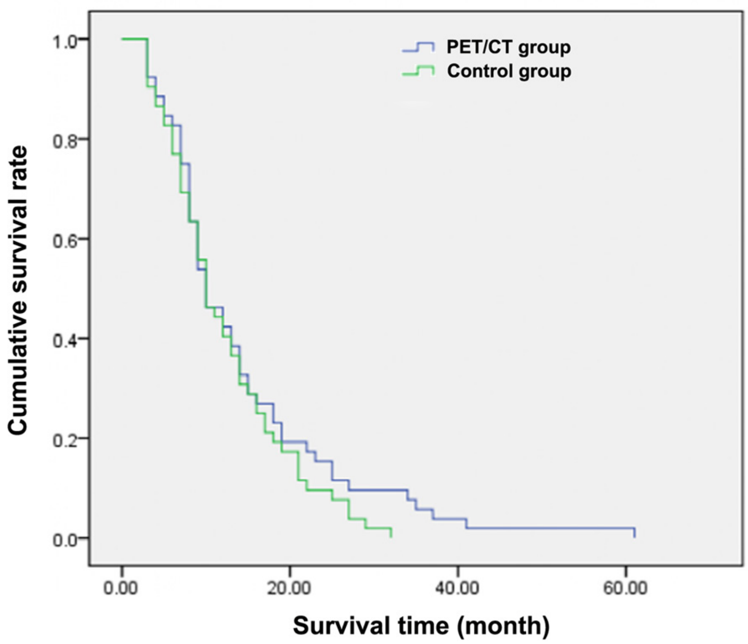

Figure 1. The cumulative survival curves of the two groups.

an 60, and the preoperative KPS scores did not significantly differ between the PET/CT and control groups. After the corresponding treatment, the KPS scores at postoperative 3 months were considerably higher than preoperative KPS scores in both groups, suggesting that gamma knife radiotherapy is an effective approach to improve the functional status of lung cancer patients with brain metastasis. The postoperative MRIs at 3 months showed that the quantity of intracranial lesions was increased or that new lesions emerged in certain patients. The low rate of tumor recurrence and the timely review of the new lesions did not lead to any focal symptoms. There was no significant difference in the KPS scores at 3 months after the treatment between the two groups. The KPS scores at 6 months after the operation were lower than they were at 3 months in both groups, but the KPS score was not significantly decreased in the PET/CT group. The possible reasons were that the tumor recurrence rate was higher in the control group, and the target delineation of the PET/CT group was more accurate and the peripheral dose was higher. Therefore, the local tumor control rate was improved in the PET/CT group. The KPS scores at 6 months and 1 year were lower than they were at 3 months after the operations in both groups, probably because of systemic disease progression and increased intracranial lesions from 6 months to 1 year, which resulted in a decrease in the overall KPS scores in both groups. As a quantitative index to evaluate the overall patient functional status, the KPS score varies with the development of the disease, so it can provide valuable information for choosing the appropriate treatment program and evaluating the patients' clinical prognoses.

Local control of brain metastases is defined as the stabilization or reduction of the metastasis after the treatment. After the gamma knife treatment, the cumulative radiation dose within a certain time window can achieve 90% of the radiation dose required to control the lesion [11]. Therefore, gamma knife treatment can be used as an effective method of controlling the growth of brain metastases. Studies have demonstrated that the local control rate of brain metastases is related to the pathology, lesion size, radiotherapy time, and dose [12]. Current studies have shown that small-cell lung cancer is the most sensitive to radiation therapy, squamous cell carcinoma is moderate, and adenocarcinoma is the least sensitive among the three types of lung cancer. Simonová's study found that the local control rates of brain metastases smaller than 2 cm in diameter were 85%, but the local control rates were reduced to 45% for brain metastases greater than 3 cm in diameter [13]. Another important independent prognostic factor affecting the local control rate of brain metastases with SRS is the maximum peripheral dose of the tumor target [14, 15]. In general, small tumors may receive higher peripheral doses, but the peripheral doses of larger tumors are more likely to be limited by the maximum tolerated doses. In this study, the tumor volume derived from 18F-FDG PET/CT was slightly smaller than the tumor volume shown by MRI, which was closer to the true tumor volume in the PET/CT group. Moreover, 18F-FDG PET/CT can be utilized to explicitly display the high metabolism area representing the activity of the tumor cells. Consequently, the PET/CT group can achieve a high radiation dose.

