FULL PAPER

11C-methyl-L-methionine PET measuring parameters for the diagnosis of tumour progression against radiation-induced changes in brain metastases

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INTRODUCTION

Brain metastases account for the majority of intracranial neoplasms, affecting approximately 20% of cancer patients throughout the course of disease.1,2 They occur most commonly, in order of incidence, in lung and breast cancers, followed by melanoma, colorectal cancer and renal-cell carcinoma.3 A diagnosed brain metastasis is, in many cases, indicative of a poor prognosis. Treatment generally consists of stereotactic radiotherapy (SRT), occasionally following resection and also combined with systemic therapy in selected cases.4 Response to such treatment is assessed primarily by MRI,5,7 recommended to be made at regular intervals.

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Anatomical MRI sequences, however, are poorly diagnostic for the differentiation between treatment induced changes and progressive disease. Radiation-induced changes (RIC) present as increased contrast-enhancement on post-contrast MRI with perilesional oedema. They thus imitate tumour progression (TP). These RIC in some tumour types are termed ‘pseudoprogression’. The one-year cumulative incidence of RIC after SRT in brain metastases is estimated to be 13–14%. Being able to accurately differentiate between TP and RIC is an urgent clinical need, as uncertainty about radiation effect might lead to further unnecessary interventions such as reirradiation.

The diagnostic inadequacy of MRI highlights the need for the use of other imaging modalities, of which 11C-methyl-L-methionine (MET)-positron emission tomography (PET) is one of the most widely utilised in both primary brain tumours and cerebral metastases. Most studies investigating metastases report a high diagnostic accuracy for MET-PET. What remains ambiguous in particular however, is a robust comparison of (semi-quantitative) PET measuring parameters so as to identify those which are the most diagnostically reliable. This need for clarity represents a gap in the literature. Our current study addresses this by investigating the accuracy of MET-PET across multiple PET parameters for the diagnosis of TP against RIC in a retrospective cohort of brain metastasis patients.

**METHODS AND MATERIALS**

**Patients**

Informed consent was waived by the local institutional review board. We retrospectively extracted all patients during the period from 2009 to 2015 who had received a MET-PET post-radiotherapy for an intra-axial intracranial metastasis at our hospital in Groningen, the Netherlands. Our selection of patients did not exceed 2015 because our institution has since phased out MET-PET in the context of the differential diagnosis of TP/RIC in favour of perfusion-MRI. Other inclusion criteria were age above 18 years and pathological evidence of primary disease. In all cases, MET-PET was performed because of an enlarging, enhancing lesion at the treatment location on T₂/MRI (contrast-enhanced) bringing about the diagnostic dilemma of radiological progression being due to either TP or RIC. The MRI diagnosis was inconclusive in all cases in that neither TP nor RIC could be definitively ruled out.

41 patients were found. 15 of these patients, however, were excluded for the following reasons: the clinical/radiological follow-up information was deemed inadequate to determine a definitive diagnosis (N = 2) and the PET scans were inaccessible (N = 13). 26 patients with 31 lesions were therefore included.

**PET protocol**

Imaging was performed in accordance with the 2006 European Association of Nuclear Medicine procedure guidelines for brain tumour imaging using labelled amino acid analogues. All patients underwent a period of fasting and were then administered intravenous 11C-MET (205 (199-213) MBq (median and interquartile range (IQR) Q1-Q3)). Static imaging was performed 20 minutes after 11C-MET administration in one bed position of five minutes using one of two scanners, a 64-slice Biograph mCT with 2-mm spatial resolution (Siemens/CTI, Knoxville, TN, USA) (N = 15 lesions) or an ECAT Exact HR+ (N = 16 lesions) (Siemens/CTI). No summed frames were used. For the lesions analysed with the Biograph mCT scanner, images were reconstructed using Truex + TOF with three iterations and 21 subsets in a 400 × 400 matrix size (zoom 1.0) and a 2-mm Gaussian filter. For the lesions analysed with the PET-HR+ camera, images were reconstructed using OSEM with three iterations and 24 subsets and a 5-mm Gaussian filter.

