

# Negative $^{18}\text{F}$ -FET PET/CT in Brain Metastasis Recurrence: a Teaching Case Report.

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## Case report

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# Abstract

Positron emission tomography (PET) using O-(2-[<sup>18</sup>F]fluoroethyl)-L-tyrosine (<sup>18</sup>F-FET) positron emission tomography (PET) has been shown to be a useful tool for differentiating radiation therapy outcomes either brain metastasis recurrence or radiation necrosis. We present the case of a female with known metastatic brain lesion with suspicion of tumor recurrence on follow-up MRI 16 months after radiosurgery. <sup>18</sup>F-FET PET was indicative of radiation necrosis. Due to the patient's medical history, the discrepancy between brain MRI and the PET/CT results, surgical biopsies were decided, which were positive for brain metastasis recurrence. Diagnosis of metastasis recurrence may be challenging also on <sup>18</sup>F-FET PET/CT. In case of discrepancies between MRI and PET/CT results, false-negative <sup>18</sup>F-FET PET/CT is still possible and should lead to careful follow-up or biopsy.

## Introduction

O-(2-[<sup>18</sup>F]fluoroethyl)-L-tyrosine PET (<sup>18</sup>F-FET) is an artificial amino acid taken up into upregulated tumoral cells but not incorporated into proteins with rising use in positron emission tomography/computed tomography (PET/CT), especially in the imaging of primary brain tumors and metastatic lesions. It demonstrated very good performance for the initial assessment of patients with new, isolated, untreated brain lesions (1). We present a case of a unique false negative metastatic lesion on an <sup>18</sup>F-FET PET/CT exam in which the treated brain metastasis showed a low to moderate avidity and quantitative metrics consistent with radionecrosis. There was initially concerns about the discordance between the PET/CT and the MRI that showed signs of tumor recurrence. Surgical biopsies were decided after multidisciplinary discussion and showed the lesion corresponding to tumoral tissue residue.

## Case Report

A 58 years female patient with cerebral metastases from pulmonary adenocarcinoma of the right upper lobe presented after a surveillance MRI showed progression of her disease. She was initially diagnosed with adenocarcinoma 4 years earlier, confirmed after a bronchoscopic biopsy and staged: cT1a (0.6 cm) cN2 (station 4R) cM1b (brain metastases), stage IV (according to the TNM 7th edition), without EGFR mutation or ALK/ROS1 rearrangement, PD-L1 negative :cT1a cN2 cM1c (brain metastases), stage IVB (according to TNM 8th edition) With KRAS mutation (G12S, exon 2) and TP53 (C275S, exon 8), without ERBB2 and BRAF mutation. Initial cerebral imaging was suggestive of metastatic disease.

Radio-chemotherapy with 4 cycles of cisplatin-pemetrexed from 15.01.2018 to 19.03.2018, with concomitant radiotherapy in the right upper lobe and mediastinum with a total dose of 66 Gy (in 33 fractions of 2 Gy) from 12.02.2018 to 30.03.2018, and on the 12.10.2018, stereotactic radiotherapy for brain metastases, with a dose of 20Gy in single fraction for each was done.

The patient was followed with surveillance MRI scans every 2–3 months. Her most recent surveillance MRI showed increase of two treated lesions, one in the right frontal lobe and one in the right parietal lobe,

suggestive of radionecrosis, and a 2-month control was recommended according to the multidisciplinary tumor board. The 2-month control MRI showed an increase in size of the right frontal lesion with a soft tissue component with contrast enhancement in its posterior part, whose perfusion (nrCBV = 2.3, nrCBF = 2.8) and spectroscopy (Cho/Cr ratio = 2.9) suggest the persistence of tumor residue in this region (Fig. 1).

A  $^{18}\text{F}$ -FET PET/CT was performed to further characterize these changes and showed a heterogeneous and low to moderate uptake of the radiotracer at the level of the right anterior frontal lesion, whose quantitative analysis (maximum tumor-to-brain ratios = 2.2, cumulative time-activity curve [TAC]) was in favor of a radionecrotic lesion (Fig. 1). No significant radiotracer uptake was seen in the other metastatic lesions treated by radiosurgery.

In this context, her case was re-discussed at the multidisciplinary meeting for brain metastases where a surgical resection of the right frontal lesion was proposed.

Histology analyses of excisional biopsies of the dura matter and of the lesion showed metastasis of her initial adenocarcinoma with partly calcified dura mater with chronic inflammatory reaction and foreign bodies with no metastatic lesions in the dura matter.

## Discussion

A current issue frequently encountered in oncological management of brain metastases is differentiating tumor recurrence from treatment-related changes following stereotactic radiation therapy. Sometimes brain MRI does not always allow a clear differentiation between local brain tumor recurrence and progression from radiation-induced changes including radiation necrosis. Radiation necrosis usually manifests within 6–12 months after radiotherapy treatment and occurs in approximately 5–25% of all treated patients. (2) (3). A similar rate is found in patients with brain metastases treated by radiosurgery (4) taking in consideration that rate could change according to the radiation total dose, field, number and frequency of doses.

