An updated review on the diagnosis and assessment of post-treatment relapse in brain metastases using PET

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Running title: Diagnosis of brain metastases relapse using PET

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ABSTRACT

Introduction: Brain metastases in patients with extracranial cancer are typically associated with increased morbidity and mortality. Stereotactic radiotherapy and immunotherapy using checkpoint inhibitors currently are essential in brain metastases treatment. Since conventional contrast-enhanced MRI alone cannot reliably differentiate between treatment-induced changes and brain metastasis relapse, several studies investigated the role of PET imaging and, more recently, radiomics, based on routinely acquired PET images, to overcome this clinically relevant challenge.

Areas covered: The current literature on PET imaging, including radiomics, in patients with brain metastases, focusing on the diagnosis and assessment of post-treatment relapse, is summarized.

Expert Commentary: Available data suggest that imaging parameters, including radiomics features, mainly derived from amino acid PET, are helpful for diagnosis and assessment of post-treatment relapse in patients with brain metastases.

KEYWORDS

Amino acid PET; FET; radiomics; pseudoprogression; radiation-induced changes; checkpoint inhibitors

1. INTRODUCTION

The manifestation of brain metastases in patients with extracranial cancer is associated with considerable morbidity and mortality. While whole-brain radiation used to be the standard for treating patients with brain metastases, radiosurgery as a local treatment option has become the standard of care in many clinical situations [1]. Besides, systemically administered checkpoint inhibitors are increasingly used to treat the intracranial tumor burden [2,3].

In these patients, physicians are frequently confronted with the necessity to differentiate brain metastasis relapse from treatment-induced changes following radiosurgery and systemic treatment options such as checkpoint inhibitors [4-8]. Treatment-related changes may be solely radiographic, asymptomatic, but may also be symptomatic, refractory to symptomatic steroid therapy, and may ever require an invasive intervention such as surgery [9].

For example, in patients with brain metastases treated by radiosurgery, a radiation necrosis rate of approximately 25% has been reported [10]. Depending on the radiation dose and the irradiated volume, the risk of radiation necrosis may increase to 50% [10]. In patients with brain metastases treated with systemic checkpoint inhibitor immunotherapy, e.g., ipilimumab, pembrolizumab, or nivolumab, some patients experience delayed tumor shrinkage after an initial tumor progression. This phenomenon is called pseudoprogression and may lead to a premature termination of an effective immunotherapy [6,11-14].

Since conventional MRI alone cannot reliably differentiate between treatment-related changes and brain metastasis relapse, several studies have investigated the role of

PET imaging and, more recently, radiomics, based on routinely acquired PET images, to overcome this clinically challenging task.

2. MOST IMPORTANT PET TRACERS IN PATIENTS WITH BRAIN METASTASES

The most relevant PET tracers for patients with glioma and brain metastases are radiolabeled amino acids, especially O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET), [^{11}C]-methyl-L-methionine (MET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA). Their clinical relevance is related to the reported high clinical value particularly for differentiating treatment-related changes from actual tumor progression in both primary and secondary brain tumors [4,7,15]. In patients with brain metastases, usually presenting with a preexisting blood-brain barrier disruption, the PET probe 3´-deoxy-3´-[^{18}F]-fluorothymidine (FLT) seems to be also of considerable interest for the monitoring of treatment effects [16]. FLT is an analog of the nucleoside thymidine which allows to assess cellular proliferation by tracking the thymidine salvage pathway. In contrast, PET using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) for brain metastases imaging plays only a minor role due to the inferior tumor-to-background contrast related to the physiologically high cortical uptake [15]. Notwithstanding, FDG PET has been particularly evaluated for the differentiation of radiation-induced changes after radiosurgery from local tumor relapse in patients with brain metastases. However, these studies included only few patients and were limited by considerable variations in methodology (e.g., visual analysis only or the use of different thresholds). Perhaps as a result, the diagnostic performance of FDG PET varied considerably in terms of both sensitivity and specificity (range, 40-100%) [17-23]. Dual-phase FDG PET may be superior to a single phase scan [20,24] but limited by long time intervals of several hours between the two scans, hampering routine clinical use especially in seriously ill patients.