Table 5. Survival times and rates after the gamma knife treatment in the two groups

Group	Case	Survival time (months)		Survival rate (cases, %)			
		Mean	Median	6 months	1 years	2 years	3 years
PET/CT group	52	14.212	10.000	44 (84.62)	24 (46.15)	8 (15.38)	3 (5.77)
Control group	52	12.212	10.000	44 (84.62)	23 (44.23)	5 (9.62)	0 (0.00)
X^2 value		1.146		-	0.039	0.791	-
P value		0.284		-	0.844	0.374	0.243

Table 6. Comparison of the adverse radioactive events in the two groups (cases, %)

Group	Cases	Acute adverse reactions	chronic adverse reactions	Sum
PET/CT group	52	9	2	11 (21.15%)
Control group	52	17	5	22 (42.30%)
X^2 value				5.371
P value				0.020

Current studies report that the local tumor control rate ranges from approximately 75.47% to 94% at 2-3 months after the gamma knife treatment. Zhang et al. [16] reported a local control rate of 92.4% in 92 patients with brain metastases at 2-3 months after their gamma knife treatment, which is consistent with the findings of the present study. In the study, the local control rates and the effective rates of the tumors in the PET/CT group at 3 months after the operations were significantly higher than they were in the control group, probably because the tumor target volume delineated in the PET/CT group was closer to biological target volume of the tumor, and the peripheral dose in the PET/CT group was higher than it was in the control group. However, complete control of the metastatic brain lesions was not achieved after the corresponding treatment in both groups, possibly due to the following causes: the current limitations of imaging technology cannot fully realize tumor visualization. It fails to obtain intraoperative 3D imaging. It functions to protect the important structures (such as the tissues adjacent to the brainstem) and severe peritumoral edema restricts the peripheral doses; radiation-insensitive hypoxic cells and radioactive resistant cells exist in the tumor tissues, so a review is not promptly conducted after the treatment [17].

For both whole brain radiotherapy and stereotactic therapy, approximately 20-40% of patients with brain metastases die due to the progression of the intracranial lesions, and roughly 60-80% of patients eventually die due to the progression of extracranial diseases [18]. The existence of extracranial active lesions is the most important factor affecting the median survival times of patients [14]. Multivariate stratification studies have demonstrated that higher KPS scores, a lower class of recursive partitioning analysis (I or II RPA), a smaller tumor volume, non-melanoma primary tumors, the control of the primary tumor, longer time intervals of primary tumor metastasis to the brain, single metastasis, and higher edge doses are the prognostic factors [3, 5, 19]. Park et al. [4] statistically evaluated the clinical efficacy of gamma knife treatment in 147 patients older than 70 years with brain metastases, and the 6-month and 1-year overall survival rates were 60.4% and 29.4%. Zhang et al. [16] reported that the average survival time of 92 patients with brain metastases after gamma knife treatment was 11.7 months, and the 1-year and 2-year survival rates were 51.7% and 19.6%, which are almost consistent with the findings of the current investigation.

The correlation between the prescription dose and patient survival is well understood. In the study, the peripheral doses in the PET/CT group were higher than they were in the control group, but the survival rates in the PET/CT group were not significantly higher than they were in the control group, possibly because of the following causes: the peripheral dose difference between the two groups was not large. The patient's survival was affected by a variety of factors, such as whether to continue active treatment of the systemic disease and a timely review. At present, studies show that the survival rate of patients receiving gamma knife treatment is close to the rates of other standard treatments [20]. There is no difference between stereotactic radiosurgery and craniotomy in terms of the local control of the tumor, so gamma knife radiotherapy can be used as the preferred treatment for patients in a good general condition and with systematic disease control [5].

