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82Rubidium chloride positron emission tomography discrimination of recurrent intracranial malignancy from radiation necrosis

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Abstract

BACKGROUND: Accurate identification and discrimination of post treatment changes from recurrent disease remains a challenge for patients with intracranial malignancies despite advances in molecular and magnetic resonance imaging. We have explored the ability of readily available Rubidium-82 chloride (82RbCl) positron emission tomography (PET) to identify and distinguish progressive intracranial disease from radiation necrosis in patients previously treated with radiation therapy.

METHODS: Six patients with a total of 9 lesions of either primary (N.=3) or metastatic (N.=6) intracranial malignancies previously treated with stereotactic radiation surgery (SRS) and persistent contrast enhancement on MRI underwent brain 82RbCl PET imaging. Two patients with arteriovenous malformations previously treated with SRS, also had brain 82RbCl PET imaging for a total of 11 lesions studied. Histological confirmation via stereotactic biopsy/excisional resection was obtained for 9 lesions with the remaining 2 classified as either recurrent tumor or radiation necrosis based on subsequent MRI examinations. 82RbCl PET time activity curve analysis was

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Authors’ contributions.—Ephraim E. Parent and Ila Sethi contributed equally to the work. Ephraim E. Parent and Ila Sethi contributed equally in analyzing the data and preparing the manuscript; Jonathon Nye contributed in preparing the protocols for scanning the patients and contributed in the preparation of manuscript; Chad Holder evaluated the MRI imaging and contributed in the preparation of manuscript; Jeffrey J. Olson participated in the surgical treatment of the patients and contributed in the preparation of manuscript; Jeffrey Switchenko did the data analysis and contributed in the preparation of manuscript; Funmilayo Tade, Oladunni O. Akin-Akintayo, Olayinka A. Aboidun-Ojo, and Akinyemi Akintayo contributed equally in collecting and maintaining the database and providing inputs for preparing the manuscript; David M. Schuster mentored the entire project and contributed in preparing the manuscript.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
performed which comprised lesion SUV$_{\text{max}}$, contralateral normal brain SUV$_{\text{max}}$, and tumor to background ratios (TB$_{\text{max}}$).

**RESULTS:** $^{82}$RbCl demonstrates uptake greater than normal brain parenchyma in all lesions studied. Time activity curves demonstrated progressive uptake of $^{82}$RbCl in all lesions without evidence of washout. While recurrent disease demonstrated a greater mean SUV$_{\text{max}}$ compared to radiation necrosis, no statistically significant difference between lesion SUV$_{\text{max}}$ nor TB$_{\text{max}}$ was found (P>0.05).

**CONCLUSIONS:** $^{82}$RbCl PET produces high-contrast uptake of both recurrent disease and radiation necrosis compared to normal brain. However, no statistically significant difference was found between recurrent tumor and radiation necrosis.

**Keywords**
Glioma; Positron emission tomography; Necrosis

Primary brain and central nervous system tumors are relatively uncommon but have a high mortality with 23,800 estimated new cases in the US in 2017 resulting in 16,700 deaths.\(^1\) In patients previously treated with stereotactic radiation surgery (SRS), both tumor recurrence and radiation necrosis lead to clinical deterioration and can have a similar appearance on both anatomic imaging with magnetic resonance imaging (MRI) and computed tomography (CT), as well as with metabolic scans such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET).\(^2\)

2-deoxy-2-[\(^{18}\)F]fluoro-D-glucose (FDG) PET has been shown to have limited ability to accurately identify intracranial malignancy recurrence after treatment with chemo-therapy and/or resection.\(^3\) This has led to a search for other readily available PET agents that can improve diagnostic accuracy. Thallium-201 ($^{201}$Tl) SPECT has some potential for the in vivo characterization of brain tumors, and in determining the post-therapy viability of intracerebral tumors.\(^4\) Na+/K+-ATPase activity is one of the most important factors for $^{201}$Tl accumulation in tumors. The grade of histopathological differentiation of tumor, the tumor retention index of $^{201}$Tl scintigraphy and the expression of Na+/K+-ATPase correlate well, indicating that Na+/K+-ATPase plays an important role in transportation for $^{201}$Tl through the tumor cell membrane.\(^5\)