**Imaging analysis**

The PET images were analysed with Syngo via (Siemens Medical Solutions Inc., Knoxville, TN, USA) with blinding to the clinical follow-up data. The images were interpreted alongside the most recent MRI, preferably contrast-enhanced T₁W images, prior to the date of the PET scan. This provided an anatomical reference for accurate localisation of the tumour. The volume-of-interest (VOI) tool was used to semi-automatically delineate the VOIs. First, a sphere large enough to include all visual uptake at the lesion site was drawn manually. Then, the VOI was computed algorithmically to include all voxels that demonstrated a tracer uptake higher than a pre-set threshold (40% of SUVmax). The 40% of SUVmax threshold for tumour delineation is a standard value used in our department and leads consistently to good tumour definition when compared to visual inspection. The VOI tool was then used to determine the MET activity count normalised to injected dose per kilogram of patient body weight, a measurement unit termed standardised-uptake value (SUVR or SUVR-bw). The SUV was generated as SUVmean (average SUV over a VOI), SUVmax (maximum single voxel SUV within a VOI) and SUVPek (average SUV calculated within a 1 cm³ VOI, which comprises the maximum voxel value).

A 1 cm³ control VOI was contralaterally placed in a region of grey matter that mirrored the site of disease. Subsequently, the tumour-to-normal tissue (T/N) ratios were calculated, expressed as T/Nmean, T/Nmax-mean and T/Npeak-mean. The T/Nmax-mean was calculated by dividing the SUVmean of the lesion by the SUVmean of the control VOI. The T/Nmax-mean was derived in the same way but using SUVmax from the lesion and the SUVmean of the control VOI, and the T/Npeak-mean using SUVpeak from the lesion and the SUVmean from the control VOI. Also determined were the metabolic-tumour-volume (MTV) (metabolically active volume of the lesion VOI), the total-lesion methionine metabolism (TLMM) (product of MTV and SUVmean) and a bidimensional measurement of the lesion size on T₂ (contrast-enhanced) MRI (maximal tumour diameter and the corresponding largest perpendicular diameter).

**Definitive diagnosis**

The definitive diagnoses for each lesion were identified as either TP or RIC. All of these diagnoses were established in a multidisciplinary team meeting on the basis of radiological and clinical follow-up. Resection by craniotomy is recommended only when...
progressive symptoms cannot be suppressed by corticosteroids or radiotherapy alone. Histologic confirmation is, therefore, rarely available and could not be found for any included patients.

A lesion was defined as showing RIC if, for a consecutive period of at least 4 months subsequent to the investigative PET scan, the lesions showed spontaneous reduction or remained stable in size on $T_1/T_2$ MRI (contrast-enhanced) without any anti-tumour treatment, as defined by the Response Assessment in Neuro-Oncology Brain Metastases criteria $^7,24$ (Figure 1). When possible, the clinical situation was also considered at 6 months, with no further clinical worsening in patients with symptomatic RIC being taken into account.$^{17,23,25}$ TP lesions were those that continued to show an increase in size by at least 20% in the longest lesion diameter on MRI for at least 4 months subsequent to the investigative PET scan. Lesions that required reirradiation and/or resection or were confirmed to be the primary cause of the patient’s death before 4 months due to a deteriorating clinical situation, with progression of symptoms (such as headache, seizures, and focal neurologic aberrations) and signs of increased intracranial pressure, were also considered as TP (Figure 2).

The follow-up time for lesions with RIC was defined as the period subsequent to the PET scan during which the lesions remained stable or showed consistent reduction in size. For TP lesions, this was defined as the period until death from progressive intracerebral disease, until reirradiation and/or resection due to progressive disease or during which the lesion showed continuous increase in size in successive $T_1/T_2$ (contrast-enhanced) MRI images.

Statistical analysis

The analyses were performed on a per-lesion basis. All collected PET measuring parameters ($SUV_{\text{mean}}$, $SUV_{\text{max}}$, $SUV_{\text{peak}}$, $T/N_{\text{mean}}$, $T/N_{\text{max-mean}}$, $T/N_{\text{peak-mean}}$, MTV and TLMM) were compared between the TP and RIC diagnostic groups using the Mann–Whitney U non-parametric test after data analysis by way of Shapiro–Wilk and histogram assessment confirmed non-normality. A receiver-operating-characteristic curve was generated and area-under the curve analysis used to determine and compare the diagnostic ability of each parameter in terms of true-positive and false-positive rates. A significance value of $p < 0.05$ was used.

