Treatment monitoring of immunotherapy and targeted therapy using amino acid PET in patients with brain metastases

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Background

Due to the lack of specificity of contrast-enhanced MRI, both the response assessment and differentiation of progression from pseudoprogression following immunotherapy using checkpoint inhibitors (ICI) or targeted therapy (TT) may be challenging, especially when ICI or TT is applied in combination with radiotherapy (**Figure 1**).

Recently, the Response Assessment in Neuro-Oncology (RANO) Working Group has analyzed the additional diagnostic value of amino acid PET in patients with primary and secondary brain tumors and recommended the use of this imaging technique in addition to conventional MRI.

Here, we investigated the value of PET using the radiolabeled amino acid *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) for treatment monitoring of ICI or TT alone or in combination with radiotherapy in patients with brain metastases (BM) secondary to malignant melanoma and non-small cell lung cancer (NSCLC) since contrast-enhanced MRI often remains inconclusive.

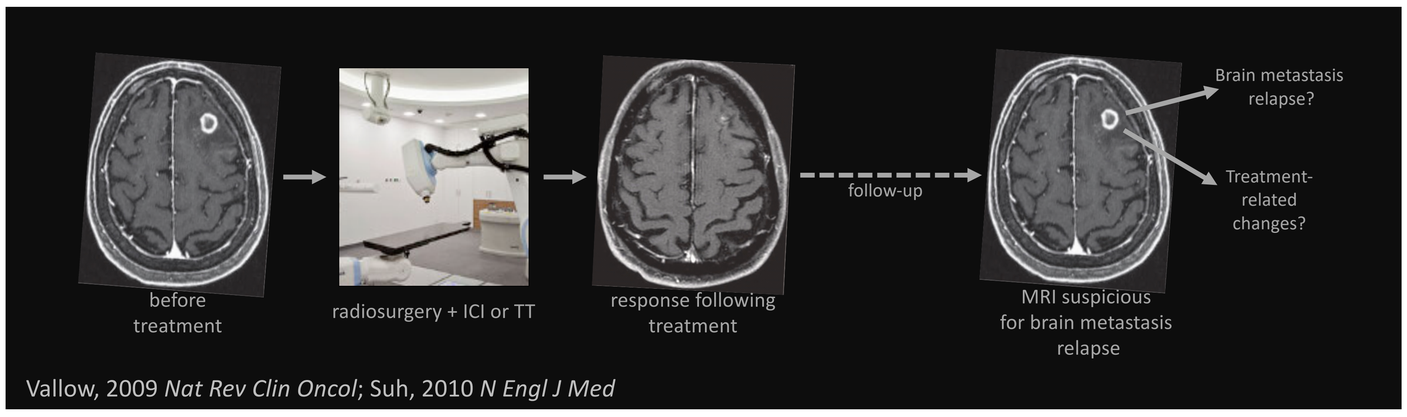

Figure 1: Following radiosurgery combined with ICI or TT, standard MRI cannot reliably differentiate between treatment-related changes and brain metastasis relapse

Patients and Methods

We retrospectively identified 40 patients with 107 brain metastases secondary to malignant melanoma (n=29 patients with 75 brain metastases) or non-small cell lung cancer (n=11 patients with 32 brain metastases) treated with ICI or TT who had FET PET (n=60 scans) for treatment monitoring from 2015-2019.

The majority of patients (n=37; 92.5%) had radiotherapy during the course of disease. In 27 patients, FET PET was used for the differentiation of treatment-related changes from brain metastases relapse following ICI or TT. In 13 patients, FET PET was performed for response assessment to ICI or TT using baseline and follow-up scans (median time between scans, 4.2 months).

In all lesions, static and dynamic FET PET parameters were obtained (i.e., mean tumor-to-brain ratios (TBR), time-to-peak values). Diagnostic accuracies of PET parameters were evaluated by receiver-operating-characteristic analyses using clinicoradiological or neuropathological findings as reference. Diagnosis of treatment-related changes or brain metastasis relapse on MRI was based on iRANO criteria. Response to the applied treatment on FET PET was considered if a decrease of metabolic activity at follow-up was associated with a stable clinical course for at least 6 months.