Rubidium-82 chloride ($^{82}$RbCl) is a perfusion radiopharmaceutical that is routinely used for evaluation of myocardial ischemia. $^{82}$RbCl does not demonstrate uptake in normal brain parenchyma in patients with an intact blood-brain-barrier (BBB) but patients with a disrupted or permeable BBB have been shown to have high levels of $^{82}$RbCl uptake.\(^6\) $^{82}$RbCl behaves physiologically in a fashion similar to $^{201}$Thallium and is initially concentrated in tissue in proportion to regional perfusion, with an extraction of 65%. Retention of $^{82}$RbCl depends at least partly on sodium-potassium adenosine triphosphate transport.\(^7\) The biological half-life of $^{82}$RbCl in normal brain tissues is several days, which is markedly greater than the physical half-life of 75 seconds.\(^8\) Patients with intracranial brain metastases and primary brain gliomas have previously been evaluated with $^{82}$RbCl PET and found that $^{82}$RbCl uptake correlates with a disrupted BBB.\(^6\), \(^9\), \(^10\) Additionally, case reports
of intracranial breast cancer metastases have demonstrated that focally increased $^{82}$RbCl uptake directly corresponds to areas of gadolinium enhancement. $^{11}$

The goal of this study was to evaluate the ability of $^{82}$RbCl PET to discriminate between recurrent intracranial metastatic and primary malignancies, and radiation necrosis after SRS. We hypothesized that quantitative metrics such as SUV$_{\text{max}}$, tumor to background ratio, and time-activity curve (TAC) analysis would reflect relative differences in uptake, and thus be able to discriminate between recurrent disease and radiation necrosis. No studies have yet explored the possibility of using the readily available PET tracer $^{82}$RbCl as a discriminator of recurrent disease.

**Materials and methods**

**Ethics committee approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The recruitment protocol was approved by the Institutional Review Board (IRB) with an IRB # 00015461 and complied with the Health Insurance Portability and Accountability Act (HIP-PA). Informed consent was obtained from all individual participants included in the study.

**Subject recruitment**

Seven patients with known intracranial malignancies previously treated with SRS were recruited between 2009 and 2015 through internal funding. Two additional patients with known arteriovenous malformations (AVM) treated with SRS were recruited to serve as radiation necrosis controls. We included these patients as both AVMs treated with SRS and intracranial malignancies that develop radiation necrosis appear similar on MRI and histopathology. Safety monitoring during the drug infusion was performed and no adverse events were recorded. In total, 9 patients were recruited and underwent $^{82}$RbCl PET imaging. In 1 patient with intracranial malignancy, $^{82}$RbCl PET images were non-diagnostic due to pump malfunction and this patient was not included in the analysis. Additionally, a single patient with recurrent intracranial disease underwent standard of care FDG PET-CT imaging and this imaging was included for internal comparison.

**Image acquisition**

PET imaging of the head was performed using a Biograph 40 scanner (Siemens Medical Solutions, Knoxville, TN). An average activity of 47.2 mCi (38 mCi- 55.9 mCi) $^{82}$RbCl was administered intravenously via pump over one minute. Continuous dynamic PET imaging of a single bed position was begun at the beginning of injection and ended at the 10-minute time point; however, the 10 minute data set was discarded due to excessive noise. The images were iteratively reconstructed (4 iterations, 21 subsets) for each one-minute frame. Image data was postreconstruction smoothed with a 5 mm FWHM Gaussian filter to reduce noise. Data was transferred to a MIM workstation (MIM Software, OH) for further analysis.
Selection of regions of interest

