Case Report

Monitoring Treatment Response to Erlotinib in *EGFR*-mutated Non–small-cell Lung Cancer Brain Metastases Using Serial *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine PET

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Clinical Practice Points

- Brain metastases emerge frequently in metastatic non–small-cell lung cancer (NSCLC).
- The efficacy of systemic treatment on brain metastases, especially of targeted therapy approaches, is usually unpredictable owing to the restrictive properties of the blood-brain barrier.
- Response evaluation is further corrupted by the technical limitations of standard brain magnetic resonance imaging scans. Improving diagnostic techniques for therapeutic response control of brain metastases is thus of great clinical interest.
- Here, we report on the diagnostic significance of *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET)-positron emission tomography (PET) for monitoring therapeutic efficacy of erlotinib on brain metastases in a patient with metastatic NSCLC harboring an activating *EGFR* mutation.
- Our observations suggest that FET-PET might have additional diagnostic value to magnetic resonance imaging scans for the assessment of early response and progression of brain metastases in patients with NSCLC subjected to tyrosine kinase inhibitor therapy.

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Introduction

Patients with advanced stage non–small-cell lung cancer (NSCLC) harboring activating epidermal growth factor receptor (*EGFR*) mutations benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs). However, brain metastases (BMs) occur frequently and contribute significantly to disease-related morbidity and mortality, and hence, constitute a critical therapeutic challenge in oncology. The central nervous system represents a sanctuary site as TKI efficacy is limited here owing to restricted penetration of the blood-brain barrier.[1,2] Though limited, intracranial responses are nevertheless particularly seen in patients receiving EGFR TKI therapy.[3] Hence, the intracranial efficacy of TKI therapy is

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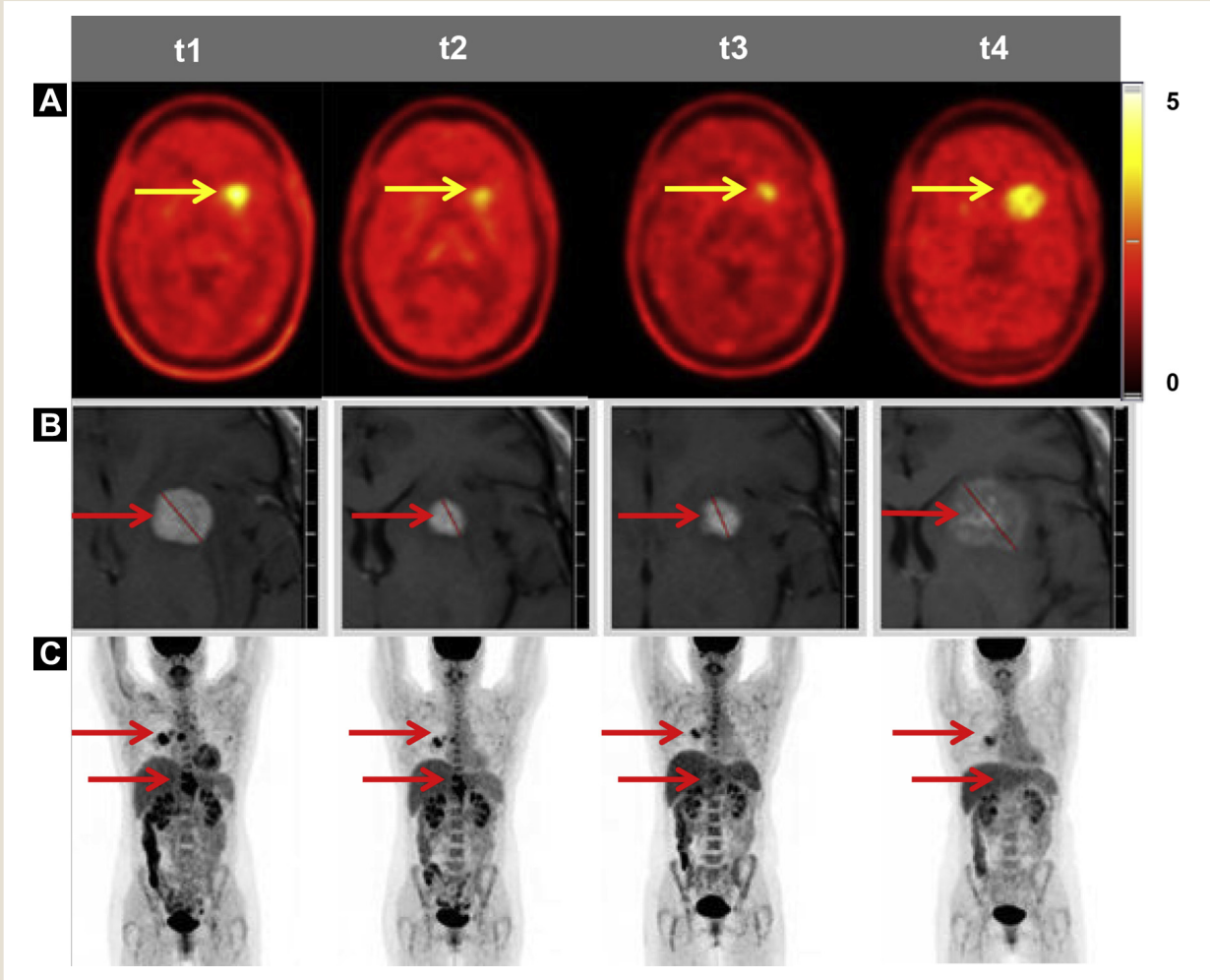
unpredictable, thereby explaining the need for specific and sensitive diagnostic techniques for evaluation of therapeutic efficacy of an applied EGFR TKI treatment. The value of ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET for early prediction of response to EGFR TKI treatment has already been shown in extracranial NSCLC tumor sites.[4] However, FDG is not an appropriate tracer for the detection and monitoring of BMs owing to the high and ubiquitous physiological glucose metabolism in the cerebral cortex. Thus, contrast-enhanced magnetic resonance imaging (MRI) is the mainstay of clinical practice and is incorporated into surgical and radiotherapy planning, monitoring of treatment response, and identification of disease progression in patients with primary and secondary brain tumors. This technique has a high availability and an excellent spatial resolution, but, especially in gliomas, the ability to accurately define the tumor volume and quantify the burden of disease is limited.[5-7] Furthermore, following neuro-oncological treatment such as resection and radiotherapy as well as drug treatment for primary and secondary brain tumors (eg, alkylating chemotherapy, immunotherapy), can lead to reactive and benign MRI signal changes (eg, hyperintensities on T2 or fluid attenuation inversion recovery sequences or an increase of the contrast enhancement extent), which are difficult to discern from true tumor progression.[8-10] Clinically, these reactive treatment-related changes, frequently named pseudoprogression, are of considerable importance because an effective treatment might be erroneously terminated too early with potentially negative influence on survival. Furthermore, these MRI signal alterations may also occur owing to demyelination, ischemia, and infection/inflammation.[11]