The receiver-operating-characteristic curve was used to define a threshold value by way of Youden’s index/$J$ statistic for the diagnosis of TP corresponding to sensitivity and specificity values according to the PET measuring parameter. Positive and negative predictive values were then calculated. The diagnostic threshold was ultimately determined on the basis of maximum positive predictive and negative predictive values, which were considered more clinically relevant diagnostic guides. All analyses with performed with SPSS Statistics v.23.0 (IBM, Armonk, NY) and figures were generated with GraphPad Prism v.9.0.1.151 (GraphPad Software Inc., San Diego, CA).

RESULTS

General characteristics

26 patients with 31 lesions were included. The population consisted of 13 males and 13 females. The median age was 63.5 (53.8–71.0 IQR Q1-Q3) years. The primary sites for each lesion were as follows: lung ($N = 17$), breast ($N = 4$), kidney...
(renal-cell carcinoma) \(N = 1\), skin (melanoma) \(N = 4\), oesophagus \(N = 2\), colon/rectum \(N = 1\), connective tissue (fibrosarcoma) \(N = 1\) and heart (myxoma) \(N = 1\). The lesions were treated either by SRT only \(N = 24\), by craniotomy/excision with whole-brain-radiotherapy and SRT \(N = 3\), by SRT and whole-brain-radiotherapy \(N = 1\), by craniotomy/excision with only whole-brain-radiotherapy \(N = 1\) or by craniotomy/excision with only SRT \(N = 2\) (Supplementary Material 1).

The median lesion-specific cumulative radiation dose was 20.00 (20.00–31.30 IQR Q1–Q3) Gy. 14 out of 26 patients were taking dexamethasone at the time of the PET scan. Although the dosage was unknown in five of these patients, the remainder was administered a median daily dosage of 8.0 (3.5–8.00 IQR Q1–Q3) mg.

The dosage was not found to be significantly different between the two diagnostic groups using the Mann–Whitney U-test \(p = 0.487\). The median interval between radiotherapy treatment and the PET scan was 8.8 (5.4–13.0 IQR Q1–Q3) months whilst the median interval between the initial MRI showing an enlarging, enhancing lesion at the treatment location (suggesting either RIC or TP) and the PET scan was 1.07 (0.57–2.43 IQR Q1–Q3) months. The median interval between the most recent pre-PET MRI and the PET scan itself was 0.83 (0.47–1.17 IQR Q1–Q3) months and the median follow-up time subsequent to the PET scan was 3.8 (2.2–5.3 IQR Q1–Q3) months.

We also performed a basic visual analysis per lesion, outlining the degree of MET uptake and an interpretation of whether this was suggestive of RIC or TP (Supplementary Material 2).

PET measuring parameter comparison
The total number of lesions diagnosed definitively as showing RIC and TP were 14 and 17, respectively. The median and IQR values were calculated for each parameter (Figure 3 and Table 1).

Comparing the parameters by definitive diagnosis with the Mann–Whitney U-test yielded significant differences for all with the exception of MTV \(SUV\text{mean}, p = 0.004; SUV\text{max}, p = 0.002; SUV\text{peak}, p = 0.004; T/N\text{mean}, p = 0.007; T/N\text{max-mean}, p = 0.006; T/N\text{peak-mean}, p = 0.008; TLMM, p = 0.039 and MTV, p = 0.781\).

A separate analysis was also performed to compare the parameter values according to camera type and definitive diagnosis (Supplementary Material 3). The Mann–Whitney U-test only showed significance for the SUVmax, T/Nmean and T/Nmax-mean parameters between the two camera types within the TP group. No significance was shown for the parameters within the RIC group.

Tests for diagnostic ability
A receiver-operating-characteristic curve was compiled using the PET measuring parameter data and the corresponding

Table 1. MET-PET measuring parameter quantitative comparison

| Definitive diagnosis | SUV\text{mean} | SUV\text{max} | SUV\text{peak} | T/N\text{mean} | T/N\text{max-mean} | T/N\text{peak-mean} | TLMM | MTV |
|----------------------|---------------|---------------|---------------|----------------|---------------------|---------------------|------|-----|
| RIC \((N = 14)\)     | 1.79 (1.46–2.13) | 2.66 (2.26–3.25) | 2.11 (1.74–2.44) | 1.09 (0.87–1.33) | 1.71 (1.41–2.18) | 1.33 (1.08–1.49) | 4.63 (2.63–6.65) | 2.59 (1.61–3.62) |
| TP \((N = 17)\)      | 2.63 (1.84–3.53) | 4.35 (2.89–5.86) | 3.27 (2.17–4.07) | 1.55 (1.19–2.23) | 2.58 (1.89–3.73) | 1.88 (1.41–2.46) | 7.37 (4.90–10.72) | 2.47 (2.05–3.54) |