A board-certified nuclear medicine physician using the Absolute Threshold Contouring Tool (MIM Software, OH, USA) drew regions of interest (ROIs) over the tumors and background ROIs (i.e. contralateral brain and venous confluence) for all time points. $^{82}$RbCl PET images were coregistered to standard of care T1 post contrast MRI sequences. Tumor regions of interest (ROIs) were defined by creating a spherical PET ROI to include the volume of tissue demonstrating enhancement. Within this PET ROI, the voxels with peak activity were used to derive a tumor maximum standardized uptake value ($SUV_{\text{max}}$). A 20 mm spherical ROI was placed over the contralateral normal brain, including both gray and white matter, to provide a normal standardized uptake value ($SUV_{\text{max}}$). Careful consideration when drawing ROIs over the tumor was used to exclude blood pool or adjacent choroid plexus which could falsely contribute to increased uptake.

Time activity curves

Time activity curves (TACs) for each lesion, normal contralateral parenchyma, and venous confluence were obtained by averaging PET metrics including $SUV_{\text{max}}$ and tumor background ($TB_{\text{max}}$) over all lesions at each time point using Excel (Microsoft, WA, USA). Differences between treated lesions, blood pool, and normal brain parenchymal SUVs were analyzed using visual inspection with statistical comparison.

Statistical analysis

$SUV_{\text{max}}$ for each tumor lesion, contralateral normal background, and venous confluence were recorded at all time points. Tumor to background ratios for each lesion were calculated as $TB_{\text{max}} = \frac{(SUV_{\text{max}} \text{ tumor})}{(SUV_{\text{max}} \text{ contralateral normal brain})}$ at each time points. As each lesion demonstrated progressive uptake without washout, the 1-minute value was subtracted from the 9-minute value to obtain a change in each variable over time. The mean change for each variable between groups was compared using ANOVA. Statistical significance was assessed at the 0.05 level, and the statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Subject demographics

Six patients (2 male and 4 female) with intracranial malignancies previously treated with SRS and a mean age of 51.6 years (range from 39y - 61y) were included per the inclusion criteria (Table I). Three of these patients had 2 lesions each, resulting in a total of 9 distinct lesions being independently evaluated. Two additional patients (1 male and 1 female) with known AVM previously treated with SRS (ages 21y and 27y) were included in the radiation necrosis group. All patients completed the $^{82}$RbCl PET scan after standard of care MRI demonstrated an enhancing lesion in an area previously treated with SRS. Histological confirmation via stereotactic biopsy/_excisional biopsy was obtained for 9 lesions with the remaining 2 lesions classified with either progressive enhancement (recurrent tumor) or stable/decreasing enhancement (radiation necrosis) on subsequent standard of care MRI.
examinations. PET imaging was performed an average of 37 months (range: 28 months - 45 months) after completion of SRS.

**TACs**

TACs of mean lesion SUV\textsubscript{max}, contralateral parenchymal uptake SUV\textsubscript{max}, and blood pool SUV\textsubscript{max} levels are shown from 1-9 min (Figure 1). Dynamic imaging of the brain was performed during the first 10 minutes after injection; however, the 10 minute time point is not shown nor was included in the analysis due to excessive noise. The arteriovenous phase of the brain is typically seen between 30-90 seconds after injection, however unlike \textsuperscript{15}O-water perfusion studies, there was no identifiable wash-in-wash-out of \textsuperscript{82}RbCl to correspond to the arteriovenous phase on the TACs. We did see progressive accumulation of \textsuperscript{82}RbCl starting by 1 minute in every lesion, including both recurrent disease and radiation necrosis, which likely corresponds to first pass extraction/perfusion and subsequent extraction from the circulating blood pool. The AVMs which had been previously treated with SRS are included as part of the radiation necrosis group as treated AVMs have been widely used to model radiation necrosis, and are identical on both imaging and histopathology. No statistically significant difference between recurrent intracranial disease and radiation necrosis was noted (P>0.05).