O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) PET was recently introduced as a useful diagnostic technique for successful treatment

Figure 1 **A, Serial FET-PET Images (SUVmax; Mean Activity, 275 MBq, Scan Start, 74 Minutes p. i.); B, Contrast-Enhanced MRI Scans; C, Whole Body FDG-PET/CT Scans (SUVmax); at Baseline (t1), After 2 Weeks (t2), 8 Weeks (t3), and 23 Weeks (t4); for Quantitative PET Analysis, Iterative Reconstruction Settings Were Applied. Arrows in (A) and (B) Indicate the Left Frontal Brain Metastasis, Showing Treatment Effects to Erlotinib in Representation for All Cerebral Lesions During the Course of Treatment. Arrows in (C) Indicate Treatment Changes of Extracranial Lesions Over Time**



Abbreviations: CT = computed tomography; FDG = ^{18}F-2-fluoro-2-deoxy-D-glucose; FET = –(2-[^{18}F]fluoroethyl)-L-tyrosine; MRI = magnetic resonance imaging; PET = positron emission tomography; SUV = standardized uptake value.

Table 1 Quantitative Values of PET Findings During Therapy With Erlotinib and Additional Radiotherapy of the Spinal Lesion

Date	FET-PET Cerebral Lesion, SUV_{max}	FDG-PET Lung Lesion, SUV_{max}	FDG-PET Spinal Lesion, SUV_{max}	MRI Diameter Cerebral Lesion, mm
Baseline (t1)	3.18	10.8	9.4	19
After 2 weeks (t2)	2.88	8.5	8.4	10
After 8 weeks (t3)	2.48	7.7	7.7	10
After 23 weeks (t4)	3.44	4.7	n/a[a]	24
Metabolic outcome (t4)	Progressive disease	Partial response	Complete response	Progressive disease

See also Figure 1.
Metabolic outcome according to PET Response Criteria in Solid Tumors (PERCIST).
Abbreviations: FDG = ^{18}F-2-fluoro-2-deoxy-D-glucose; FET = −(2-[^{18}F]fluoroethyl)-L-tyrosine; MRI = magnetic resonance imaging; PET = positron emission tomography; SUV = standardized uptake value.
[a]After concomitant radiation.

response evaluation, especially detection of pseudoprogression, in patients with malignant melanoma BM treated with immune checkpoint inhibitors ipilimumab or nivolumab.[12] Especially in gliomas, various studies have demonstrated that the metabolically active tumor volume and the metabolic tumor activity (as assessed by standardized uptake values [SUVs] or tumor-to-brain ratios) provide more information in terms of treatment response assessment than standard MRI based on Response Assessment in Neuro-Oncology (RANO) criteria.[13,14] FET-PET is used in the management of glioma patients, and the additional diagnostic value to standard MRI has been predominantly demonstrated for the delineation of tumor extent, treatment monitoring, and the differentiation of tumor recurrence from treatment-related changes such as pseudoprogression and radionecrosis.