Regarding PET imaging using choline derivates such as ^{18}F-fluorocholine, experience with these tracers - despite promising initial results - is based mainly on single cases or case series in patients with brain metastases [25], and their usefulness needs to be confirmed in larger studies.

3. DIAGNOSIS OF POST-TREATMENT RELAPSE AFTER RADIOTHERAPY USING AMINO ACID PET

Amino acid PET has been investigated for distinguishing radiotherapy-induced changes from tumor relapse after radiotherapy, including radiosurgery (Figure 1). MET PET has demonstrated a sensitivity and specificity of about 70-80% for this indication using an easily applicable semiquantitative regions-of-interest analysis [26-30]. That type of analysis describes the tumoral uptake relative to the uptake in the reference region projected onto the unaffected brain, usually located on the contralateral hemisphere. It has also been reported that FDOPA PET differentiates recurrent brain metastases from radiation-induced changes with 80-90% sensitivity and specificity [31,32]. A similarly high diagnostic performance has also been observed for FET PET using static and dynamic parameters (sensitivity, 95%; specificity, 91%) [33]. Further studies evaluating dynamic FET PET acquisition demonstrated comparable sensitivity and specificity of 80-90% [34,35]. This technique allows the characterization of the temporal pattern of tracer uptake by deriving a time-activity curve. Subsequently, dynamic uptake parameters such as time-to-peak values can be calculated from time-activity curves for further data analysis, e.g., to increase the diagnostic performance. Other efforts such as combining feature-based radiomics analysis with static FET PET parameters may also have the potential to improve the diagnostic performance to distinguish between local brain metastasis relapse and radiation injury without the acquisition of dynamic FET PET scans [36]. Furthermore, the diagnostic value of amino acid PET using FDOPA or MET seems to be superior to perfusion- and diffusion-weighted MR imaging and FDG PET [23,32]. Moreover, the cost-effectiveness of amino acid PET has been demonstrated for the differentiation of recurrent brain metastases from radiation-induced changes [37]. A detailed overview of the discussed studies in this paragraph is presented in Table 1.

Nevertheless, it has to be pointed out that in almost all studies, this distinction after radiosurgery is based solely on a single amino acid PET scan. However, many imaging abnormalities after radiosurgery may regress, remain relatively stable, or progress in in a variable period of time. Thus, serial amino acid PET may be more suitable to characterize the long-term evolution of these imaging abnormalities. Recently, a serial FDOPA PET study (median number of scans, 3) suggested that the FDOPA uptake remained stable over time (median follow-up, 18 months) in radionecrotic lesions, whereas it increased significantly in patients with brain metastases relapse [38].

4. DIAGNOSIS OF POST-TREATMENT RELAPSE AFTER CHECKPOINT INHIBITION USING PET

One of the earliest investigations reported that PET imaging using the radiolabeled amino acid FET has the potential to diagnose pseudoprogression in patients with brain metastases undergoing immunotherapy [39]. In that small pilot study with 5 patients with melanoma brain metastases treated with the checkpoint inhibitor ipilimumab, imaging findings were correlated with the clinical course after treatment initiation. In one patient with pseudoprogression and a favorable outcome with a progression-free survival longer than 6 months, FET PET showed only low metabolic activity. A more recent study in 40 patients with 107 brain metastases secondary to melanoma or non-small cell lung cancer treated with radiosurgery, checkpoint inhibitors, or combinations thereof evaluated whether FET PET may provide important diagnostic information regarding both response assessment and diagnosis of pseudoprogression [40]. In that study, static FET parameters differentiated brain metastasis relapse from treatment-related changes with an accuracy of 85%. An illustrative patient example is presented in Figure 2.

A small prospective imaging study using FLT PET suggested that in a subset of patients with brain metastases secondary to melanoma treated with targeted therapy or immune checkpoint blockade, metabolic responders may have improved survival of more than one year after treatment initiation. Importantly, FLT PET responders had at follow-up a diminished proliferative activity of the tumor despite unchanged contrast enhancement on conventional MRI [41].