**Semiquantitative PET metrics and threshold values**

TAC analysis was performed for each lesion (Table II) and compared to contralateral normal brain parenchyma. Each lesion, including those with radiation necrosis, demonstrated statistically greater radiotracer accumulation compared to normal brain parenchyma at each time point. In order to normalize differences in physiologic vascular flow, the SUV\textsubscript{max} of each lesion was normalized to the contralateral brain, TB\textsubscript{max} = (SUV\textsubscript{max tumor})/(SUV\textsubscript{max contralateral normal brain}) and these values were compared between the two groups. Additionally, as each lesion demonstrated progressive uptake of \textsuperscript{82}RbCl without evidence of washout, the 1-minute SUV\textsubscript{max} was subtracted from the 9-minute SUV\textsubscript{max} value to obtain the interval change in each variable. While the mean and median SUV\textsubscript{max} for recurrent disease was greater than that of radiation necrosis, there was considerable overlap on a lesion to lesion basis and standard deviations. Thus for each variable, the group values did not differ significantly, and we failed to reject the null hypothesis between the groups (P>0.05). The fact that three patients had observations in both groups was ignored for the purpose of this analysis.

**Discussion**

The goal of this project was to determine if perfusion PET imaging with \textsuperscript{82}RbCl could discriminate between true progression of disease and radiation necrosis in patients with intracranial malignancies after SRS. While there are reports of \textsuperscript{82}RbCl uptake in intracranial malignancies, there are no studies available evaluating the ability of \textsuperscript{82}RbCl to differentiate malignant from benign lesions. We evaluated 2 different semiquantitative PET metrics as means to identify and discriminate \textsuperscript{82}RbCl uptake between recurrent disease and radiation necrosis, SUV\textsubscript{max} and TB\textsubscript{max}. While the median and mean SUV\textsubscript{max} and TB\textsubscript{max} of recurrent disease were greater than those of radiation necrosis, on a per lesion basis there was
considerable overlap between the two groups (Figure 2, 3). Additionally, statistical analysis of the TACs found that these metrics were not robust discriminators of treated disease. We included 2 patients with an AVM previously treated with SRS as internal controls of radiation necrosis as both treated AVMs and intracranial malignancies appear similar on MRI and histopathology.12

External beam radiation therapy, in particular SRS, is considered part of first line therapy for high-grade gliomas and intracranial metastases.13 Metastatic brain tumors are the most common brain tumor in adults and the frequency of brain metastasis is increasing.14 The efficacy of SRS in patients with intracranial metastases has been shown to have control rates of 70-90%.15 One of the most common complications of SRS for both primary brain gliomas and intracranial metastases is correctly identifying progressive reactive changes from radiation injury. Early true progression is difficult to distinguish from reactive changes (pseudoprogression) in the short term and irreversible injury (radiation necrosis) at latter time points.16 Radiation necrosis is difficult to distinguish from tumor recurrence by both clinical presentation and imaging studies, and can be seen in up to 25% of patients after SRS.17 Both recurrent tumor and radiation necrosis demonstrate increased FLAIR signal and disruption of the BBB resulting in contrast enhancement. The ability to accurately identify true progression from therapy-related changes is critical as it enables appropriate therapeutic intervention. Several imaging MRI techniques have been explored as methods for this purpose including perfusion-weighted imaging,18 dynamic contrast-enhanced imaging,19 diffusion-weighted imaging,20 and MR spectroscopy.21 However, each technique has its limitations and technical difficulties. Amino acid PET agents such as 18F-fluoroethyltyrosine,22 F-fluciclovine,23 have been used as means to identify radiation necrosis and grade brain gliomas; however, none of these amino acid PET radiopharmaceuticals are yet FDA approved for evaluation of intracranial malignancies.

13N-ammonia, and 82RbCl are perfusion radiopharmaceuticals commonly used for evaluation of myocardial ischemia and myocardial blood flow and 15O-water is used to evaluate cerebral blood flow and oxygen consumption.24 Perfusion radiopharmaceuticals can be divided into either category I radiotracers that are freely diffusible between tissue and blood (e.g. 15O-water) and radiotracers that are physiologically retained in tissue such (e.g. 82RbCl and 13N-ammonia). 82RbCl is a positron emitting potassium analog with a short half-life of 75s and a maximum positron energy of 3.35 MeV. Facile 82RbCl production is available from commercially available 82Sr/82Rb generators, does not require an onsite cyclotron, and is an ideal agent to evaluate organ perfusion in community PET centers.