Case Report

A 44-year-old female patient (50 pack-years) presented with a tumor in the right upper lobe of the lung and metastases in mediastinal lymph nodes, thoracic vertebrae 9-11, and 9 infra- and supratentorial BMs, with the largest BM measuring 19 mm in diameter in the left frontal lobe (cT3 cN2 cM1b, UICC stage IV) (Figure 1). Biopsy revealed a highly differentiated, thyroid transcription factor1-positive adenocarcinoma of the lung. The patient received 1 cycle of cisplatin/pemetrexed prior to molecular diagnostics and refused both further chemotherapy and whole-brain radiation (WBR) of the BM.

Next-generation sequencing (NGS) of the biopsy specimen demonstrated an unusual *EGFR* double mutation partly affecting the activating loop on exon 21, p.L858R, beside a p.A859S mutation of unknown significance (p.[L858R;A859S]). Although imaging scans of the brain showed rapid progression of BM, the patient still refused WBR. An interdisciplinary tumor board suggested treatment with erlotinib with close monitoring. After informed patient consent, erlotinib treatment was initiated immediately (150 mg/d).

Extracranial therapy response was monitored using serial whole body FDG-PET/computed tomography scans. BMs were monitored by both serial standard MRI and FET-PET scans. After 2 weeks of erlotinib treatment, PET imaging showed significant reductions in metabolic activity in extracranial lesions as well as in BMs (Table 1), indicating response (Figure 1, time points t1, t2). Six weeks later, tracer uptake of the left frontal lesion further decreased as compared with time point t2 (SUV_{max} decrease, 13%) (Table 1). In contrast, MRI scans did not show further shrinkage of the left frontal contrast-enhancing lesion (Figure 1, time point t2, t3). The extracranial metabolic activity as assessed by FDG-PET remained very low. The patient finally agreed to palliative radiotherapy of the vertebral bone metastases, leading to a complete metabolic response in this tumor site (Figure 1, time point t4).

After 23 weeks of erlotinib therapy, FET-PET revealed, in line with the brain MRI, an increased metabolic activity in the left frontal lobe (Table 1 and Figure 1, time point t4), indicating tumor progression. Conversely, extracranial metabolic activity determined by FDG-PET remained low with no signs of progressive disease according to the PET Response Criteria in Solid Tumors (PERCIST) (Figure 1, time point t3, t4). A stereotactic biopsy of the progressive left frontal brain metastasis confirmed NSCLC histology and persistence of the *EGFR* p.[L858R;A859S] double mutation, with no detection of a resistance mechanism such as *EGFR* T790M mutation, *MET*, or *HER2* amplification nor any other relevant genetic mutation in our 14 gene NGS panel. The patient subsequently received brachytherapy of the left frontal lesion using iodine-125 seeds[15] and WBR owing to further extensive intracranial tumor progression with detection of over 50 new supra- and infratentorial BMs. Hereafter, the patient received erlotinib 300 mg/d and died 22 months later.

Conclusion

Our case suggests the diagnostic potential of FET-PET for the assessment of early response and disease progression of BMs in *EGFR*-mutated NSCLC treated with TKI therapy. Although FDG-PET was useful in repeatedly monitoring extracranial tumor response, FET-PET was of superior diagnostic value in assessment of intracranial response. In contrast to MRI, FET-PET in our patient even seemed to be a more sensitive diagnostic imaging technique for detection of early response of BMs during treatment before morphologic changes became evident in contrast-enhanced MRI. Nevertheless, the strong progression in BMs in our patient was also detectable by MRI, and smaller lesions could not be detected in FET-PET.

The lack of an identified mode of acquired resistance to *EGFR*-targeted therapy underlines the need for proper diagnostic tools in the assessment of intracranial therapy response. Our observations suggest that FET-PET might be a highly sensitive and effective imaging technique and moreover, might add functional insights to standard MRI scans in monitoring BMs. Further clinical

investigation of the diagnostic significance of FET-PET, especially regarding response evaluation of targeted therapy in tumor brain metastases, is warranted.

Disclosure

The authors have stated that they have no conflicts of interest.

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