The growing use of checkpoint inhibitors has also promoted the development of PET tracers to image the expression of immune checkpoints such as PD-1 or PD-L1 [42,43]. Animal studies [44,45] and initial first-in-human studies [46] suggested that these tracers may be of clinical value for treatment monitoring including response evaluation. In the latter fist-in-human study, all non-small cell lung cancer cancers of 13 patients exhibited increased PD-1 expression as assessed by ^{89}Zr-nivolumab PET. Furthermore, ^{89}Zr-nivolumab accumulation was observed in the majority but not all brain metastases, most probably related to a small lesion size and/or lacking PD-1 and PD-L1 expression [46]. In a subsequent first-in-human study of the same group, similar results could be obtained using pembrolizumab labeled with Zr-89 [47].

Nevertheless, antibody tracers linked with Zr-89 are less suitable for clinical routine due to the relatively long physical half-life of 72 h. To overcome this shortcoming, Nienhuis and colleagues used an adnectin-based PD-L1 ligand ^{18}F-BMS986192 labeled with F-18 (half-life, 110 minutes) [48]. Adnectins are engineered target-binding proteins, highly specific to therapeutically relevant targets such as immune checkpoints (e.g., PD-L1). Compared to antibodies labeled with Zr-89, adnectins labeled with F-18 exposes patients to a lower radiation dose, allowing serial PET imaging within shorter time intervals. An initial suggested that baseline uptake of the adnectin-based PD-L1 ligand ^{18}F-BMS986192 may predict an atezolizumab-induced reduction in tumor volume in patients with melanoma brain metastases [48].

5. METHODOLOGY OF PET RADIOMICS

Radiomics is a method from the field of artificial intelligence that allows the extraction of quantitative imaging features that are not accessible by conventional visual image analysis. Importantly, radiomics can be fully automated applied to any medical imaging modality (e.g., MRI, PET, or CT), which are routinely acquired during clinical follow-up [49]. These features can be combined with clinical data (e.g., molecular markers, survival time) to generate mathematical models for radiomics analysis [49-51]. These models can be used for various clinical purposes, such as to estimate the prognosis, predict molecular biomarkers non-invasively, or evaluate post-treatment relapse. Therefore, radiomics provides additional diagnostic information with great potential to support clinical decision-making, especially in combination with other clinical parameters.

One common approach to radiomics is to extract mathematically predefined image features, so called feature-based radiomics. In contrast, deep learning-based radiomics uses artificial neural networks to generate, identify, and learn characteristic image features from the input image data.

Typical preprocessing steps for feature-based radiomics analyses usually include intensity normalization, spatial smoothing and resampling, noise reduction, and further corrections, e.g., MRI field inhomogeneities [52-54]. Another essential prerequisite for radiomics analysis is the three-dimensional segmentation of brain tumor subareas such as contrast enhancement, necrosis, and perifocal edema. This can be obtained manually, which is laborious and time-consuming, or automatically using deep learning algorithms [55,56].

After these preprocessing steps, radiomics features can be extracted. These features have the potential to uncover tumoral characteristics that are beyond the means of human perception. Basically, shape features (i.e., geometrical properties), histogram-based features (i.e., distribution of individual voxel intensity values), textural features (i.e., statistical relationships between the intensity values of neighboring voxels and groups of voxels), and higher-order statistics features (i.e., features extracted after the application of mathematical transformations such as filters) can be extracted. Thus, hundreds to thousands of features can be easily obtained from the respective medical image modality.

Related to the high number of features, most of them may be either constant, redundant, duplicated, irrelevant, or highly correlated. Thus, overfitting the model may result in a perfect classification accuracy but fails in an external validation data set, i.e., the model is not generalizable and cannot be applied in clinical routine. Therefore, feature selection is an important step in the radiomics workflow prior to model generation to remove highly correlated and unimportant features, thereby reducing the risk of overfitting [57,58].

Once a subset of relevant features is identified, a mathematical model can be generated to evaluate the clinical question of interest. The most popular machine learning algorithms for model generation are regression models, support vector machines, and decision trees using random forests. Notably, the final model should be finally applied to an independent test dataset. Ideally, heterogenous multi-institutional data acquired at different scanners with varying acquisition protocols and segmentations are used as test dataset to simulate the situation in clinical routine. Finally, model performance, generalizability, robustness, and reliability of the developed model is evaluated based on the test dataset.