MTV, Metabolic-tumour-volume; RIC, Radiation-induced changes; SUV, Standardised-uptake-value; TLMM, Total-lesion methionine metabolism; T/N, Tumour-to-normal tissue ratio; TP, Tumour progression.

Median and IQR (Q1–Q3) for each MET-PET measuring parameter according to the definitive diagnosis.

ap < 0.05 (Mann–Whitney U-test).
bp < 0.01 (Mann–Whitney U-test).
definitive diagnoses (Figure 4). The area under the curve analysis yielded the following results: $SUV_{\text{mean}} = 0.809$ (95% CI (0.656, 0.961)); $SUV_{\text{max}} = 0.834$ (95% CI (0.693, 0.975)); $SUV_{\text{peak}} = 0.807$ (95% CI (0.653, 0.961)); $T/N_{\text{mean}} = 0.779$ (95% CI (0.614, 0.945)); $T/N_{\text{max-mean}} = 0.779$ (95% CI (0.617, 0.942)); $T/N_{\text{peak-mean}} = 0.767$ (95% CI (0.602, 0.932)); TLMM = 0.719 (95% CI (0.527, 0.910)) and MTV = 0.529 (95% CI (0.312, 0.747)).

According to Youden’s index/J statistic by way of maximising both the positive and negative predictive values, the threshold value for the diagnosis of TP for $SUV_{\text{max}}$ was 3.29 (sensitivity: 78.57%, specificity: 70.39%, positive predictive value: 74.32% and negative predictive value: 75.25%). The values for $SUV_{\text{mean}}$, $SUV_{\text{peak}}$, $T/N_{\text{max-mean}}$, $T/N_{\text{mean}}$, $T/N_{\text{peak-mean}}$ and TLMM respectively were 2.00 (sensitivity: 71.43%, specificity: 70.59%, positive predictive value: 74.97% and negative predictive value: 66.37%), 2.45 (sensitivity: 78.57%, specificity: 70.59%, positive predictive value: 74.32% and negative predictive value: 75.70%), 2.03 (sensitivity: 71.43%, specificity: 70.59%, positive predictive value: 72.46% and negative predictive value: 69.52%), 1.33 (sensitivity: 71.43%, specificity: 64.71%, positive predictive value: 68.68% and negative predictive value: 67.65%), 1.40 (sensitivity: 71.43%, specificity: 64.71%, positive predictive value: 70.56% and negative predictive value: 64.32%) and 6.45 (sensitivity: 64.29%, specificity: 64.71%, positive predictive value: 66.37% and negative predictive value: 62.58%).

**DISCUSSION**

The current study is one of the few to comprehensively compare multiple PET measuring parameters in distinguishing RIC and TP during the follow-up of brain metastases. Furthermore, this is one of the only studies to investigate the diagnostic performance of $SUV_{\text{peak}}$, $T/N_{\text{peak-mean}}$ and TLMM in brain metastasis patients. We have now demonstrated the utility of MET-PET in this context and have shown that $SUV_{\text{max}}$ is the most diagnostically reliable parameter in our patient group.

The ability of MET to distinguish between RIC and TP has been widely documented in primary brain tumours.15–17 This represents the majority of the available literature. The Response Assessment in Neuro-Oncology Brain Metastases criteria consider amino acid PET modalities to be useful in the differentiation between recurrent tumours and post-therapeutic changes following radiotherapy.7,24 The current study is one of a handful that evaluates the diagnostic performance of MET-PET in brain metastases.16–21,27 The majority of these, with some exceptions,16 have focused either on comparisons with other tracers, involve smaller sample sizes, or address the question of diagnostic performance as a secondary outcome measurement. Some studies have also not analysed brain metastases separately from other intracranial tumour types (glioblastoma for example) when determining diagnostic metrics and accuracy thresholds, making the results less relevant to brain metastases specifically. We have addressed these caveats in our investigation and have, in a retrospective setting, provided a more comprehensive clarification of the diagnostic accuracy of the most widely use PET measuring parameters.