On MRI, A usual characteristic of radiation necrosis on contrast-enhanced sequences is what is called geographic enhancement or Swiss cheese-like enhancement (5). Nonetheless, conventional MRI is not all the times sufficient to differentiate tumor progression/recurrence from treatment-related effects (6). Some sequences may have additive value in oncological imaging. Diffusion-weighted imaging, especially the apparent diffusion coefficient (ADC) sequences can help differentiating tumor recurrence and radiation necrosis. Because of less water mobility properties in high cellular lesions, the ADC will be low in the case of tumor recurrence. On the other hand, an increased ADC is attributed to increased water mobility in cases of radiation necrosis (7). In addition, magnetic resonance spectroscopy (MRS) is ongoing subject of research and may show N-acetyl aspartate (NAA) and creatinine (Cr) decrease in case of radiation necrosis, whereas high choline (Cho) is correlated with tumor recurrence.<sup>(8)</sup>, (9). The Cho/Cr ratio and the Cho/NAA ratio have been described as good markers for differential diagnosis (10) (11). MR perfusion techniques using contrast enhancement can measure the relative cerebral blood volume (rCBV)

and estimate the vascularity and hemodynamics. Hyperperfusion is seen in tumor progression, and hypoperfusion is seen in radiation necrosis (12) (13). It has been reported that rCBV values < 0.6 suggest radiation necrosis and values > 2.6 suggest tumor progression (14).

Several PET/CT tracers have been investigated as an imaging modality to distinguish treatment effect from tumor in clinical practice (15). Among them was the  $^{18}\text{F}$ -FET PET, which showed a high diagnostic performance; using tumor/brain ratios and dynamic parameters with a sensitivity of 95% and specificity of 91% (16). At present, the differentiation of radiation injury from metastasis recurrence using amino acid PET has been the most thoroughly investigated indication (15), repeatedly demonstrating high diagnostic accuracy. Galldiks et al. notably reported that the combined evaluation of the TBRmean of  $^{18}\text{F}$ -FET uptake and the pattern of the TAC can differentiate local brain metastasis recurrence from radionecrosis with high accuracy (16). This study and others were confirmed by Ceccon et al., where they set the cut-off for TBRmax = 2.55 with a sensitivity of 83% and a specificity of 85%, TBRmean cutoff = 1.95 with a sensitivity of 86% and a specificity of 88%, and for TAC slope of 0.125 SUV/h, with a sensitivity of 68% and a specificity of 61% (17). It is worth mentioning that these results were obtained mainly from retrospective analyses in small cohorts, and that there was no histological confirmation of the diagnosis in many cases. In addition, it remains unknown whether all metastases from different primary tumors behave the same regarding  $^{18}\text{F}$ -FET uptake at baseline or during follow-up, which could limit the reproducibility of these preliminary reports. One point to be considered in the differential diagnosis is that very small lesions of which the SUV may not be sufficient to reach the threshold value of 2.55 due to the partial volume effect. Further histological correlation and prospective studies are now needed, especially to optimize  $^{18}\text{F}$ -FET uptake cut-off values according to primary tumor types to detect progression.

## Conclusions

In conclusion, causes of false negative  $^{18}\text{F}$ -FET uptake are not well investigated yet and actual evidence of this in the literature is scarce. This case demonstrates important teaching points for the tumor board team involved in the management of brain metastases patients. In the event of inconsistent findings between MRI and  $^{18}\text{F}$ -FET PET/CT, care must be taken before giving the final diagnosis. Collaborative discussion between radio-oncologists, radiologists and nuclear physicians can help favoring one diagnosis over the other. Another point is although  $^{18}\text{F}$ -FET PET/CT is sensitive and specific to detect post treatment changes in brain metastases, it is however important to be careful about the pattern of lesion uptake, as in our case.

## List Of Abbreviations

(PET) Positron emission tomography

( $^{18}\text{F}$ -FET) O-(2-[ $^{18}\text{F}$ ]fluoroethyl)-L-tyrosine

(TAC) time-activity curve

(ADC) apparent diffusion coefficient

(MRS) magnetic resonance spectroscopy

(NAA) N-acetyl aspartate

(Cr) creatinine

(Cho) choline

(rCBV) relative cerebral blood volume

(TBR) tumor/brain ratios

## **Declarations**

**Ethics approval and consent to participate (statement on ethics approval and consent / name of the ethics committee that approved the study):**

Not applicable

**Consent for publication (consent to publish must be obtained from that person):**

Ready if needed

**Availability of data and material:**

All data generated or analysed during this study are included in this published article.

**Competing interests:**

The authors declare that they have no competing interests

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**Authors' contributions:**

JP analyzed and interpreted the patient PET CT images and participate in writing the manuscript. MM and VD analyzed and interpreted the patients MRI examinations and were contributors in writing the manuscript. LS and SA were on charge of treating the patient by radiation, following her during the entire time. SA is the main author and wrote the manuscript. All authors read and approved the final manuscript."