6. CLINICAL VALUE OF PET RADIOMICS FOR THE DIAGNOSIS OF POST-TREATMENT RELAPSE

The potential of MET PET radiomics for the diagnosis of post-treatment relapse was investigated by Hotta and co-workers [59]. In their study, 41 patients with brain tumors (n=23 patients with gliomas; n=21 patients with gliomas) underwent MET PET, and 42 radiomics features were calculated. The most important features for the differentiation between recurrent brain tumor from radiation necrosis was identified by the Gini index. The developed random forest classifier achieved an AUC of 0.98 after 10-fold cross-validation for this important clinical indication.

In another study, Lohmann et al. investigated the value of combining structural MRI and FET PET radiomics for the diagnosis of post-treatment relapse [60]. After image preprocessing and tumor segmentation, the images were filtered using wavelet transformation and Laplacian-of-Gaussian filters. In total, 168 radiomics features were calculated from the filtered and unfiltered images for each patient. The Wilcoxon ranksum test was used for feature selection. The best performing logistic regression model was identified based on the Akaike information criterion was a combination of both FET PET and MRI and achieved a diagnostic accuracy of 89%, suggesting that a combined evaluation obtains more diagnostic information compared to the respective single modality.

7. CONCLUSIONS

The present literature deploys evidence that amino acid PET and newer PET probes provide clinically relevant diagnostic information for differentiating treatment-related changes from post-treatment relapse induced by frequently used treatment options for patients with brain metastases, i.e., radiosurgery and checkpoint inhibitor immunotherapy. Furthermore, PET-based radiomics may provide valuable additional information for this clinically critical distinction.

8. EXPERT OPINION

Advanced PET imaging for brain tumors including brain metastases is a rapidly emerging field. Overall, available results on the value of PET imaging, including radiomics, in patients with brain metastases, focusing on the diagnosis and assessment of post-treatment relapse, are encouraging. Nevertheless, the available data in this field has to be improved, and an intensification of research is necessary. To confirm these initial encouraging findings, further studies with a higher number of patients are warranted in which both harmonized imaging protocols and post-processing procedures are used. To evaluate imaging findings derived from PET and PET radiomics, neuropathological validation of imaging findings including target expression, preferentially by obtaining tissue samples using stereotactic biopsy, is also necessary, and should be performed more frequently.

In addition, the combination of PET imaging with advanced MRI techniques such as perfusion-weighted imaging or proton spectroscopic imaging is not well established. On the other hand, the advent of hybrid PET/MRI scanners offers the opportunity to improve this constellation since it is possible to investigate several multimodal imaging parameters in a time-saving manner under the same (patho)physiological conditions. Although hybrid PET/MR imaging has more practical advantages and is convenient for patients, the higher cost of these systems should be weighed against the effort of serial imaging at different time points.

Other challenges regarding the implementation of PET imaging in this group of patients are the availability of tracers and general access for brain tumor patients to these modalities. Many of these challenges are currently still driven by cost and reimbursement issues.

To further promote clinical translation, the use of liquid biopsies as a surrogate for tumor tissue seems to be a promising diagnostic method for detecting circulating tumor DNA, circulating tumor cells, and extracellular vesicles in blood or cerebrospinal fluid [61]. For example, a recent study suggested that in patients with newly diagnosed leptomeningeal metastatic disease, the quantification of circulating tumor cells predicts survival time and outperforms conventional neuroimaging about survival prediction [62]. Thus, a correlation with advanced neuroimaging findings would be of considerable interest.

ARTICLE HIGHLIGHTS

- Amino acid PET and newer PET probes have the potential to provide valuable additional diagnostic information in patients with brain metastases for differentiating treatment-related changes from post-treatment relapse induced by radiosurgery and checkpoint inhibitor immunotherapy.

- PET-based radiomics may provide valuable additional information for this clinically critical distinction.

DECLARATION OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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FIGURE LEGENDS

Figure 1: Contrast-enhanced MRI and FET PET of a 64-year-old female patient with a BRAF-wildtype melanoma with a right frontal brain metastasis. The brain metastasis was treated with radiosurgery, and pembrolizumab was administered concurrently. Three months later, conventional MRI revealed a slight increase of contrast enhancement and a markedly perifocal edema. In addition, FET PET showed pathologically increased metabolic activity, indicating that a treatment-related effect is unlikely. Subsequently, neuropathological evaluation of the resected tissue confirmed neoplastic tissue.