It is generally believed that stereotactic radiosurgery with high target doses is a feasible and effective treatment for increasing the local tumor control rate and prolonging patient survival time. However, higher peripheral doses and greater tumor target volumes may lead to more severe radiology toxicity [10]. Peripheral doses are related to the occurrence of radiation brain necrosis. Studies have shown that prescription doses exceeding 20 Gy are an important factor contributing to neurological deterioration after gamma knife therapy [21]. Ranjan [12] also found that the probabilities of radiation necrosis were 20%, 20%, and 12% for the lesions treated with 20 Gy, 18 Gy, and 15 Gy, respectively. The tumor target size correlates with the occurrence of radiation brain edema, and large brain metastases are more prone to radiation cerebral edema and radiation necrosis. Therefore, large brain metastases may be difficult to control with stereotactic radiosurgery [22]. In this study, the peripheral dose in the PET/CT group was higher than it was in the control group, but the incidence of adverse reactions was lower than it was in the control group. The reason may be that the tumor targets of the PET/CT images was closer to the biological target volumes of the tumors, and the normal brain tissue surrounding the tumor avoided being irradiated.

Conclusion

Taken together, PET/CT assists in the management of lung cancer patients with brain metastases by revealing the metabolism rather than the histology [23]. The application of PET/CT in a gamma knife radiotherapy program for lung cancer patients with brain metastases can make the tumor targets closer to the biological target volumes and can increase the local radiation doses in the high metabolic areas, improving the effective and local control rates, and reducing the incidence of adverse radioactive reactions. Due to the limitation of the small sample size, the PET/CT target delineation method has no uniform standards, because of the existence of physiological FDG high accumulation areas and current radiotherapy technology. Metabolic tumor volume can improve the diagnostic performance of ^{11}C-MET PET/CT for the diagnosis of recurrence in patients with metastatic brain tumors [24]. Nevertheless, the findings obtained from our study need to be validated by subsequent investigations with larger sample sizes.

Appendix: case report

The patient, a middle-aged man, was diagnosed with lung cancer brain metastases (pathology: moderate-poorly differentiated adenocarcinoma). His preoperative ^{18}F-FDG PET/CT showed a CT visible group-like high density shadow in the right temporal lobe, and visible liquid density in it, the midline compression shifted to the left; a PET mass with the imaging agent of a group-like abnormal concentration, an SUV_{max} of about 12.3, so the patient was diagnosed with right temporal lobe metastasis with peripheral edema. Enhanced positioning MRI in the gamma knife radiotherapy showed visible irregular and uneven enhancement shadows in the right temporal lobe. The lesion size was about 45 × 38 mm, and edema could be seen in the surrounding tissues. The right lateral ventricle and the three ventricles were compressed, and the midline structure was shifted to the left. In the formulation of the gamma knife radiotherapy, we compared the MRI and PET/CT images (**Figure 2A**, **2B**): the ^{18}F-FDG abnormal concentration area represented tumor cells with a high metabolism area in the PET/CT imaging. The tumor volume derived from PET/CT was smaller than what showed on the MRI. Based on the PET/CT images, we narrowed the tumor target volume and made the target volume closer to the biological target volume of the tumor. And for the relatively small tumor target volume, we further increased the radiation dose of the high metabolic area. Finally, we developed a radiotherapy plan with PET/CT and MRI images: the isotonic curve was 45%, the peripheral dose was 14 Gy, and the central dose was 31.1 Gy. A review of the MRI at 2 months after the treatment showed that compared with the previous MRI imaging, the right temporal lobe metastases were significantly reduced after the treatment (**Figure 2C**, **2D**).