Results

TBR values were significantly higher in patients with BM relapse (n=10) than in patients with treatment-related changes (n=17) (2.4 ± 0.8 vs. 1.7 ± 0.3, $P < 0.001$). A TBR threshold of 1.95 differentiated BM relapse from treatment-related changes with an accuracy of 85% (AUC, 0.85 ± 0.09; sensitivity, 70%; specificity, 94%; $P = 0.003$) (**Figure 2**).

Metabolic Responders to ICI or TT on FET PET (threshold of TBR reduction relative to baseline, ≥ 10%; accuracy, 82%) had a significantly longer stable follow-up than non-responding patients (median time, 10.5 vs. 4 months; $P = 0.004$). Additionally, at follow-up, time-to-peak values in metabolic responders increased significantly ($P = 0.019$).

Furthermore, in 4 of 13 patients (31%), FET PET at follow-up provided additional information for treatment response evaluation beyond the information provided by contrast-enhanced MRI alone: (i) in two metabolic responders on FET PET, MRI changes were consistent with progression according to RANO criteria (**Figure 3**); (ii) one patient with an unchanged MRI ("stable disease") at follow-up had a metabolic response on FET PET (**Figure 4**); and (iii) one patient had increased metabolic activity (metabolic non-responder) despite "partial response" according to RANO criteria on contrast-enhanced MRI.

Conclusions

FET-PET may add valuable information for treatment monitoring in individual BM patients undergoing RT in combination with ICI or TT.

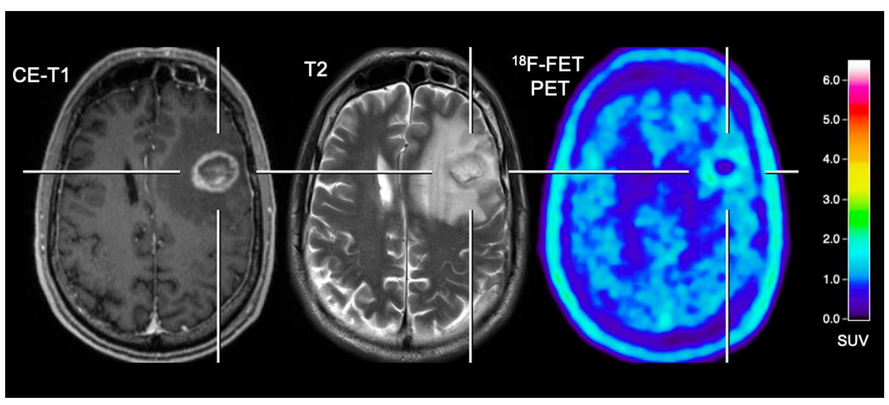

Figure 2: Patient with a melanoma brain metastasis pretreated with radiosurgery, dabrafenib+trametinib, and nivolumab. In contrast to the progressive MRI, amino acid PET using FET shows no significant uptake and is consistent with treatment-related changes