Figure 2: MRI and FET PET of a 78-year-old male patient with brain metastases of an adenocarcinoma of the lung in the left cerebellum and right precentral gyrus treated with radiosurgery. Sixteen months later, contrast-enhanced MRI suggested tumor progression (right column). In contrast, FET PET showed no increased metabolic activity and indicated radiation-induced changes. Neuropathological examination of extracted tissue samples revealed reactive and necrotic tissue without signs of neoplastic tissue.

Figure 1

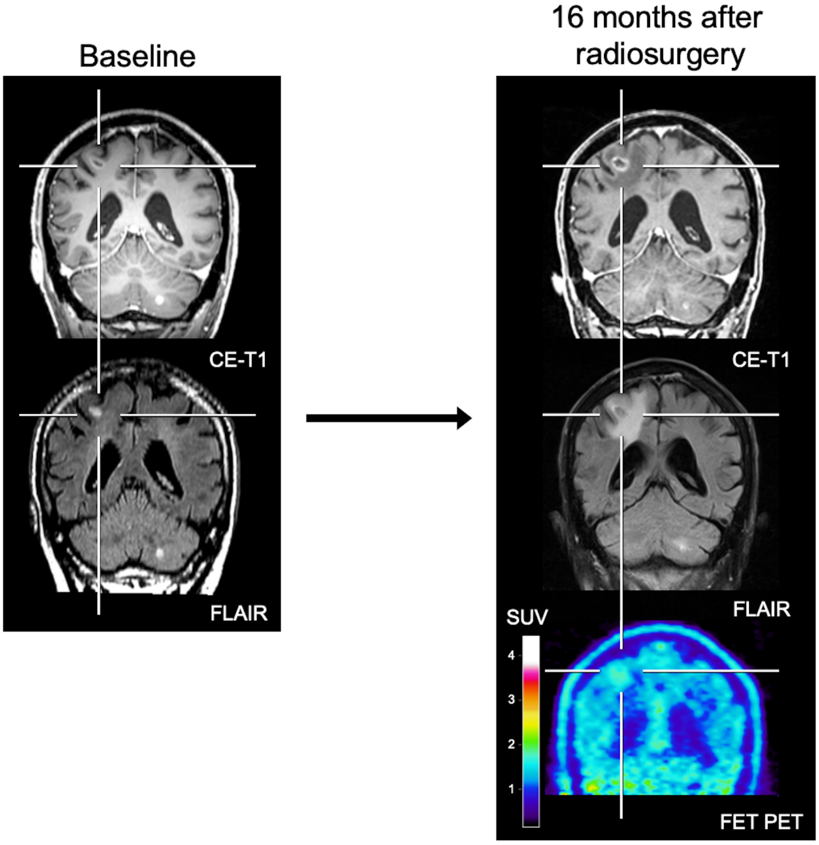
Baseline
16 months after radiosurgery
CE-T1
FLAIR
CE-T1
FLAIR
SUV
4
3
2
1
FET PET