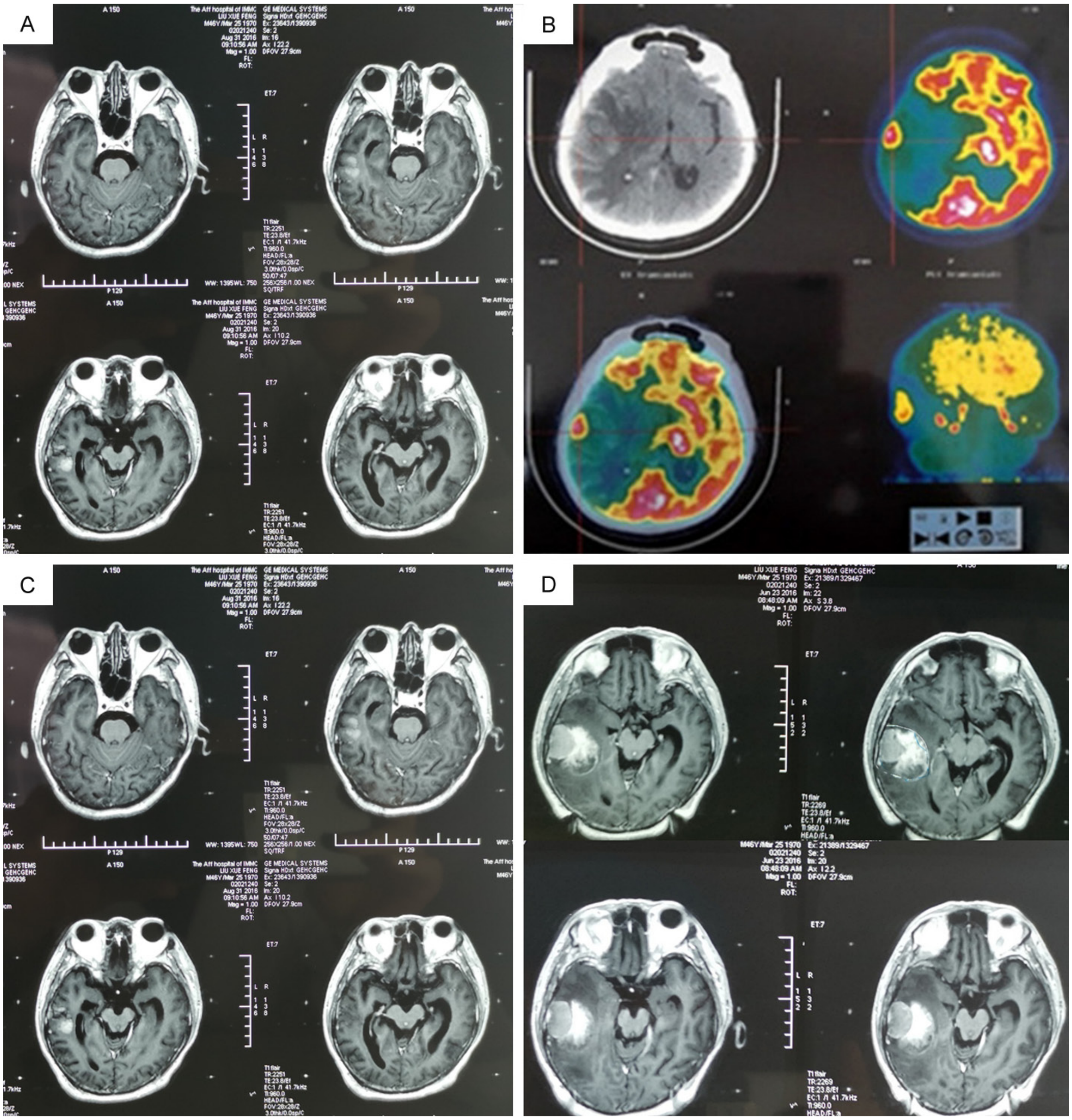

Figure 2. Right temporal lobe brain metastasis (lung cancer: moderately poorly differentiated adenocarcinoma). A. Intraoperative enhanced localization MRI; B. ^{18}F-FDG PET/CT imaging; C. Intraoperative enhanced localization MRI; D. Enhanced MRI at 2 months after the treatment.

Disclosure of conflict of interest

None.

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