Comparing our results of diagnostic performance to analogous studies, we note both an underestimation of sensitivity and specificity and a difference in area-under-the-curve analysis results. Terakawa et al.16 in their study of 56 metastatic lesions, reported the highest area-under-the-curve of 0.780 for $T/N_{\text{mean}}$, with a threshold of 1.41 corresponding to sensitivity, specificity, positive-predictive and negative-predictive values of 79%, 75%, 70 and 83%, respectively. Tsuyuguchi et al.27 in their prospective analysis of 21 metastasis patients found sensitivity and specificity values for $T/N_{\text{mean}}$ of 77.7% and 100.0%, respectively. For $SUV_{\text{mean}}$, these values were 77.7% and 75.0%. They determined a threshold value for $T/N_{\text{mean}}$ of 1.42. These are both higher thresholds than ours 1.33 for $T/N_{\text{mean}}$ and associated with consistently better diagnostic performance for most metrics. These differences may be due to these studies’ larger sample size. Also notable is that the definitive diagnoses were made according to pathological assessment in both studies, which is the gold standard. The study by Tsuyuguchi et al.27 was also prospective, allowing the control of variables such as camera type, methionine dosage and treatment modality. This being said, our analysis reports higher positive-predictive values when using $SUV_{\text{max}}$ at a threshold of 3.29. In theory, the utility of $SUV_{\text{max}}$ in brain metastases is due to its reliable detection of small progressive lesions, which are highly prevalent in our cohort. Interestingly, MTV was not predictive. TLMM, on the other hand, appears to be a useful parameter, with an area-under-the-curve value of 0.719.
In a recent study by van Dijken et al\textsuperscript{23}, greater values for both TLMM and MTV were shown to be significantly associated with a poorer prognosis in glioma patients. Volume on its own may, therefore, be predictive for aggressiveness in confirmed TP cases, but it must be combined with uptake for it to be diagnostic for RIC. Our data show that even large contrast-enhanced lesions on MRI do not necessarily indicate underlying progressive disease.

\textit{SUV}_\text{peak} is a noticeably underused measuring parameter in PET-related literature.\textsuperscript{29} For intracranial neoplasms, a handful of articles are available utilising \textit{SUV}_\text{peak} as a measure of treatment response, but only in other radiotracers such as FDG-PET.\textsuperscript{29} We report a promising diagnostic accuracy for MET-PET derived \textit{SUV}_\text{peak} according to its area-under-the-curve value of 0.807. \textit{SUV}_\text{peak} is interesting because it is generated by measuring the average voxels over a 3D sphere of specific volume, which is focused on the highest uptake portion of a tumour. This way it is not reliant on a single voxel of maximum uptake, as in \textit{SUV}_{\text{max}}.\textsuperscript{30} It is thus also theoretically a more flexible parameter and adaptable according to tumour size. This is probably why it seemed successful in our patient group, as it possibly adjusted to the heterogeneity both within tumours and across different tumour types. We suspect that part of the reason \textit{SUV}_{\text{max}} saw greater success in our cohort as compared with \textit{SUV}_\text{peak} was that in larger lesions with considerable heterogeneity, there is a higher probability for voxels with marked SUVs. These likely distorted the diagnostic tests in favour of this parameter, the effects of which are compounded by our relatively small sample size. Given the until now limited study into the dynamics of \textit{SUV}_\text{peak} and its utility in treatment follow-up, we stress the need for future evaluation comparing the value of this parameter with \textit{SUV}_{\text{max}}.