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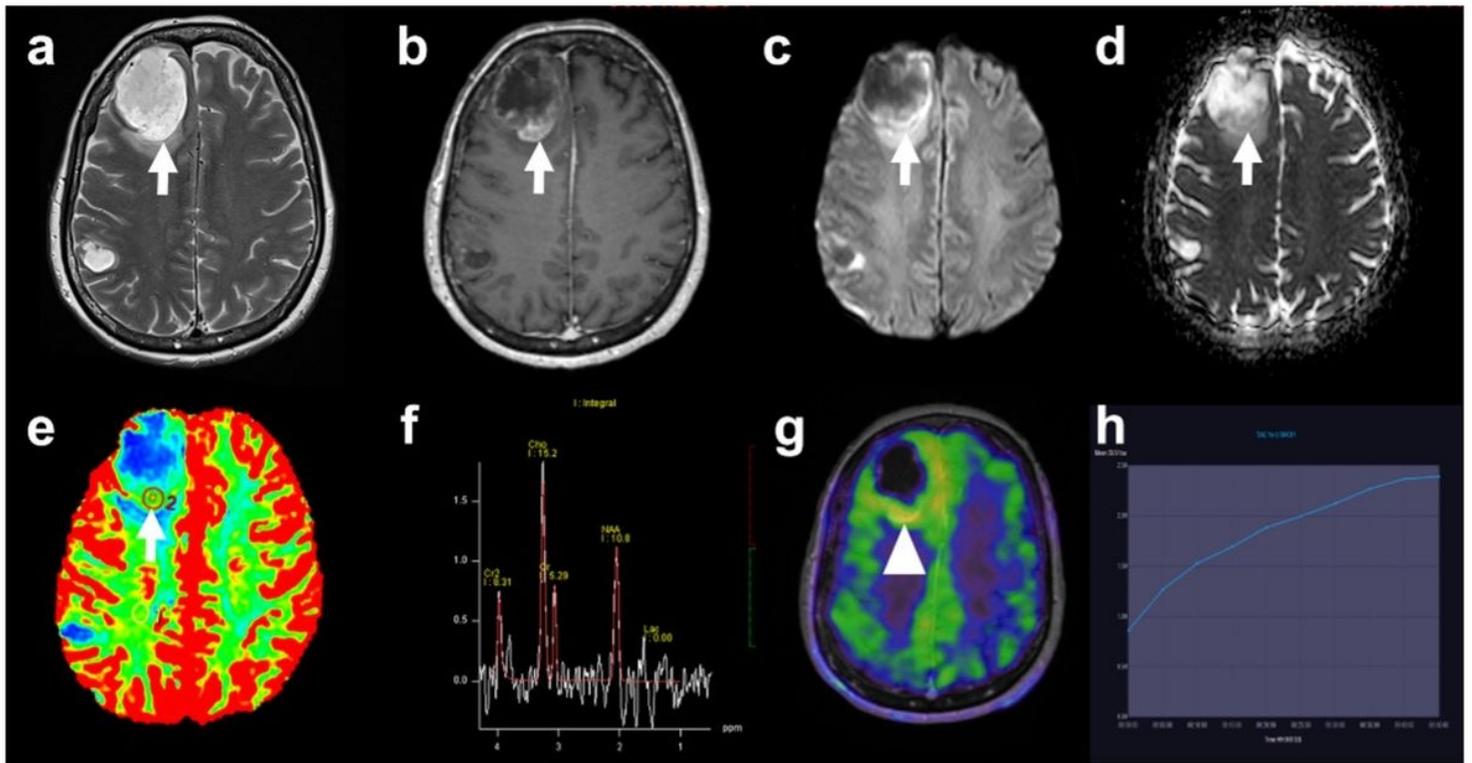
Not applicable

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## Figures



**Figure 1**

MRI and  $^{18}\text{F}$ -FET PET/CT findings. In our 58 year-old female patient, follow-up brain MRI performed 16 months after radiosurgery showed increase in size of a treated right frontal lesion (white arrow) that appeared hyperintense on T2 weighted images (a), with central necrosis and peripheral thick contrast enhancement on T1 weighted images (b). The periphery of the lesion was bright on diffusion weighted imaging (c) with moderately low ADC (d). On perfusion weighted images, the nrCBV was 2.3 (e) and nrCBF was 2.8 (not shown) while MR spectroscopy (f) showed a high peak of choline with Cho/Cr ratio of 2.9, which overall indicated tumor residue. While  $^{18}\text{F}$ -FET PET/CT raw images showed moderate peripheral uptake (g, arrow head), the maximum target-to-background ratio was of 2.2 (i.e. lower than 2.55) and the time-activity-curve showed increasing uptake over time (h), which was interpreted as signs of radiation necrosis.