In this study, all lesions were found to demonstrate progressive accumulation of 82RbCl in areas corresponding to SRS. We found that each lesion demonstrated initial accumulation of 82RbCl between 30 seconds and 1 minute with no temporal difference between recurrent disease and radiation necrosis. The two AVMs that were included in this analysis were both previously treated with SRS, and these treated AVMs are widely used to model radiation necrosis, with one of our lesions being later excised and found on histopathology to be consistent with radiation necrosis. In this study, the treated AVMs demonstrated similar TACs when compared to the other lesions with radiation necrosis, and were thus included in the radiation necrosis group. The slow progressive accumulation that is observed

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with both sets of lesions between 6-9 minutes is believed to be continued extraction from the circulating blood pool as there no substantial uptake in normal brain tissue to suggest local redistribution as a mechanism of uptake. Given that $^{82}$RbCl extraction occurs via Na+/K+-ATPase, we were not surprised that lesions with recurrent disease did not demonstrate any identifiable washout; however, it was somewhat unexpected that the radiation necrosis lesions did not demonstrate any appreciable washout after first pass wash-in. This progressive uptake of $^{82}$RbCl in lesions with radiation necrosis implies that there may be active extraction and trapping in the cellular stoma by Na+/K+-ATPase, rather than simple increased inflammatory blood flow but this would need to be evaluated in a separate study.

All lesions with recurrent disease (Figure 2) and radiation necrosis (Figure 3) demonstrated progressive $^{82}$RbCl uptake greater than normal brain parenchyma by both visual analysis and semiquantitative image analysis. But, while the lesions with recurrent disease demonstrated a higher mean and median $^{82}$RbCl uptake compared to radiation necrosis (Figure 1), dynamic TAC analysis with either SUV$_{\text{max}}$ or TB$_{\text{max}}$ failed to adequately resolved radiation necrosis from recurrent disease on a statistical or per lesion basis. One of the patients with recurrent melanoma had a standard of care FDG PET-CT to evaluate for other sites of disease (Figure 4) and there was FDG no appreciable FDG uptake in the area of recurrent disease greater than the adjacent brain parenchyma. This is in line with other evidence that suggests the FDG PET is of limited utility in distinguishing recurrent disease from radiation necrosis.$^3$

**Limitations of the study**

This study has several limitations primary of which is the small sample size which limits the ability to statistically differentiate between recurrent disease and radiation necrosis. An additional limitation is that this study included several different malignancies (e.g. primary glioma and intracranial metastases) as well as SRS treated AVMs. The heterogeneous sample population may introduce a negative confounding error that obscures the ability to correctly distinguish radiation necrosis in a specific disease etiology, such as in primary brain gliomas. Additionally, while there was no statistical difference in $^{82}$RbCl uptake in recurrent disease compared to radiation necrosis, the greater mean SUV$_{\text{max}}$ of recurrent disease suggests that $^{82}$RbCl may be able to discriminate between benign and malignant lesions if done on a larger sample population. Finally, PET imaging with positron amino acids or a freely diffusible perfusion agent such as $^{15}$O-water was not performed which may have provided complementary information on a per lesion basis to help explain the lack of $^{82}$RbCl washout seen on lesions with radiation necrosis.

**Conclusions**

Visual and semiquantitative analysis of $^{82}$RbCl PET is able to distinguish between normal brain parenchyma and uptake of intracranial malignancies previously treated with stereotactic radiation surgery. $^{82}$RbCl does demonstrate a greater mean SUV$_{\text{max}}$ in lesions with recurrent disease compared to necrosis; however, on a per lesion basis and by statistical analysis, $^{82}$RbCl is not able to satisfactorily discriminate between recurrent disease and
radiation necrosis which is needed to accurately guide future treatment decisions. Based on these results, confirmation that $^{82}$RbCl is able to discriminate recurrent disease from radiation necrosis this would require a larger sample size for validation and no future studies are planned at this time.