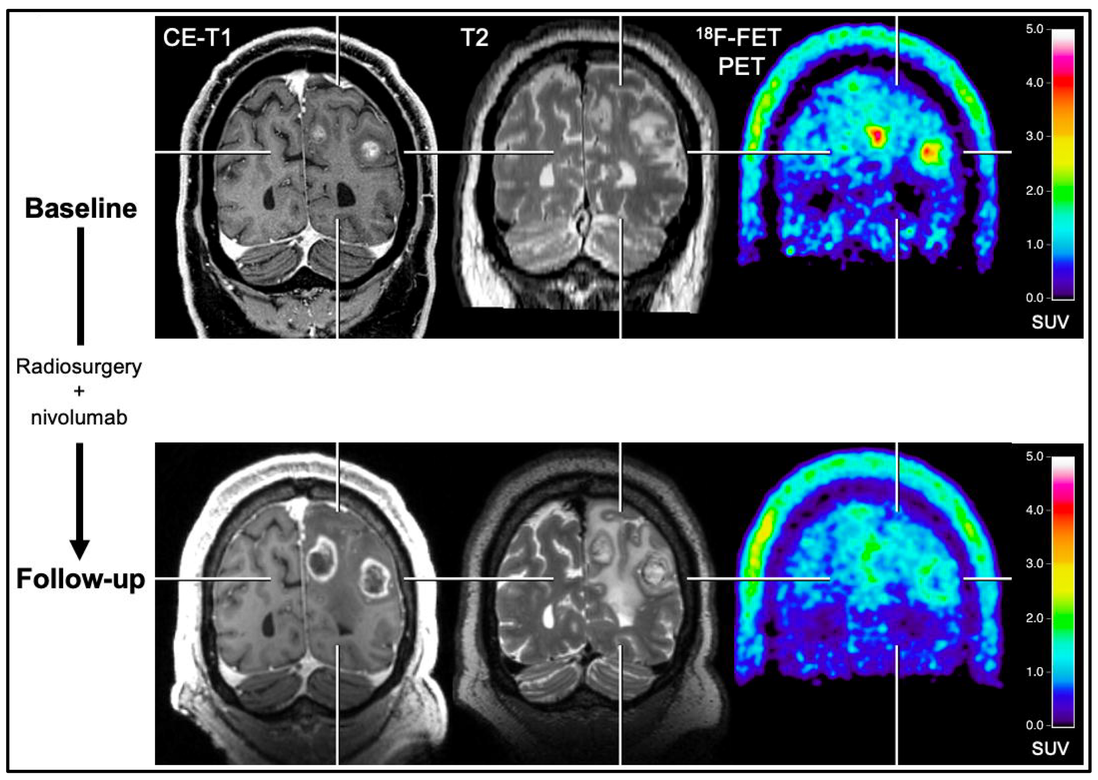

Figure 3: Following radiosurgery concurrent to nivolumab in patient with melanoma brain metastases, FET PET at follow-up 12 weeks after treatment initiation (bottom row) shows a significant decrease of metabolic activity (TBRmean, -28%) compared to baseline (top row). In contrast, MRI changes were consistent with progression according to RANO criteria for brain metastases. The reduction of metabolic activity was associated with a stable clinical course over 10 months

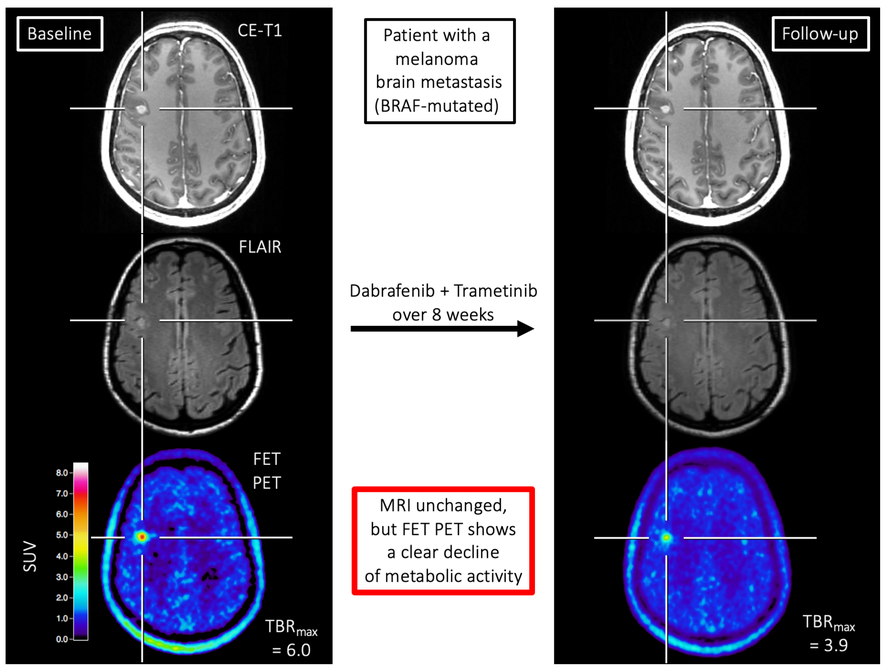

Figure 4: Baseline and follow-up images of patient with a melanoma brain metastasis. At follow-up, a clear decrease of the tumor/brain ratios (-35%) is observed whereas the MRI shows no significant change of both the contrast enhancement and FLAIR signal defined as stable disease according to RANO criteria for brain metastases

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