Comparing our findings to PET studies using other radiolabelled amino acids showed distinct differences in diagnostic metrics. A study investigating \textit{O}-(2-[\textsuperscript{18}F]fluoroethyl)-L-tyrosine (FET) in 62 brain metastasis patients with 76 lesions showed higher sensitivity and specificity values both for \textit{T/N}_{\text{max}} (sensitivity = 83%; specificity = 85%) and \textit{T/N}_{\text{mean}} (sensitivity = 86%; specificity = 88%).\textsuperscript{31} The threshold values for these two parameters were 2.55 and 1.95, respectively. A study investigating L-3,4-dihydroxy-6-\textsuperscript{18}F-fluoro-phenylalanine (FDOPA) in 32 brain metastasis patients with 83 lesions also reported diagnostic accuracy for \textit{T/N}_{\text{max}} and \textit{T/N}_{\text{mean}}. These parameters showed sensitivity and specificity values of 81.3% and 72.5% at thresholds of 2.02 and 1.70, respectively.\textsuperscript{31} It is difficult to state whether or not the results of these studies imply a greater utility of FET and FDOPA-PET compared to MET-PET. These studies, in addition to this investigation, were performed retrospectively. Whilst of course still valuable, this makes direct comparison difficult. There are other studies investigating MET-PET reporting similarly high diagnostic accuracy measurements to these two examples such that the RANO/PET group does not make concrete statements as to which radiolabelled amino acid is superior.\textsuperscript{32} This highlights the need for prospective studies comparing all three analogues using similar protocols in the same patient cohort.

Notable is that our institution has since the end of patient inclusion for this study (2015) phased out MET-PET in favour of perfusion-MRI. The primary reason for this was cost related (maintenance and manning of an on-site cyclotron) and the fact that perfusion-MRI has been found to be sufficiently reliable in the context of the diagnostic dilemma of RIC against TP.

Interestingly, two lesions, cases 2 and 3, which were found in the same NSCLC patient, were notable in that they were ultimately diagnosed as showing TP although displaying very low SUV and \textit{T/N} values. The PET images showed slight increased MET activity with localisations corresponding to the lesions on the most recent pre-PET MRI. Visually the MET activity would suggest RIC for both lesions, yet they continued to show progression on MRI for several months after follow-up (the uncertainty about the diagnosis led to an additional MET-PET, which showed similar MET activity as previously) to the point that the lesions were reirradiated for symptom relief. This suggests that some lesions might continue to show progression despite minimal corresponding amino acid uptake, stressing the need to always consider clinical presentation and lesion growth on sequential MRI.

Our study has several limitations. Most are inherent to the retrospective design. The first is that the results of the PET scans were known to the treating physicians at the multidisciplinary team meetings. This implies that the scans may have affected clinical decision-making during follow-up, representing a bias. Noteworthy also is that the median follow-up length is less than 4 months in our cohort. This is because of the TP lesions, for which resection and/or radiotherapy was often performed before 4 months to alleviate progressive symptoms. The second limitation is that different PET cameras were used for the lesion analysis. The spatial resolution is greater for the mCT as compared with the HR+, and this has important implications in terms of an underestimation of smaller-volume lesions due to partial volume effects. This is amplified as the spatial resolution of a camera decreases and is most pronounced in the \textit{SUV}_{\text{max}} Parameter. The effect minimises with the \textit{SUV}_{\text{mean}} and \textit{SUV}_\text{peak} parameters. This is reflected in our results and the large variation in \textit{SUV}_{\text{max}} values in the TP lesions is striking. Systematic underestimation of the SUVs for small volume lesions has led to marked overlap in values for TP and RIC (Figure 3). We consider this to be compounded also by the heterogeneity of the primary lesions. A similar trend of variation is not as noticeable for the lesions with RIC, which is expected as there is less detectable tumour activity in these cases to bring about partial volume effects. It can be further reasoned based on partial volume effects that the HR+ \textit{SUV}_{\text{max}} measurements in smaller lesions in our cohort have been undervalued comparatively to similar-sized lesions captured with the mCT. The explanation outlined above is also partially why we have placed emphasis on the \textit{SUV}_\text{peak} parameter results, where partial volume effects play a significantly less important role.

A third limitation is that using the clinical context as follow up could theoretically lead to a misdiagnosis of TP. This is because RIC are frequently observed in the background of clinical deterioration.\textsuperscript{26,33} The last drawback is that we could not control the treatment modality in our patients, as this was determined on an individual basis in the clinic.
CONCLUSION
We have demonstrated the utility of several MET-PET measuring parameters and, in particular, of $SUV_{\text{max}}$ in differentiating between RIC and TP in brain metastasis patients. $SUV_{\text{peak}}$ due to its similar and in theory more flexible method of measurement, also shows promise. Further understanding of $SUV_{\text{peak}}$ and how it compares with $SUV_{\text{max}}$ in the context of brain metastases could lead to more effective follow-up treatment through earlier and improved clinical decision-making.

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