Figure 2

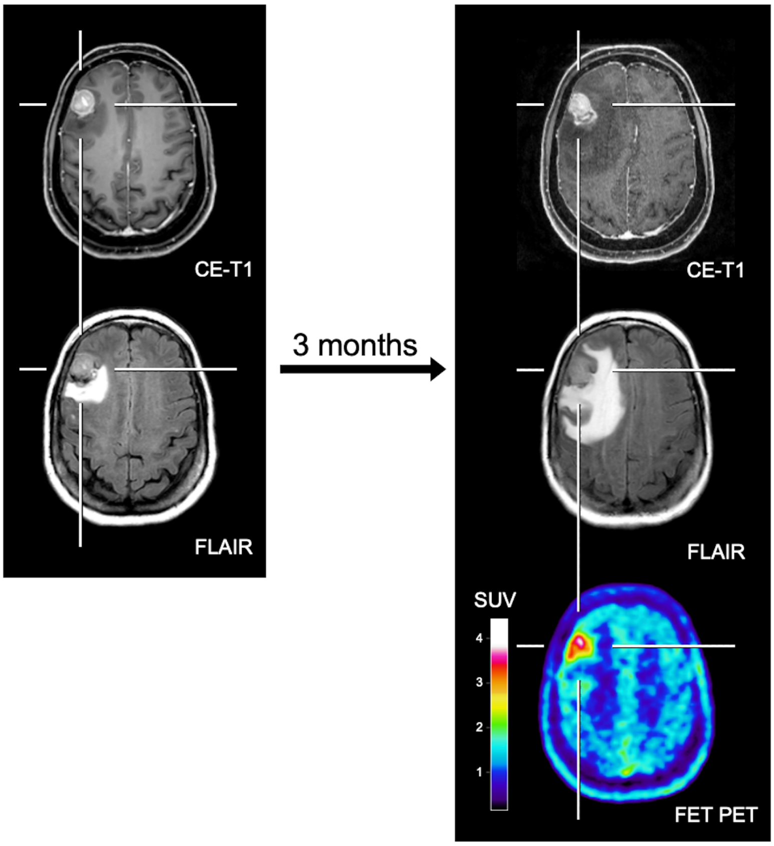

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Table 1: Overview of studies evaluating the differentiation of radiation-induced changes from brain metastases relapse using amino acid PET

	Tsuyuguchi et al. [27]	Terakawa et al. [26]	Galldiks et al. [33]	Lizarraga et al. [31]	Cicone et al. [32]	Minamimoto et al. [28]	Romagna et al. [35]	Ceccon et al. [34]	Tomura et al. [23]	Yomo et al. [30]	Govaerts et al. [29]
n Patients	21	51	31	32	42	39	22	62	15	32	26
n Lesions	21	56	40	83	46	42	50	76	18	37	31
n recurrent metastases	9	24	19	32	20	n.a.	21	36	10	19	17
n radiation-induced changes	12	32	21	51	26	n.a.	29	40	8	18	14
Neuropathological confirmation of diagnosis	52%	n.a.	28%	11%	24%	n.a.	40%	34%	56%	46%	n.a.
Tracer	MET	MET	FET	FDOPA	FDOPA	MET	FET	FET	MET	MET	MET
Dynamic PET acquisition	no	no	yes	no	no	no	yes	yes	no	no	no
Additional advanced imaging method	n.a.	n.a.	n.a.	n.a.	DSC PWI	n.a.	n.a.	n.a.	DCE parameters, DWI, FDG PET	n.a.	n.a.
Sensitivity	78%	79%	74%	81%	90%	82%	86%	86%	90%	82%	79%
Specificity	100%	75%	90%	73%	92%	86%	79%	88%	75%	75%	71%
Accuracy	n.a.	n.a.	83%	76%	91%	83%	82%	87%	n.a.	n.a.	n.a.
Optimal threshold	TBR_{mean} 1.4	TBR_{mean} 1.4	TBR_{mean} 2.0	TBR_{mean} 1.7	TBR_{max} 1.6	TBR_{max} 1.3	TBR_{mean} 2.0	TBR_{mean} 2.0	TBR_{max} 1.4	TBR_{max} 1.4	SUV_{max} 3.3
Increase of accuracy by integrating dynamic FET PET parameters	n.a.	n.a.	10%	n.a.	n.a.	n.a.	6%	1%	n.a.	n.a.	n.a.
Performance of amino acid PET compared to other imaging modalities	n.a.	n.a.	n.a.	n.a.	superior	n.a.	n.a.	n.a.	superior	n.a.	n.a.

ABBREVIATIONS: DCE = dynamic contrast-enhanced MR imaging; **DSC PWI** = dynamic susceptibility contrast-enhanced perfusion-weighted imaging; **DWI** = diffusion-weighted imaging; **FDG** = [^{18}F]-2-fluoro-2-deoxy-D-glucose; **FDOPA** = 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine; **FET** = *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine; **MET** = [^{11}C]-methyl-L-methionine; **n** = number; **n.a.** = not available; **SUV =** standardized uptake value; **TBR$_{mean/max}$** = mean or maximum standardized uptake value of the lesion divided by the maximum standardized uptake value of the reference region