**Acknowledgements.**

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**References**


Figure 1.
SUV\textsubscript{max} Time Activity Curve. Mean time activity curves of recurrent tumor (1, blue in the online version) and radiation necrosis SUV\textsubscript{max} (2, red in the online version) show progressive increased uptake after injection. Statistically significant difference is noted for both recurrent disease and radiation necrosis as compared to normal brain parenchyma (3, green in the online version). No statistical significance was between recurrent disease and radiation necrosis.
Figure 2.
A 74-year-old female with biopsy proven recurrent malignant meningioma after stereotactic radiation surgery. Axial post contrast T1 image (A) demonstrates an enhancing lesion in the right temporal lobe. Corresponding axial $^{82}$RbCl PET (B) and fused PET-CT images (C) also demonstrate increased $^{82}$RbCl uptake with an 8 minute SUV$_{\text{max}}$ of 4.3.
Figure 3.
A 21-year-old man with arteriovenous malformation treated with stereotactic radiation surgery found to be radiation necrosis on excisional biopsy. Axial post contrast T1 image (A) demonstrates an enhancing lesion in the paramedian left posterior parietal lobe. Axial $^{82}$RbCl PET (B) and fused PET-CT images (C) demonstrate increased $^{82}$RbCl uptake in the same lesion with 8 minute SUV$_{max}$ of 5.2.
Figure 4.
A 39-year-old female with intracranial metastatic melanoma treated with stereotactic radiation surgery found to be recurrent disease on biopsy. Axial post contrast T1 image (A) demonstrates an enhancing lesion in the right posterior parietal lobe. Axial $^{82}\text{RbCl}$ PET (B) and fused PET-CT images (C) demonstrate increased $^{82}\text{RbCl}$ uptake in the same lesion with an 8 minute SUV$_{\text{max}}$ of 6.3. FDG PET-CT was unable to identify the presence of recurrent disease due to intense physiologic FDG uptake in adjacent brain parenchyma as evidenced on transaxial CT (D) FDG PET (E) and fused FDG PET-CT images (F).
Table I.

Patient demographics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
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<th>Lesion 2&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
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<tr>
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<td>EB</td>
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<td>EB</td>
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<tr>
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<tr>
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<td>F</td>
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<td></td>
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</tr>
<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>Glioblastoma</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

SB: stereotactic biopsy; EB: excisional biopsy/partial resection; NA: not available (imaging verification).

<sup>a</sup>Lesions from same patient.
Table II.

Statistical analysis of $^{82}$RbCl uptake in recurrent disease (malignant) and radiation necrosis (benign).

<table>
<thead>
<tr>
<th>Co variate</th>
<th>Change over time</th>
<th>Lesion SUV$_{\text{max}}$</th>
<th>Normal brain SUV$_{\text{max}}$</th>
<th>SUV$_{\text{max}}$</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Malignant N.=5 Benign N.=6</td>
<td>Malignant N.=5 Benign N.=6</td>
<td>Malignant N.=5 Benign N.=6</td>
</tr>
<tr>
<td>Mean</td>
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<td>2.23</td>
<td>0.47</td>
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<tr>
<td>Max</td>
<td></td>
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<td>4.54</td>
<td>26.33</td>
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<tr>
<td>Standard deviation</td>
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<td>3.39</td>
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<tr>
<td>P value (ANOVA)</td>
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<td>0.927</td>
<td>0.108</td>
</tr>
</tbody>
</table>

$^a$Aggregate change in SUV$_{\text{max}}$ in each lesion (9 minute SUV$_{\text{max}}$ – 1 minute SUV$_{\text{max}}$)

$^b$Aggregate change in SUV$_{\text{max}}$ in normal brain (9 minute SUV$_{\text{max}}$ – 1 minute SUV$_{\text{max}}$)

$^c$indicates aggregate change in normalized lesion uptake TB$_{\text{max}}$ = (SUV$_{\text{max}}$ tumor)/ (SUV$_{\text{max}}$ contralateral normal brain).